21 March 2024
EMA/146690/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Awiqli

International non-proprietary name: Insulin icodec

Procedure No. EMEA/H/C/005978/0000

Note

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

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List of abbreviations

ADA   American Diabetes Association
ADME   Absorption, distribution, metabolism and excretion
ANCOVA   analysis of co-variance
BA -   bioanalysis
BG   Blood glucose
BMI   body mass index
CFB   Change from baseline
CGM   continuous glucose monitoring
CI   confidence interval
COVID-19   Coronavirus disease 19
CTR   clinical trial report
DBL   database lock
DKA   diabetic ketoacidosis
DPP-4   dipeptidyl peptidase 4
DTSQ   Diabetes treatment satisfaction questionnaire
eGFR   estimated glomerular filtration rate
ETD   estimated treatment difference
ETR   estimated treatment ratio
FAS   full analysis set
FPG   fasting plasma glucose
GLP   Good laboratory practice
GLP-1   glucagon like peptide 1
HbA$_{1c}$ glycated haemoglobin
IDeg   Insulin degludec
IGlar   Insulin glargine
IMP   investigational medicinal product
ISR   incurred sample reanalysis
i.v.   intravenous(ly)
LOCI   Luminescence oxygen channelling immunoassay
NAbs   Neutralising antibodies
NPH   Neutral protamine Hagedorn
OAD   oral anti-diabetic drug
OC   Other concern
OW   ONWARDS
PD   pharmacodynamics
PK   pharmacokinetics
PRO   patient-reported outcome
QWBA   Quantitative whole-body autoradiography
PYE   patient years of exposure
RA   Receptor agonist
SAS   safety analysis set
s.c.   subcutaneous(ly)
SMPG   self-measure plasma glucose
SS   steady state
SU   sulphonylurea
T1DM   type 1 diabetes
T2DM   type 2 diabetes
TAR   time above glycaemic range
TBR   time below glycaemic range
TIR   time in glycaemic range
TK -   toxicokinetics
T$_{max}$ time to reach maximum observed concentration

TRIM-D   Treatment related impact measures – diabetes
U   unit(s)
USA   United States of America

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novo Nordisk A/S submitted on 4 April 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Awiqli, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Treatment of diabetes mellitus in adults

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

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

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0263/2020 on the granting of a product-specific waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.4.2. New active Substance status

The applicant requested the active substance *insulin icodec* contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
31 May 2018	EMEA/CHMP/SAWP/302624/2018	Peter Mol, Kolbeinn Gudmundsson
12 December 2019	EMA/CHMP/SAWP/649857/2019	Walter Janssens, Jeanette McCallion
30 April 2020	EMA/CHMP/SAWP/221272/2020	Armin Koch, Kolbeinn Gudmundsson
25 March 2021	EMA/CHMP/SAWP/221272/2020	Stephan Lehr, Karin Janssen van Doorn

The scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- Acceptability of the proposed comparability study to support changes to the manufacturing process for the drug substance;

- Acceptability of the proposed comparability programme and the stability data package for the drug product;

- Adequacy of the proposed stability programme at long term and accelerated storage conditions to support the proposed drug product shelf-life for both 3 ml and 1.5 ml cartridges for the MAA;

- Adequacy of the proposed strategy for defining the drug product shelf life in-use limit;

- Adequacy of a 12-month rat study (including proposed design) for assessment of carcinogenic potential;

- Adequacy of the proposed strategy to characterise ADME;

- Adequacy of the proposed characterisation of potential effects on ECG and blood pressure;

- Adequacy of the proposed clinical development programme to support an indication 'for treatment of diabetes mellitus';

- Adequacy of the proposed clinical pharmacology programme including PopPK modelling to support MAA;

- Sufficiency of the proposed evidence to support information on flexible dosing;

- Adequacy of the measures foreseen to collect and evaluate hypoglycaemic episodes in the phase 3 programme;

- Adequacy of the planned characterisation of immunogenicity;

- Adequacy of the envisaged safety database to inform benefit/risk assessment;

- Acceptability of the proposed safety monitoring and adjudication strategy for the phase 3 clinical programme;

- Ability of the proposed hierarchical testing plan for trial 4481 to demonstrate superiority in terms of HbA1c;

- Adequacy of the proposed estimands for the phase 3 trials;

- Adequacy of the plans for prevention and handling of missing data;

- Acceptability of the proposed non-inferiority margin for HbA1c in the phase 3 studies;

- Suitability of the proposed on-treatment period for safety evaluation;

- Acceptability of the provisions foreseen to manage multi-regional trials with flexible sample size;

- Acceptability of the proposed pre-specified cardiovascular meta-analysis plan.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder   Co-Rapporteur: Robert Porszasz

CHMP Peer reviewer(s): N/A

The application was received by the EMA on	4 April 2023
The procedure started on	18 May 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	7 August 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	22 Aug 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	22 August 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 September 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	13 December 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	29 January 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	02 February 2024
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	15 February 2024
The CHMP agreed on a List of Outstanding Issues to be sent to the applicant on	22 February 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	28 February 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues	06 March 2024

to all CHMP and PRAC members on	
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Awiqli on	21 March 2024
The CHMP adopted a report on similarity of Awiqli with Amglidia on (see Appendix on similarity)	21 March 2024
Furthermore, the CHMP adopted a report on new active substance (NAS) status of the active substance contained in the medicinal product	21 March 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Insulin icodec is intended to be used in the following indication:

"Treatment of diabetes mellitus in adults"

Insulin icodec is a basal insulin for once-weekly subcutaneous administration.

2.1.2. Epidemiology and risk factors

Diabetes mellitus is a metabolic disorder characterised by the presence of hyperglycaemia due to defective insulin secretion, insulin action or both. In both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), various genetic and environmental factors can result in the progressive loss of b-cell mass and/or function that manifests clinically as hyperglycaemia. In 2021, the estimated worldwide diabetes prevalence was in 537 million, with a prediction that by 2045 the number of people with diabetes will have increased to 783 million (IDF 2021).

2.1.3. Aetiology and pathogenesis

T2DM is characterised by peripheral tissue insulin resistance, impaired insulin secretion, and/or increased hepatic glucose output due to glucagon dysregulation resulting in chronic hyperglycaemia. The pathogenesis seemingly heterogeneous, involving environmental, lifestyle, and genetic factors.

T1DM is a heterogeneous disorder characterised by T cell-mediated autoimmune destruction of insulin-producing beta cells in the pancreas. The destruction of beta cell function leads to insulin deficiency and the requirement of lifelong administration of exogenous insulin. The fundamental principle for insulin treatment of T1DM is to mimic normal physiological patterns as closely as possible.

2.1.4. Clinical presentation and diagnosis

The typical presentation of diabetes includes polyuria and polydipsia, characterised by hyperglycaemia. Diabetes, especially type 2 diabetes, is frequently associated with overweight, hypertension and dyslipidaemia, making multiple cardiovascular risk factor intervention a key issue.

2.1.5. Management

In T2DM patients, the current treatment follows a stepwise approach comprising lifestyle changes in combination with pharmacological intervention. In asymptomatic individuals, the first line of treatment is always lifestyle such as diet and exercise, with the aim of reducing weight and improving insulin sensitivity. Such changes may also have a beneficial effect on lipids and blood pressure. Glucose-lowering agent monotherapy, primarily metformin as first-line therapy, is generally recommended as initial pharmacological

therapy. Single agent therapy is followed by combination therapy with other oral antidiabetic drugs, GLP-1 receptor agonists and/or insulin as the disease progresses. In T1DM patients, lifelong administration of exogenous insulin is required. Not achieving adequate glycaemic control is associated with an increased risk of diabetes-associated complications and co-morbidities (including multiple micro- and macrovascular complications).

Maintaining a low HbA1c is critical to reduce the risk of development and progression of micro- and macrovascular complications in patients with diabetes. Besides anti-hyperglycaemic therapy, antihypertensive, antithrombotic and lipid lowering treatment may be indicated to avoid other associated co-morbidities (e.g., hypertension, obesity, dyslipidaemia) and macrovascular complications.

2.2. About the product

Insulin icodec is a basal insulin for once-weekly subcutaneous administration.

Proposed indication:

"Treatment of diabetes mellitus in adults"

Proposed posology:

In patients with type 2 diabetes mellitus, this medicinal product can be administered alone or in any combination with oral antidiabetic medicinal products, GLP-1 receptor agonists and bolus insulin.

In patients with type 1 diabetes mellitus, this medicinal product must be combined with bolus insulin to cover mealtime insulin requirements.

Patients with type 2 diabetes mellitus (insulin-naïve)

The recommended weekly starting dose is 70 units and followed by individual once-weekly dose adjustments.

Switch from once- or twice-daily basal insulin medicinal products to insulin icodec in type 2 and type 1 diabetes

When switching patients from once- or twice-daily basal insulin, the recommended once-weekly insulin icodec dose is the total daily basal dose multiplied by 7. For the first injection only, a one-time additional 50% insulin icodec dose is recommended.

2.3. Aspects on development

This application for insulin icodec, as a novel long-acting human insulin analogue for a once-weekly subcutaneous administration intended for treatment of diabetes mellitus in adults, is supported by data from 18 clinical studies:

- 9 clinical pharmacology trials
- 3 phase 2 exploratory trials
- 6 phase 3a confirmatory trials (ONWARDS 1-6)

The 3 exploratory phase 2 studies (4383, 4465 and 4466) investigated the effect on glycaemic control and safety of insulin icodec compared to daily basal insulin.

The efficacy of once weekly insulin icodec has been investigated in six confirmatory phase 3 studies, of which five trials in T2DM patients (ONWARDS 1-5) and one trial in T1DM patients (ONWARDS 6). All studies were open-label, except for one T2DM study which was double-blinded with a double dummy design (trial ONWARDS 3). The efficacy was evaluated in insulin naïve T2DM patients (ONWARDS 1, 3 and 5), in T2DM patients previously treated with basal insulin (ONWARDS 2) and in T2DM and T1DM patients previously treated with basal-bolus insulin (ONWARDS 4 and 6). All trials applied a treat to target design, except for ONWARDS 5 which was to evaluate effectiveness of insulin icodec and was designed to mimic a clinical practice setting with fewer dedicated visits and routine assessment left to the treating physician.

The T2DM trials were 26-52 weeks of duration and the T1DM trial was 26 weeks, including a 26-week extension period. The 52-week T2DM trial (ONWARDS 1 in insulin naïve subjects) also included a 26-week extension part. The extension of these studies was not finalised at the time of the submission of the application.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as a solution for injection containing 700 units/mL of insulin icodec as active substance. Other ingredients are: glycerol, metacresol, phenol, zinc acetate, sodium chloride, hydrochloric acid and sodium hydroxide (for pH adjustment) and water for injections.

Insulin icodec 700 units/ml is a drug device combination product containing either a 3 mL or 1.5 mL size cartridge assembled into the PDS290 icodec pen-injector with nominal fill volumes of 1, 1.5 and 3 mL.

1 mL solution contains 700 units of insulin icodec (equivalent to 26.8 mg insulin icodec). The product is available as 1, 1.5 or 3 mL solution:

Each pre-filled pen contains 700 units of insulin icodec in 1 mL solution.
Each pre-filled pen contains 1 050 units of insulin icodec in 1.5 mL solution.
Each pre-filled pen contains 2 100 units of insulin icodec in 3 mL solution.

2.4.2. Active Substance

2.4.2.1. General information

Insulin icodec is an analogue of insulin human where ThrB30 has been omitted, TyrA14 has been substituted with Glu, and TyrB16 and PheB25 have been substituted with His. A C20 fatty acid derivative sidechain is added to the peptide backbone via the amino group in the side chain at LysB29. The predicted molecular weight (MW) is 6380 Da. Insulin icodec binds to and activates the human insulin receptor.

The molecular mode of action of insulin icodec active substance is equal to human insulin: insulin icodec is an acylated analogue, which is a specific, low affinity insulin receptor agonist with full efficacy that binds strongly, but reversibly, to albumin. Compared to human insulin, insulin icodec has a prolonged half-life of around 1 week making it suitable for once-weekly subcutaneous administration. The principal mechanism of protraction is binding to albumin, which results in decreased renal clearance and protection from metabolic degradation.

Figure 1. Insulin icodec structure
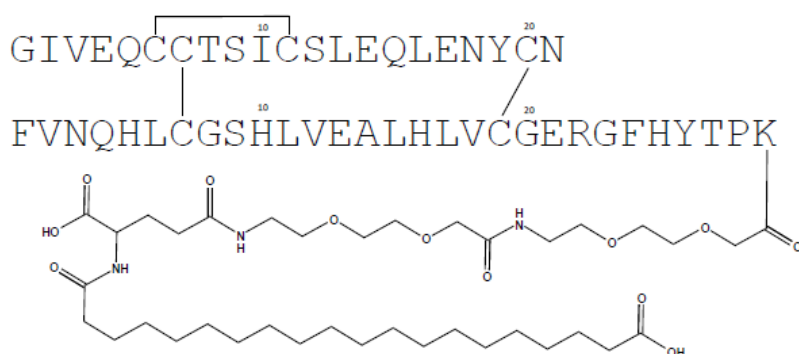
2.4.2.2. Manufacture, characterisation and process controls

<u>Manufacturers</u>

The manufacturer of the active substance is Novo Nordisk A/S, Kalundborg, Denmark. The sites for Master Cell Bank (MSB) storage, WCB storage and quality control are listed. The information on active substance manufacturing sites is found sufficient and in compliance with GMP.

<u>Description of the manufacturing process</u>

Insulin icodec is manufactured in *Saccharomyces cerevisiae (S. cerevisiae)* cells.

The manufacturing process for insulin icodec active substance consists of four major parts: fermentation, recovery, synthesis of the acylating agent and purification of active substance. The structures of the molecules formed during the fermentation, recovery and purification processes have been provided. A brief outline of the overall process has been provided and separate detailed flow charts for each of the four process parts have also been provided in the dossier, including operational parameters and in-process tests.

The applicant defines the propagation and fermentation process as one step divided into three phases. The main purpose is to produce a fermentation broth containing the recombinant insulin icodec precursor. In the recovery process, yeast cells are removed from the fermentation broth and the precursor is concentrated. In order to maintain a constant broth volume in the fermenter, the culture broth is constantly delivered to a harvest tank. The purification process is divided into several steps. During this part of the process, the precursor is modified first into the open precursor through enzymatic cleavage, then the acylating agent is attached, followed by cleavage, resulting in the insulin icodec target molecule. The purification process also involves various chromatographic purification steps, ultrafiltration and the final drying.

The purpose of each step during active substance manufacturing is sufficiently described. Operational parameters and in-process tests have been provided. Microbial contamination is tested as in-process controls (IPC) with acceptable limits at each upstream step. It is stated that if the microbial test result exceeds the acceptable limit, the "the rejection of culture broth and the affected recovery batches is traced back to the point in time when the culture broth fulfils the acceptance criteria". The applicant states that microbial test is carried out from the fermentation tank and in case of negative infection control results, the fermentation

broth and all possibly affected recovery batches are discarded. A description of the drying process has been provided, including the operational principle and general details of the procedure.

The description of the manufacturing process for the acylating agent is found sufficient. The batch size of the acylating agent and splitting of batches are adequately described.

Storage and shipping of intermediates and active substance are described. The storage temperatures and hold times, are supported by stability studies. For intermediates and for the active substance, it is stated that short time excursions outside the freezers are acceptable. This is supported by data from stability studies performed at accelerated conditions. It is stated in the dossier that the cells can be kept under cold conditions before inoculation, and the applicant has provided an acceptable justification.

Transportation of active substance is conducted according to written procedures. A summary report on the performance qualification (PQ), performed for the transport system frozen truck with temperature limits, is provided. This is found acceptable.

During the active substance manufacturing process, pooling and splitting of batches occur. The Applicant explains that the primary criterion for pooling and splitting of intermediate batches is to meet the starting amount of incoming material at the following process step, which is further illustrated in a batch tree. A batch of insulin icodec active substance is defined as the active substance obtained from one cycle. The batch size is found acceptably defined.

Control of materials

Lists of raw materials used in each stage of manufacturing have been provided in a tabular format. Tables include the name of the raw material; compendial reference, if applicable, and/or method of analysis; and acceptance criteria in case of non-compendial raw materials. Starting materials of the acylation step of insulin icodec production are well characterised and justification is provided.

There are no raw materials of human/animal origin used during insulin icodec manufacturing.

Fermentation media composition is listed and is tested upon arrival according to the Applicant's quality assurance (QA) system. Grade, analytical methods and acceptance criteria are provided. Media and their composition used for new WCB manufacture is listed. Solution and reagents used during recovery and the purification process and their composition, grade and specification are listed.

The types of chromatography resins and their materials and controls are listed. Filters and their materials are listed as well together with information on at what step the different filters are used.

Development of the production yeast strain and the clone selection process is described. Final clonal strain was tested for genetic integrity and plasmid retention.

Preparation and storage of master and working cell banks is adequately described. MCB testing is in accordance with ICH Q5D. Testing includes identity, genetic integrity, purity. Regarding microbial contamination testing, several IPC of microbial contamination were carried out during the MCB manufacturing process. No contamination was found. The stability during storage is evaluated by viability testing of the cell banks.

Characterisation results are provided. Characterisation includes microbial purity, DNA sequencing, plasmid rearrangement, viability, phenotype, plasmid copy number and plasmid frequency. All results comply with acceptance criteria.

Generation of future WCB is described and testing panel is registered in the dossier. Acceptance criteria are provided.

Control of critical steps and intermediates

The control strategy for the insulin icodec active substance manufacturing process is described. The applicant uses the term in-process controls for operational parameters, used to control the process, and for in-process tests, measured as a control of the outcome of the process. Operational parameters and in-process tests are defined as critical or non-critical. A table presenting critical operational parameters and critical limits is provided. In addition, critical in-process tests, analytical procedures numbers and acceptance criteria are provided. The information is found acceptable.

The non-critical operational parameters and the corresponding ranges are also listed in this section. Analytical procedures used for in-process control are sufficiently described.

Furthermore, stability studies for the intermediates are presented. The control of critical steps and intermediates in the manufacture of the acylating agent is considered acceptable.

Process validation and/or evaluation

Process validation (PV) was performed to demonstrate that the commercial process is capable of consistently producing insulin icodec active substance of the desired quality. The term process validation used by the applicant is equivalent to process performance qualification (PPQ). The applicant states that the PV design has been based on the extensive experience gained in-house from other recombinant yeast products, as well as the experience gained from laboratory experiments, pilot, and commercial scale production campaigns of insulin icodec active substance.

Process justification to establish the final active substance manufacturing process and to define acceptance criteria is provided in the dossier. Data demonstrating removal of impurities is provided. Analytical method descriptions have been provided as well. The applicant submitted acceptable information concerning the methods. Spiking experiments sufficiently demonstrate that the purification process is adequate.

The PV evaluated critical and non-critical operational parameters, results from in-process tests and additional tests on in-process samples, and active substance specification tests. The three active substance PV batches were manufactured from start, middle and end of the fermentation to demonstrate that the quality of active substance is not influenced by the fermentation time.

All results obtained from the PV fulfilled the acceptance criteria and were considered consistent. Overall, the design of the process validation is found acceptable. The results support consistent and adequate production of insulin icodec active substance. A continued process verification has been initiated. This is endorsed. A validation report supporting transportation of active substance has been provided. Since the manufacture of the acylating agent is part of active substance manufacture and a purely synthetic process, the absence of process validation data for this process is considered acceptable.

Manufacturing process development

Process development

Three process versions, referred to as Process A, Process B and the commercial process have been applied during development. Batches manufactured by Process A have been used in non-clinical studies, Phase 1 and Phase 2 clinical trials. Batches from Process B have been used during development, non-clinical studies and

phase 3 clinical trials. The commercial process has been used to manufacture batches for development, process validation and an extension of clinical phase 3.

The process change from Process A to Process B was implemented to increase manufacturing capacity, allowing for phase 3 clinical trials and prepare for commercial manufacturing. The changes were extensive and included the introduction of a new MCB, modification of the precursor molecule, introduction of a concentration step and an additional enzymatic modification step, changes in the final concentration step and the drying process. The changes from Process B to the commercial process were minor and involved removal of a couple of steps. In addition, the process was moved to the final commercial facility. The differences between processes are found adequately described.

Comparability

To demonstrate comparability between batches manufactured by the different processes two separate comparability studies were conducted. The first one compares batches from Process A and Process B, and the second one compares batches from Process B and the commercial Process.

Several Process A batches and several Process B batches were included in the comparability study. The batches were chosen to demonstrate comparability of active substance batches from non-clinical, phase 1 and phase 2 clinical trials with active substance batches from phase 3 clinical trials. The selection of batches is found acceptable.

The comparability exercise involved characterisation tests including evaluation of structural and physical characteristics, physicochemical properties and the product-related impurity profile. Bioactivity was evaluated by three orthogonal methods. The acceptance criteria for all comparability tests are listed. In general, the results from the characterisation tests demonstrate that batches manufactured by Process B and batches manufactured by the commercial process are comparable. Even though the acceptance criteria for the bioactivity assays are vaguely defined, the tabulated data for individual samples and the dose-response curves support comparability. The product-related impurity profile was demonstrated to differ between Process A and Process B batches in that some impurities present in the Process A batches were not found in Process B batches. This is a consequence of the optimised process and thus considered in favour of Process B, not precluding comparability. The applicant states that no new product-related impurities were identified in active substance from Process B. A discussion on the potential impurities formed from Process B was provided upon request. Results from specification test analysis and stability data also support the comparability claim.

Several active substance batches from Process B and several active substance batches from the commercial process were included in the second comparability study. The Process B batches were selected to include one batch used for non-clinical studies and three batches used for Phase 3 clinical trials. The batches from the commercial process include the PV batches and an additional development batch. The comparability study also involved representative in-process batches. The selection of batches is found acceptable. It is also noted that data from more batches are presented graphically when evaluating comparability of the specification parameters.

The comparability exercise involved characterisation tests including evaluation of structural and physical characteristics, physicochemical properties and the product-related impurity profile. Bioactivity was evaluated by three orthogonal methods. The acceptance criteria for all comparability tests are listed. In conclusion, the results from the characterisation tests demonstrate that batches manufactured by Process B and batches manufactured by the commercial process are comparable. The tabulated data presented for individual samples and the dose-response curves support comparability.

In addition, comparison of results from batch release testing is presented. All results comply with the specification limits. In addition, the batches produced with the commercial process was compared to historical data from Process B batches. Overall, the results are found comparable. A few deviations from the defined acceptance ranges were detected, but these are sufficiently justified to be of no quality concern. This is acceptable. Furthermore, no changes in stability are seen neither at the recommended nor at the accelerated storage conditions for any of the active substance batches.

In conclusion, batches manufactured by Process B and the commercial process are found comparable.

Process justification

The manufacturing process design for insulin icodec active substance consisted of repeated cycles of process characterisation and evaluation, followed by process justification.

Process justification is further described in this section. As part of the process justification, in-process controls are classified as either critical or non-critical based on an impact assessment. Operational parameters are defined as critical if the variability of the parameter has a significant impact on the desired active substance quality and thereby impacting the critical quality attributes (CQAs). In contrast, an operational parameter is defined as non-critical if the variability of the parameter has no or insignificant impact on the desired active substance quality within the established ranges. Process steps having one or more critical operational parameters are defined as a critical step. During the process justification studies, there is an extended focus on the evaluation of the critical operational parameters, as their variability has an impact on the desired active substance quality.

In-process tests are critical if conformance with the acceptance criteria is necessary for obtaining the desired quality of the active substance. Non-critical in-process tests are used for monitoring and verifying the robustness of the process.

The process justification studies were initially found too briefly described. The applicant has updated the dossier to include details on the laboratory and pilot scale and the number of experiments performed to establish the ranges for the critical operational parameters and to confirm the acceptance criteria for the critical in-process test. The applicant sufficiently explains what is defined as a significant effect on a CQA. In conclusion, the process justification studies are found acceptable.

Manufacturing process development - acylating agent

In view of the nature and synthesis routes of the proposed starting materials, the justifications for assigning them as starting materials in the manufacture of the acylating agent and subsequently to insulin icodec are considered sufficient.

The description of the manufacture and potential impurities of the proposed starting materials is considered sufficient, and the specifications for the proposed starting materials have been sufficiently justified by presenting results from purging studies and satisfactory batch analysis data.

The development of the synthesis of the acylating agent and the process justification studies are considered sufficiently described. The assignment of the process parameters as critical or non-critical has been sufficiently justified.

The discussions regarding impurities purging in the manufacturing process and the setting of limits for impurities are considered sufficient. The justifications for the acylating agent specifications are considered acceptable. The batch sizes of the acylating agent used in Phase 3 and the commercial batches of acylating agent are stated.

Characterisation

Characterisation of insulin icodec

The batches used for characterisation are adequately listed. The selection of batches is sufficiently justified.

Primary sequence was characterised. The masses of intact insulin icodec and the reduced chains agreed with the calculated masses. Primary sequence was confirmed. Representative data is included in the dossier and the position of the sidechain at LysB29 is confirmed. Furthermore, the disulphide linkage was confirmed.

In conclusion, the results confirm the expected peptide sequence, the position of the sidechain and the presence of disulphide bridges.

The molar extinction coefficient was determined. The procedure of determining the extinction coefficient has been explained. The secondary structure of insulin icodec was determined. The secondary structure was demonstrated to be primarily α-helical but also with some parts being assigned as β-strand. The tertiary/quaternary structures of insulin icodec were evaluated, which indicated that some of the aromatic residues are located in an asymmetric environment. The characterisation of higher order structures is found acceptable.

Bioactivity was evaluated. Furthermore, absolute and relative binding affinities for human insulin-like growth faction 1 receptor and human insulin receptor isoforms A and B were determined by competition radioligand binding studies. The affinity of insulin icodec for the human insulin receptor isoforms A and B was 0.49% and 0.78%, respectively, relative to human insulin. In addition, the affinity of insulin icodec for the human IGF1 receptor was approx. 0.14% relative to human insulin which in turn is 0.53% relative to human IGF1. The insulin icodec show significantly reduced insulin receptor family affinity compared to human insulin. The provided data demonstrates that the insulin receptor binding characteristics of human insulin and insulin icodec correlate with the results obtained by the bioassay. The choice of the bioassay as the bioactivity assay used in the active substance specification is found sufficiently justified. In addition, the main results from a study exploring binding of insulin icodec and other insulins to albumin have been included, further supporting the biological functionality of insulin icodec.

The correlation between the insulin icodec bioactivity as determined by the bioactivity assay and the content of the main peak and related substances was investigated. The applicant concludes that there is a direct correlation between the results and that this precludes the necessity to conduct a bioactivity assay on the finished product and support a reduced frequency for testing of active substance. This is found acceptable.

The physico-chemical properties appearance, solubility, pH in water, isoelectric point, UV absorbance and water absorption were determined by appropriate methods.

Extensive evaluation of product related variants and product related substances is provided. Product-related substances and impurities are described. The substances/impurities were identified. *In vitro* bioactivity of the components purified for characterisation was determined relative to insulin icodec using the insulin bioassay. The characterisation of product-related substances and impurities is found extensive and the correlation between the peaks observed in the chromatogram and the product-related substances and impurities is described. Upon request, the applicant provided data confirming the absence of appreciable amount of insulin icodec without intact size chain in the finished product. Data referred to are consistent with the lack of structural changes in the acylating agent during the acylating reaction.

A comprehensive list of process related impurities is provided. The steps at which each impurity is reduced or removed are indicated. The information provided on process-related impurities is found acceptable.

Characterisation of the acylating agent

The structural characterisation of the acylating agent presented is considered sufficient. The information presented regarding the origin and fate of acylating agent related impurities (acylating and non-acylating), process related impurities, and theoretical related impurities is considered acceptable. The control of these impurities is also acceptable. Information has been provided regarding the mutagenicity assessment of impurities from the manufacture of the acylating agent in accordance with ICH M7.

2.4.2.3. Specification

<u>Specifications</u>

Active substance specification includes methods to evaluate identity, product-related substances and impurities, content, high molecular weight proteins, bioactivity, loss on drying, bacterial endotoxins, appearance, host cell proteins, total aerobic microbial count (TAMC) and total yeast and mould count (TYMC).

For compendial methods, references are made to the corresponding Ph. Eur. chapters. For non-compendial methods, the type of method used for analysis is stated and in-house method numbers are defined. This is acknowledged and found acceptable.

The level of host cell proteins (HCP) is tested in-process. This is found acceptable. The approach proposed for testing bioactivity is found acceptable since correlation between the bioactivity and the content results has been demonstrated.

The method specification includes relevant analytical tests. Changes introduced in the specification parameters and acceptance criteria during development are also presented and justified.

The general approach to establish active substance acceptance criteria is stated to be based on active substance process capability, analytical variation, stability data, product characteristics and relation to the proposed finished product specification and clinical relevance. Calculations of acceptance criterion are presented for each parameter. It is noted that the proposed active substance acceptance criteria for hydrophilic and hydrophobic substances and impurities, and high molecular weight proteins are aligned with those in the finished product specification. The acceptance criteria are found acceptable.

The proposed acceptance criteria for content, loss on drying, identity, bacterial endotoxins, TAMC, TYMC and appearance are found acceptable.

<u>Analytical procedures</u>

The tests for loss on drying, bacterial endotoxins, TAMC and TYMC are stated to comply with Ph. Eur. This is found acceptable. Method descriptions for all non-compendial procedures are provided. In addition, a separate document describing analytical development for active substance has been provided.

For all methods, chemicals and reagents, equipment, reference material and sample solutions are sufficiently described. Procedures and calculations are presented at an acceptable level of detail, and chromatograms are shown, where applicable. System suitability tests and acceptance criteria are adequately described for all assays. In conclusion, the method descriptions are found acceptable for all analytical procedures.

Validation reports for all in-house methods, except for the appearance method, are provided. This is acceptable. Concise verification reports for compendial analytical procedures have been submitted. It is agreed that the visual evaluation performed to verify that the insulin icodec active substance released is a white or almost white powder does not require a validation exercise. The validation reports are overall found

comprehensive, including relevant calculations, acceptance criteria, description of results obtained for individual samples. Chromatograms are shown for the chromatographic methods. Relevant validation characteristics have been evaluated and the analytical procedures are found to be validated according to ICH Q2(R1).

<u>Batch analyses</u>

Results from batch analyses of insulin icodec active substance manufactured during development are presented. Batch analyses data from several batches are provided.

All results complied with the proposed specification limits at the time of release. The provided release data from the commercial process is in support of a consistent manufacture of the active substance.

<u>Reference standards</u>

The reference standard system consists of an insulin icodec primary reference material (PRM) and an insulin icodec secondary reference material (SRM).

The current PRM and SRM were manufactured from an insulin icodec active substance batch produced by Process B. The selected batch is considered acceptable. A provisional shelf life is proposed both for the lyophilised insulin icodec PRM and the SRM. The applicant confirms that an internal system is in place taking the necessary precautions in due time to ensure that only a reference material batch in control is used. Adequate verification protocols are provided. Data supporting the proposed intermediate storage of the SRM has been submitted.

Former PRM and SRM batches have been used during development. Adequate information with respect to lot number, usage period and reference standard use is provided. This is found acceptable. Separate documents are provided to describe establishment of new PRMs and new SRMs, respectively. The applicant thoroughly describes how the Content will be calculated and how the Bioactivity will be assigned. The approaches are found acceptable.

<u>Container closure</u>

The insulin icodec active substance, which is a solid active substance, is stored in a double bag container closure system.

Both bags are stated to comply with EU Commission Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food. Regarding sizes, the applicant explains that appropriate sizes are utilised depending on the amount filled. Representative sizes are provided in the dossier. It is further stated that stability samples are stored in an equivalent container closure system of reduced size. This is found acceptable. A schematic design of the container has been submitted and is included in the dossier.

A specification is presented for the inner bag. Three batches of the inner bag are confirmed to comply with the specification.

In conclusion, the information provided is considered adequate and sufficient for a container closure system of a solid active substance.

2.4.2.4. Stability

The stability programme presented for insulin icodec active substance involves long-term and accelerated stability studies. The batches included in the study are manufactured either by Process B or the commercial process. Several batches manufactured by Process B are referred to as the primary batches. This is found acceptable, since comparability between Process B and the commercial process has been demonstrated. Several batches manufactured by the commercial process, i.e., the PV batches and additional batches, referred to as supportive batches, are also included in the study. All batches are stored in containers representative of those used for commercial batches.

Long-term stability data, obtained for the primary batches is provided. In addition, long-term data for the supportive batches and for the PV batches manufactured by the commercial process are presented. All results at all time-points met the acceptance criteria and no trends were observed for any of the attributes. It is noted that the long-term studies are planned to continue for up to 60 months.

In addition, accelerated stability studies were performed. Results are presented for the primary and supportive batches. Data is presented for the PV batches. In conclusion, no change over time is noted during accelerated conditions. The stability data from batches manufactured with process B and the commercial process are found comparable.

Based on the obtained stability data, the proposed shelf life at the recommended storage conditions for the active substance is found acceptable.

A forced degradation study has been performed, including both active substance and finished product. The aim of the study was to evaluate the degradation of insulin icodec under extreme conditions. The active substance is a dried material and has therefore only been subjected to forced degradation by heat, light and humidity. It was sufficiently demonstrated that the impurity levels were influenced by extreme conditions and that the methods used were able to detect degradation.

It is acknowledged that one batch per year, for those years in which manufacture is undertaken, will be placed into the stability programme. Approval of this type of annual stability studies is a matter of GMP and not within the remit of the current assessment. The applicant is reminded that the stability protocol may need to be revised due to post-approval process changes, depending on the nature of the changes.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Description of the product

The finished product is presented as a solution for injection containing 700 units/mL of insulin icodec as active substance. Other ingredients are: glycerol, metacresol, phenol, zinc acetate, sodium chloride, hydrochloric acid and sodium hydroxide (for pH adjustment) and water for injections.

Insulin icodec is a drug-device combination product (integral) containing 700 units/mL. There are three presentations, 1, 1.5 and 3 ml, the volumes are provided in two cartridge sizes of 1.5 mL or 3 mL. The respective cartridge is assembled into product specific PDS290 icodec pen-injectors.

The qualitative and quantitative composition of the finished product has been provided as well as the function of the components. All excipients in the composition comply with the Ph. Eur. The cartridges and rubber

closures are compliant with Ph. Eur. monographs for primary containers and closures. An acceptable device description in line with EMA/CHMP/QWP/BWP/259165/2019 has been provided, and also a notified body opinion. The information provided is considered acceptable.

<u>Pharmaceutical development</u>

There are no novel excipients and there are no materials of human or animal origin.

Medical Device

The applicant has described the intended use of the medical device part with therapeutic indication and relevant target patients and functionality and suitability. The to-be-marketed PDS290 insulin icodec pen-injector variants are based on the approved PDS290 pen-injectors used for FlexTouch and Tresiba. The differences are colours of plastic components, piston rod, cartridge holder and cap due to cartridge size, also the dose indicator, scale drum imprints, max dose stop and dose increments differ. The notified body concludes that the assessment of the documents shows evidence that the medical device part fulfils the applicable general safety and performance requirements of the medical device regulation (MDR).

Finished product

The finished product composition and the container closure has remained unchanged throughout phase 1 to phase 3. A comparative study was made, side by side, for the variants of finished product, i.e. cartridge size of 1.5 or 3 mL and fill volumes of 1, 1.5 and 3 mL.

Analytical methodologies used for tertiary structure as well as for thermal stability, all showed comparable results. A more extensive comparability in line with ICH Q5E, between sites and scale is addressed below.

The conformation of insulin in the presence of stabilising agents such as Zn per hexamer and the ratio of phenol and metacresol has been acceptably described. The hexamer can adopt two different conformational states, T-or R-state. In the presence of phenol and sodium chloride human insulin adopts the R conformation, which is the most favourable conformation with regards to physical and chemical stability. A forced degradation study under acidic, alkaline, oxidation, reduction, temperature, light and mechanical stress conditions was performed to show that the analytical methods proposed can detect degradation.

Control strategy

A summary of the control strategy is provided for the drug-device combination product and defines CQAs for action profile, dosage form and delivery, physical, chemical, biological/microbiological attributes with rationales for control and reference to further information in the dossier. The approach and identified CQAs seems acceptable and in-line with ICH Q8.

Manufacturing process development – device assembly

The manufacturing process for the insulin icodec PDS290 used for phase 3 clinical trials and commercial manufacturing is based on experience from an existing process developed and implemented for the PDS290 pen-injector family. No changes were introduced in the assembly process for insulin icodec PDS290 used for phase 3 clinical trials and for commercial manufacturing with exception for scale-up.

Manufacturing process development – finished product

Development of the insulin icodec manufacturing process has been based on experience from the applicants marketed insulin products. The composition and container closure has been the same from clinical phase 1 trial to clinical phase 3 to the commercial insulin icodec. The development is found sufficiently described.

A comparability study on phase 3 and representative batches for commercial finished product originated from different sites and batch sizes has been made in-line with ICH Q5E with release, extended characterisation and stability (referred to the stability section). Finished product batches used in clinical phase 3 trials were compared to a process validation batch from the commercial site. Impurity profiles were examined side-by-side with presented chromatograms. The samples were stored at +5°C first since respective manufacturing date and then further stored for 13 weeks at +30°C. The results were within acceptance criteria and visually comparable in a graphic presentation. The levels of impurities found across facilities, batch sizes, and variants were comparable. The results demonstrate comparability.

Container closure system

The 3 ml and 1.5 ml cartridge are both made of colourless glass. All materials are of pharmacopoeial grade.

Suitability testing of the materials has been performed with studies on compatibility with the finished product at exaggerated ratios of rubber areas to finished product and then stored at 30°C for 13 weeks with comparable stability trend.

Extractables and leachables has been studied as well as exposure of metals and trace elements (ICH Q3D) based on the worst case finished product dose regime and permitted daily exposure (PDE). All concentrations of inorganic extractables, were found to be lower than the PDE's and low levels of inorganic anions were observed, concluding that no analysis for inorganic anions, metal, and trace elemental leachables were to be performed in the leachable studies which was found acceptable.

Long-term leachable testing has been performed for up to 24 months and will continue for up to 36 months at 5°C ± 3°C. Samples will be transferred to 30°C ± 2°C (in-use condition) and stored for up to 13 weeks prior analysis. A safety evaluation according to ICH M7 (R1) demonstrated that the calculated maximum patient exposure per injection and per week for all leachables were below the relevant exposure or threshold limit. In conclusion, the results raise no concern.

Analysis of Functional Performance and Control Strategy

Performance requirements have been tested according to ISO 11608-1 & 2 (standards for pen-injectors and needles). A summary traceability matrix and control strategy is presented with acceptance criteria and design verification. The information provided was found acceptable.

Product Risk Management Summary

The risk management process (EN ISO 14971) is described on a high level with system risk analysis (SRA) for use errors, component error risk analysis (CERA) for technical errors for the device, as well as human factors engineering (HFE)/usability studies. A biological evaluation has been performed in accordance with EN ISO 10993-1. Risk mitigation strategies and residual risk are discussed. It is stated that all identified risks have been reduced as far as possible. The residual risks have been evaluated against defined criteria for risk acceptability and accepted. The production and post-production follow-up plan is an integrated part of the applicants quality management system. No questions were raised.

Microbial attributes

Insulin icodec finished product must be preserved against microbial contamination as the product is intended for multiple use which is acceptable. The choice of preservatives is based on the applicants prior experience with other insulin products and consists of phenol and metacresol. The efficacy of preservation was tested at target and lower specification limits of preservatives, for all the tested studies, the log reductions for all microorganisms and Ph. Eur. B criterion was fulfilled.

The integrity of the container closure system has been tested using pharmacopeial microbial ingress testing. For microbial ingress the test was performed using media filled cartridges and the correlation between residual seal force (RSF) and the container closure integrity was determined by performing cartridges sealed with different RSF values.

Compatibility

Insulin icodec finished product was shown to be compatible with the 1.5 ml and 3 ml cartridge and does not contact the PDS290 icodec pen-injector. As the formulation is ready-to-use, there are no issues related to compatibility with reconstitution diluents. Mixing of insulin icodec finished product with other products has not been investigated which is noted in the SmPC section 6.2 incompatibilities.

2.4.3.2. Manufacture of the product and process controls

Manufacturers and batch formula

Names, addresses and responsibilities of the finished product manufacturers have been acceptably presented. All manufacturers involved in the finished product manufacture are GMP compliant.

The batch formula is provided for both finished product batch sizes. Components, quality and amounts are provided.

Manufacturing process and process controls - Finished product

Schematic flow diagrams of the finished product manufacturing process have been provided with in process controls for the formulation and sterile filtration. Insulin icodec is added to an aqueous solution. A solution of excipients is added. The solution is pH adjusted.

Procedures are controlled by weight. The pre-treatment, sterilisation and depyrogenation of primary packaging materials are sufficiently described. The final finished product formulation is filtered through two sterile filters (0.2 μm), (the first filtration just after formulation, the second at point of filling). A design risk assessment and clarifications on the bioburden testing were provided and accepted.

Non-critical parameters

Some process parameters are classified as non-critical within established ranges. Ranges are derived from at-scale process characterisation studies. It is stated by the applicant that variation from the established ranges for non-critical parameters are considered of minor importance to the manufacturing process since they are not assessed to have impact on the CQAs for the finished product when kept within their limits. The approach and criticality assignments are accepted.

Manufacturing process and process controls – assembly of device

The assembly process flow and process controls system established for the drug-device combination product is satisfactorily described with subassembly steps.

Control of critical steps and intermediates- assembly of insulin icodec PDS290

The control strategy is found generally acceptable. Process controls involves temperature outside refrigeration during assembly for the finished product in cartridge, exposure time to light is also controlled.

Control of critical steps and intermediates

Critical steps have been identified. Control limits and actions are defined for these steps and the limits and actions proposed are agreed.

Process characterisation

Non-scalable parameters were studied during the formulation process through homogeneity, chemical/physical stability and microbial data for aseptic holding time at finished product scales. Finished product batches included batches originated from several different active substance batches. The aseptic process was challenged with approved results for bioburden and endotoxin. Chemical stability from start of first sterile filtration to end of filling was confirmed for the active substance.

Process validation

A matrix approach, several batches were used to cover for the variants of cartridge sizes of 1.5 ml & 3 ml and the filling volumes of 1.5 ml & 3 ml, for the validation. Additional batches covered for the 1 ml presentation. The approach was found acceptable. The validation covered the formulation process that confirmed homogeneity, pH, sterile filtration with filtration times and filter integrity, aseptic process times, bioburden & endotoxin results, filling and chemical stability. Reproducibility was demonstrated. Product specific qualification reports on the sterile filters are in-line with *EMA/CHMP/CVMP/QWP/850374/2015 "Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container"*. Information on media fills is provided, filling parameters are tabled including min and max line speed. The media fills were performed with aseptic processing times from end of filtration to end of filling with approved results, zero (0) positive.

Process validation and/or evaluation for assembly

Validated activities for assembly of the drug device combination product are injection time, activation and hold force and dose accuracy. Three batches were tested each for the 3 ml, the 1.5 and the 1 ml variant. The tests were according to ISO 3951-1:2005 or ISO 3951-2:2006. All results were pass/ complied.

2.4.3.3. Product specification

Specifications

The finished product specifications include methods to evaluate identity, content, macroscopy, pH, product-related substances and impurities, high molecular weight proteins, process-related impurities, bacterial endotoxins, sterility and particulate matter. Dose accuracy is also part of the specifications.

There are separate specifications proposed for 1, 1.5 and 3 mL variants of the finished product with differences only in extractable volume.

Limits are defined for release and shelf life, including the in-use period of 12 weeks at or below 30°C.

The approach to set acceptance criteria differs for non-quantitative parameters, quantitative parameters without a systematic change during storage and in-use, and parameters with such change.

For quantitative parameters with a change during storage, a calculation of degradation trends was performed. Batches used for statistical calculations are late stage development batches with identical composition and primary container closure system as the commercial finished product.

The calculations apply to content of insulin icodec, HMW, hydrophilic and hydrophobic impurities and related substances. The estimate is used for setting the shelf life limit and covers the proposed shelf life including an in-use period of 12 weeks at or below 30°C.

The general approach to establish finished product acceptance criteria is stated to be based on consistency of the manufacturing process, analytical variation, stability data and evaluated in relation to performed clinical studies. The potential weekly exposure based on the proposed shelf-life specification limits for HMWP, product-related impurities and product-related substances were compared to the calculated maximum exposure and the 98th percentile dose administered in clinical trial ONWARDS 5. It is agreed that the proposed limits can be regarded as clinically justified for HMWP, hydrophilic impurities, hydrophilic-related substances, hydrophobic impurities and hydrophobic-related substances.

Risk assessments for elemental impurities according to ICH Q3D and for nitrosamine contamination are included in the dossier. The risk assessments provided are found acceptable.

Analytical procedures

Analytical procedures during development for finished product are listed with method identifiers, enabling traceability. No changes have been made during phase 3 studies. The analytical method development is acceptably described.

The analytical procedures are validated in accordance with ICH Q2 (R1) where applicable, otherwise following a standard (dose accuracy, ISO11608-1) or suitability is confirmed with relevant pharmacopeia's. Procedures and chromatograms are provided.

Batch analysis

Batch data from several batches is presented, from laboratory non-clinical, pilot clinical, process characterisation batches, clinical phase 3, stability and process validation batches. The results were within specifications and found acceptable.

The major degradation products found in the finished product have been identified and are also detected in the active substance. The impurities were evaluated according to ICH M7(R1) and were found not to carry mutagenicity or carcinogenicity potential except for the finished product - related impurity of insulin icodec and a potential impurity who were well below acceptable limits for mutagenic impurities.

Container closure system

Insulin icodec 700 units/ml is a drug device combination product consisting of insulin icodec 700 units/ml finished product provided in a 3 ml or 1.5 ml size cartridge assembled into the PDS290 icodec pen-injector with nominal fill volumes of 1, 1.5 and 3 ml.

The product is available as 1, 1.5 or 3 mL solution in a cartridge (Type I glass) with a plunger and a laminated rubber sheet contained in a pre-filled multidose disposable pen.

The PDS290 icodec pen-injector is multidose, disposable and prefilled and intended for insulin icodec finished product. The pen-injector delivers identical doses per increment (10 units) and have the same maximum dose stop (700 units) irrespective of cartridge size or fill volume. Compliance with ISO 13485 and ISO 11608-1:2014 is stated. This is found acceptable.

The applicant has described the principle of operation of the PDS290 icodec pen-injector as two interacting systems: the dial system involved in setting/resetting the dose and the dose system involved in dosing out of the finished product. A description is provided on the dial system, setting of the dose, the dose system,

injection activation and dose completion/pausing together with additional pen-injector features such as: max dose stop, end-of-dose click, end-of-content stop and overload protection. This is found acceptable.

The components in contact with insulin icodec 700 units/ml are the cartridge made of colourless glass and the type I rubbers. All materials in contact with the product are declared to comply with the Ph.Eur. requirements and compatibility has been demonstrated. The materials and components of the device have been described as well as specifications and test procedures for the device. Detailed drawings together with a detailed view (3 ml variant) are also provided including information on dimensions of the different parts of the device. A detailed schematic view of sub and final assembly of 1.5 ml and 3 ml cartridge PDS290 icodec pen-injector variants has been provided by the applicant. This is found acceptable.

The notified body opinion report (NBO) has been provided for the pre-filled pen and compliance with the relevant general safety and performance requirements (GSPRs) in the Annex I Regulation has been verified.

A description of PDS 290 icodec pen-injector variants is also provided in the NBO together with a graphical comparison regarding the two sizes of the cartridge. The information provided is acceptable.

2.4.3.4. Stability of the product

A shelf life of 30 months is claimed for the finished product.

Stability data for batches of the proposed three variants of insulin icodec finished product: 3 ml (2100 U), 1.5 ml (1050 U), 1 ml variant (700 U) has been submitted. The stability programme includes data for long-term stability at 5°C ± 3°C, accelerated and in-use stability at 25°C ± 2°C and 30°C ± 2°C, respectively, for each of the variants both in cartridge and in drug-device combination product. Chemical, physical, and microbiological parameters have been tested as well as essential performance requirements.

The results for the long-term study are within the specification limits and the observed changes do not raise concerns.

For the drug device-combination product, long-term stability data, obtained at 5°C ± 3°C, is provided. The studies are on-going. In addition, accelerated stability studies were performed at 25 ± 2 °C. Results from six months are presented for the 3ml, 1.5ml and 1 ml variant batches. All results at all time-points met the acceptance criteria.

In conclusion, the proposed shelf life and storage for the drug-device combination product is 30 months when stored between 2°C to 8°C and protected from light. The current data supports the proposed shelf life.

<u>In-use stability</u>

Two in-use stability studies at 30°C for up to 13 weeks have been performed, one for the single cartridge and one for the pre-filled pen. All variants of cartridge/fill volumes are covered, and the studies were performed shortly after production, during shelf life and near to the end of shelf life.

The in-use study on the pen was designed to simulate patient usage including penetration of the rubber disc, movement, and storage at 30°C ± 2°C. The studies are performed for 13 weeks as worst case to support the intended in-use period of 12 weeks. The results from chemical and physical testing complied with acceptance criteria. Comparable trends were seen between the variants as well as between cartridge and pre-filled pen. The bioactivity is maintained throughout storage and the effectiveness of the preservative system complies with the requirements according to Ph. Eur. criteria B at the end of the in-use study. The preservatives were however by large unchanged.

For the in-use stability on cartridge the similar approach is used. Results have been provided for the on-going study.

All results comply with the acceptance criteria. Stability trends for test samples are comparable for all tested parameters independent of when the study was performed. The results indicate acceptable preservative effect for 12 weeks when stored at 30°C. Also, the results are comparable between the studies on cartridge and pre-filled pen respectively.

The results collected up to now demonstrate compliance with the acceptance criteria when stored at 12 weeks at 30°C ± 2°C within the proposed shelf life of 30 months.

Photostability

Photostability studies were performed according to ICH Q1B on Insulin icodec finished product in 3 ml, 1.5 ml, and 1 ml variants in the primary container closure systems, insulin icodec 700 U/ml in the pen injector PDS290 with the cap on and insulin icodec finished product in primary container wrapped in aluminium foil (reference samples). After exposure to light, the cartridge test samples and insulin icodec PDS290 test samples were compared to the reference samples.

According to the photostability data submitted by the applicant the insulin icodec finished product is sensitive to light when stored in the primary container alone. However, photostability tests show that the PDS290 pen-injector with the cap on provide adequate protection from light (keep the cap on the pen in order to protect from light). The photostability data supports further the storage conditions as mentioned in the SmPC.

In conclusion, based on the stability data provided, the claimed shelf life of 30 months at 2°C - 8°C is acceptable for the finished product. After first opening, the medicinal product may be stored (below 30°C) for a maximum of 12 weeks. The cap on the pen should be kept in order to protect from light.

2.4.3.5. Adventitious agents

No raw materials or excipients of human or animal origin are used in the manufacture of insulin icodec active substance or insulin icodec finished product. No propagation of mammalian virus occurs in *Saccharomyces cerevisiae*.

It is concluded that the insulin icodec 700 U/ml finished product is safe with regards to both virus and transmissible spongiform encephalopathy (TSE) agents.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

The dossier is appropriately structured and no outstanding issues on quality aspects remain.

Information on development, manufacture and control of active substance and finished product has been presented in a satisfactory way. The presented documentation indicate that the finished substance and finished product is manufactured in a well-controlled and validated process.

There are no issues with the medical device part for insulin icodec pen-injector. A notified body opinion has been submitted assessing that the general safety and performance requirements are fulfilled in accordance with the MDR.

From a quality perspective, it is concluded that a positive CHMP opinion can be granted.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Awiqli is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

In conclusion, based on the review of the data provided, the MAA for Awiqli is considered approvable from the quality point of view.

2.4.6. Recommendation(s) for future quality development

N/A

2.5. Non-clinical aspects

2.5.1. Introduction

Insulin icodec is a human insulin (HI) analogue engineered to have an extended pharmacodynamic action following a single subcutaneous (s.c.) dose and intended for once-weekly administration for the treatment of diabetes mellitus (T2DM and T1DM). In order to obtain an insulin molecule with long duration and suitable for once-weekly administration, insulin icodec was designed with four key features: (i) strong, reversible binding to albumin intended to provide an internal, easily accessible "reservoir" of insulin, (ii) reduced insulin receptor (IR) affinity which is supposed to be associated with a prolongation of plasma half-lives by reducing the rate of receptor mediated clearance of insulin (iii) a stabilised insulin backbone, more resistant to enzymatic degradation, and (iv) high solubility, allowing the suggested clinical dose of insulin icodec to be administrated once weekly in the same volume as once daily insulin.

By attaching a C20 fatty acid sidechain by a small linker at the C-terminal of the B-chain a strong but reversible binding to fatty acid binding sites on albumin was obtained, which is suggested by the applicant to prolong the plasma half-life of insulin icodec. To further extend the half-life, three amino acid substitutions ((GluA14, HisB16 and HisB25) were introduced to lower binding affinity to the IR and confer molecular stability by minimizing proteolytic degradation of insulin icodec. The substitutions at GluA14 in combination with HisB25 also improves the solubility of insulin icodec. In addition, ThrB30 was omitted for a reason not described, however claimed to not affect the IR affinity. The relative contributions of albumin binding, reduced IR affinity and reduced sensitivity to enzymatic degradation to the prolonged half-life is not known.

Insulin induces a wide variety of metabolic and mitogenic actions in animals and man. The major metabolic actions include glucose uptake in muscles and adipose tissue, antilipolytic activity in adipose tissue and suppression of glycogenolysis in the liver. The actions of insulin are mediated via membrane associated insulin receptors existing in two isoforms, a short (IR-A) and long form (IR-B). IR-B is preferentially expressed in the liver, whereas the two isoforms are equally expressed in most other peripheral tissues.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Primary pharmacodynamics in vitro

The primary pharmacodynamic testing has focused on demonstrating that insulin icodec achieve the desired PD effects while maintaining the same biological and safety profile as human insulin. Therefore, a series of *in vitro* studies were conducted to demonstrate that insulin icodec is a specific and full agonist at the human insulin receptor (IR) and that the same post-receptor signalling pathways are activated. For the individual *in vitro* biological assays presented the albumin concentration varies, depending on the cell's sensitivity to albumin. Insulin icodec was designed to have high affinity for serum albumin and consequently, the variable human serum albumin (HSA) concentrations have affected the reported *in vitro* potency values.

The relative affinities of insulin icodec, compared to human insulin (HI) for solubilised cloned insulin receptors of the A- and B-isoforms, in absence of HSA were 0.50% (range 0.43-0.57%, n=3) and 0.78% (range 0.68-0.89%, n=3), respectively. The affinities of insulin icodec relative to HI, at 0.1% HSA, were not significantly different between short (A) and long (B) isoforms of membrane associated insulin receptors of rat, pig and human origin and the interspecies variations were not significantly different for neither HI nor insulin icodec. Thus, insulin icodec has similar affinities for the A and B isoform of insulin receptors from the rat, pig and human and including dog for the A isoform (the B isoform from dog was not tested for) supporting the relevance of the pivotal toxicity species (no data for rabbit presented).

As a consequence of the intentionally high affinity to albumin, the presence of HSA in the *in vitro* assays generally resulted in reduction of the apparent affinity of insulin icodec for the IR receptor and a lower potency in various test systems. E.g., a dose-dependent reduced relative affinity of Icodec, as compared to HI, to membrane associated human insulin receptor isoform A was demonstrated by the addition of HSA at three concentrations (0.02 – 0.1 – 0.5%) that reduced the relative affinity from 0.17% to 0.05% and 0.02%, respectively. In addition, the affinity for soluble human IR receptors of both the A- and B-isoform was approximately 20-fold lower in presence 1.5% HSA.

Insulin analogues showing a disproportionate increase in IGF-1 receptor affinity over IR affinity may indicate a greater mitogenic potential compared to HI. Therefore, IGF-1 receptor affinity is generally regarded as a valuable parameter in the characterisation of insulin analogues, although binding of insulin to the IGF-1 receptor has no significance at physiological insulin concentrations due to the low affinity. The affinity of insulin icodec for solubilised IGF-I receptors in the absence of HSA was determined to be 0.14% (range 0.13-0.15%, n=3) relative to HI. When studying the binding of insulin icodec to membrane-associated recombinant human IGF-1 receptors, a relative potency of Insulin icodec could not be determined due to that Insulin icodec had a too low affinity for human IGF-1 receptors relative to ^{125}I-IGF-1 (in the presence of 0.1% HSA). IC_{50} for IGF-I were estimated to 0.49 nM (range 0.29-0.83 nM) and 265 nM (range 105-674) for HI. Similar results were obtained using membrane-associated recombinant IGF-1 receptors of rat and dog origin. Thus, the reduction for insulin icodec in relative affinity for the IGF-1r was stronger than for the IR, indicating the potential to maintain a desired metabolic response without increasing the relative risk for IGF-1 mediated mitogenicity during treatment with insulin icodec.

Moreover, it was shown that the dissociation of insulin icodec from the human insulin receptor is faster than that of HI which, based on a known association of slow dissociation with an increased risk for mitogenicity, further supports that the mitogenic potential is lower for the product at hand. This was confirmed in a set of

four studies (three of which were GLP compliant), where the mitogenic response to insulin icodec was tested in primary human mammary epithelial cells (HMEC) and various tumour cell lines (human mammary adenocarcinoma cell line (MCF-7); human colon adenocarcinoma cell line (COLO-205) and rat myoblast cell line transfected with the HI receptor A isotype (L6-hIR)). All tested cell lines proliferated in a dose-related fashion in response to in vitro exposure to insulin icodec with a relative potency of 0.2-2.0 % as compared to HI. However, it was noted that although in these experiments the cell cultures contained foetal calf serum, the albumin concentration was not set to 0.1% as in most metabolic studies. As albumin binding is supposed to result in reduced free insulin icodec concentration, it will also result in a reduced mitogenic effect. Though, in this context this is acceptable.

The ability of insulin icodec to stimulate two essential elements in insulin signalling demonstrated that insulin icodec is a full agonist and can stimulate the same signalling events as native human insulin albeit with a lower potency. Insulin icodec induced autophosphorylation of the hIR-A and hIR- B isoforms in a concentration-dependent manner. The relative *in vitro* potencies, in the absence of albumin, for IR-A and IR-B phosphorylation was not different and estimated to 0.25% (range 0.16 – 0.45%) and 0.31% (range 0.17 – 0.54%), respectively. Moreover, Insulin icodec, at 0.1% HSA, stimulated phosphorylation of the IR-A and PKB in CHO-hIR cells in a typical dose-response fashion, similar to that of HI. The relative in vitro potencies of insulin icodec for hIR-A and PKB phosphorylation, at 0.1% HSA, was estimated to 0.08% (range 0.05 – 0.11%) and 0.19% (range 0.10 – 0.29), respectively.

The metabolic activity of insulin icodec was investigated in cells from typical insulin target tissues such as fat, muscle and liver:

- Insulin icodec stimulated lipogenesis in primary rat adipocytes in a dose-response fashion, similarly to HI, and resulted in the same maximal response as HI, albeit with a lower in vitro potency. The relative potency of insulin icodec compared to HI at 0.1% HSA was 0.03% (range 0.03-0.03, n=4) while at higher HSA concentrations (1%) the relative potency decreased to 0.02% (n=4);

- Insulin icodec activated glucose uptake in human SGBS adipocytes with an EC50 value of 24.5 nM compared to an EC50 of 0.039 nM for HI. The relative biological potency of insulin icodec was 0.16% in the presence of 0.1% HAS. The maximal effect that insulin icodec could produce was not significantly different from the maximal effect produced by human insulin;

- Insulin icodec induced a dose-dependent glycogen accumulation and the same maximal response in glycogen storage in rat hepatocytes as HI. The relative potency of insulin icodec was 4.9% (range 2.9-8.4%, n=8) compared to HI, determined in the absence of any added albumin, and 0.34% (range 0.07-1.07, n=8) in the presence of 0.1% HSA.

Primary pharmacodynamics in vivo

In vivo pharmacology studies were performed in rats, dogs and pigs to demonstrate that insulin icodec retains the ability to lower blood glucose during an extended time period. Human insulin, dosed as NPH insulin or insulin glargine, was included as comparator.

The PK/PD relationship, measured as blood glucose, plasma levels of glucagon, triglyceride and non-esterified fatty acids (data not shown for the latter three), was investigated after a single s.c. dose of insulin icodec in normoglycaemic dogs. Duration of action was approximately 7 days with a t_{max} 24 hours and a $t\frac{1}{2}$ of 63 hours. There were no clinical signs of hypoglycaemia in these studies.

In obese diabetic ZDF male rats, modelling type 2 diabetes, the estimated potency of insulin icodec, administered s.c. every 8th day, was found to be 40-50% compared to twice-daily dosed NPH human insulin,

based on a dose-dependent reduction in HbA1c levels. However, as bioavailability data was not available, exact potency determination was not possible. A direct demonstration of that insulin icodec reduced blood sugar levels in the ZDF rats after 20 days of repeated administration was also shown. There was an apparent decrease in insulin 287 concentrations from day 8 to 16. The applicant suspects that the cause may be an unexpectedly high exposure level on day 8 (331,000 and 518,000 pM for 122 and 245 nmol per animal) perhaps due to an error in timing of sampling, i.e. samples were drawn mistakenly after and not before dosing. Based on the PK profile of insulin 287 demonstrated in another study, where a full 4-day profile was obtained after a single dose of 122 nmol, there is a clear peak in insulin 287 on the day of injection after which there is a decline over the next four days to a low level (45,180 pM). If the samples on day 8 were mistakenly drawn after dosing, this could possibly explain the high exposure levels. On the other hand, there is no reason to doubt the exposure level observed on day 16 as this is within the expected range for the nadir, prior to dosing.

The glucose-lowering effects of insulin icodec was studied in normoglycaemic dog and pig using a euglycaemic insulin clamp technique. With this method, the potency of s.c. insulin icodec was determined to be approximately 200% compared to insulin glargine, in both dogs and pigs, as compared to the potency of 40-50 % in rats based on the HbA1c lowering effect. No explanation was provided for this discrepancy. However, clinical data have demonstrated that s.c. insulin icodec in humans is equipotent with daily basal insulin. Nevertheless, the observed higher potency of insulin icodec in these *in vivo* systems is not in contradiction with the low *in vitro* potency as the exposure after administration of equimolar doses of insulin icodec and insulin glargine is different due to different pharmacokinetics or other reasons (e.g., production of anti-drug antibodies). This is supported by the fact that insulin icodec resulted in around three orders of magnitude higher plasma concentrations during the clamp period than insulin glargine (e.g., in the low dose (2.1 nmol/kg/day) groups the range of insulin icodec plasma concentrations was around 35000-75000 pM while insulin glargine concentrations was measured around 4-100 pM).

2.5.2.2. Secondary pharmacodynamic studies

Off-target-activities were screened for in an assay with 67 receptors, ion channels and transporters. Potential off-target binding of insulin icodec (at a concentration ~38-fold the average clinical Cmax) to the GABAA and thyroid hormone receptors were noted *in vitro* using radioligand binding displacement assay. In a functional follow-up study in guinea pig ileum, no signs of inhibition or stimulation of the GABAA receptor were detected. No functional study was performed to investigate further the potential interaction with thyroid hormone receptor.

2.5.2.3. Safety pharmacology programme

A standard safety pharmacology package was conducted covering the vital organ systems (cardiovascular, CNS and respiratory). A weak inhibition of the I_{kr} (hERG channel) current was observed at 10 µmol/L (38-fold average clinical Cmax). However, in the absence of effects on action potential parameters in rabbit Purkinje fibres and on the QT interval *in vivo* in the single- and repeat-dose studies in dogs, overall, the applicant conclude, no risk for human QT prolongation secondary to hERG channel blockade was identified. This is agreed.

Furthermore, no effects were identified in the *in vivo* safety pharmacology studies covering the central nervous and respiratory systems.

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted with insulin icodec. Considering the availability of information on pharmacodynamic interactions for various insulin products, this is agreed.

2.5.3. Pharmacokinetics

A range of studies have been performed to characterise the absorption, distribution, metabolism, and excretion (ADME) of insulin icodec, using intravenous (IV) infusion in addition to the intended clinical route of administration, i.e., subcutaneous (SC) injection, and the species selected for non-clinical safety testing, e.g., Spraque Dawley (SD) rats and Beagle dogs as the main non-clinical species but also New Zealand White rabbits.

The long $t_{1/2}$ of insulin icodec is proposed to be due to a strong reversible affinity to plasma albumin (achieved by addition of the C_{20} fatty acid sidechain to the B-chain of the human insulin molecule) and resulting reduced renal clearance together with a low IR affinity (see Pharmacology section above, further lowered by 3 amino acid substitutions (Glu^{A14}, His^{B16}, His^{B25}) and a subsequently reduced IR mediated clearance. In addition, the amino acid modifications are also proposed to increase the molecular stability by reducing enzymatic degradation. The relative contributions of albumin binding, reduced IR affinity and reduced sensitivity to enzymatic degradation for the prolonged half-life is not known.

Methods of analysis

Insulin icodec in plasma was quantified by Luminescence Oxygen Channeling Immunoassay (LOCI) also called AlphaLISA, which is a homogenous bead-based sandwich enzyme-linkedimmunosorbent assay (ELISA). The methods used in pivotal toxicity studies in rats, dogs and rabbits were validated in accordance with the applicable guideline on bioanalytical method validation and the principles of GLP in a GLP test facility. Distribution of [^{3}H]-insulin icodec derived radioactivity in rats was investigated by quantitative whole-body autoradiography (QWBA). Metabolic profiling of radioactivity in plasma and excreta from ADME-studies of [^{3}H]-insulin icodec in rats and dogs was assessed by high-performance liquid chromatography (HPLC) coupled with UV and radiochemical detection (HPLC-UV-RAD) analyses for fractionating and liquid scintillation counting (LSC) for quantification. Metabolites in plasma from rats and dogs and in urine from dogs were structurally identified by HPLC coupled with mass spectrophotometry and radiochemical monitoring (HPLC-MS-RAM). In addition, metabolites in plasma from rats in a toxicity study were assessed by LC-MS.

Plasma kinetics

Single dose pharmacokinetics

Following an IV infusion of 1.6 nmol/kg to male Wistar rats and male Beagle dogs mean plasma clearance (CL) and mean apparent volume of distribution (V_z) of insulin icodec were low; mean CL ranged from 0.00089 L/h/kg in dogs to 0.0043 L/h/kg in rats and mean V_z ranged from 0.078 L/kg in dogs to 0.16 L/kg in rats. This resulted in a long mean terminal elimination half-life ($t_{1/2}$) from 26 h in rats to 60 h in dogs. Following a single IV infusion of 1.7 and 2.0 nmol/kg to female LYD pigs mean terminal t½ was 43 h.

Following a SC administration of 121, 236 and 479 nmol/kg to male SD rats, 17 nmol/kg to male Beagle dogs, 10 nmol/kg to female New Zealand White rabbits and 8.5 to 34 nmol/kg to female LYD pigs, median time to C_{max} (t_{max}) ranged from 2 to 6 h in rats, from 3 to 24 h in dogs, from 8 to 12 h in rabbits and from 6 to 52 h in pigs and mean terminal t½ was 20 h in rats, 56 h in dogs, 25 h in rabbits and 37 to 54 in pigs. Based on dose normalised AUC_{inf} from SC and IV studies, the relative bioavailability for SC administration (F)

was estimated to 64% in dogs, above 100% in rats and to 56-104% in pigs. As F is determined from data obtained from separate studies, often with a high SC dose versus a low IV dose, the F values should be interpreted with caution.

In rats and pigs, plasma exposure (C_{max} and AUC_{inf}) increased with increasing dose in a dose proportional manner.

Repeated dose pharmacokinetics

No apparent gender differences (less than 2-fold) were observed following repeated SC administration to rats and dogs. The TK variables obtained for rats and dogs are therefore summarised with both genders combined whereas for rabbits only data for females are provided.

Following once daily SC administration of 20 to 150 nmol/kg to SD rats, once daily SC administration of 6 to 50 nmol/kg to New Zealand rabbits and twice weekly SC administration of 6 to 18 nmol/kg to Beagle dogs median t_{max} at the last sampling at steady state ranged from 0 to 24 h in rats, from 4 to 8 h in rabbits and from 3 to 24 h in dogs. Values for $t_{1/2}$ ranged from 19 to 40 h in rats (mean 28 h) and from 41 to 115 h in dogs (mean 61 h).

Plasma exposure (C_{max} and AUC_{0-168h} [rats and rabbits; $7 \times AUC_{0-24h}$, dogs; $7/4 \times AUC_{0-96h}$]) at steady state increased with increasing dose in an approximately dose proportional manner. The dose normalised exposure was similar in rats, dogs, and humans, and slightly higher in rabbits.

Observed accumulation in terms of AUC_{tau} (AUC_{0-24h} for rats and rabbits and AUC_{0-96h} for dogs) from Day 1 to the day of the last dose administration in repeated dose toxicity studies ranged from 2.1- to 5.6-fold in rats (in general somewhat higher than expected based on $t_{1/2}$ and dosing interval), from 1.3- to 2.5-fold in dogs and from 1.1- to 3.8-fold in rabbits.

Distribution

Plasma protein binding

Dissociation constants, K_d, and percentage fraction unbound (fu) of insulin icodec to albumin was determined in plasma of female rabbit (New Zealand White) and male and female mouse (CD-1), rat (SD), dog (Beagle) and humans by surface plasmon resonance (SPR) biosensor technology. Nine protein concentrations (0.0005%-2.5% [v/v]) were investigated. The K_d to albumin was in the range of 0.028 µM in female rats to 0.128 µM in male dogs. The fu was in the range of 0.006% in female rats to 0.033% in male dogs. The values for humans were within this range with an fu of 0.015% in males and 0.017% in females. Thus, more than 99.9% of insulin icodec in plasma was bound to albumin in all studied species.

In another study the affinity of insulin icodec for rat, dog, pig and human serum albumin (0-5 µM) was estimated in an equilibrium binding assay. The K_d values ranged from 0.070 µM in humans to 0.337 µM in rat.

Tissue distribution

Tissue distribution was investigated by QWBA at 4 to 168 h following a single SC administration of 75 nmol/kg (50 MBq/kg) [³H]-Eic-insulin icodec ([³H] in the fatty acid) to male SD rats. Drug derived radioactivity was mainly distributed to the plasma compartment of the blood with lower amounts detected in tissues. The highest radioactivity levels were present in the tooth pulp and the eliminating organs kidney (outer cortex) and bile duct (with content) for which the overall exposure in terms of AUCall exceeded that in blood (tissue/blood ratios of 1.53, 1.39 and 1.27, respectively). The lowest radioactivity levels

(approximately 1% of the overall exposure in blood) were detected in the brain and spinal cord, suggesting no or low penetration of the blood-brain-barrier. Maximum tissue concentrations were generally noted at 12 or 24 h.

The plasma concentrations were higher than whole blood concentrations, suggesting little or no association of insulin icodec and metabolites with red blood cells. This was observed also in other studies. At 4 to 168 h and 4 to 336 h following a single SC administration of 75 nmol/kg (50 MBq/kg) and 18 nmol/kg (20 MBq/kg) [^{3}H]-ADO-insulin icodec ([^{3}H] in the linker) to SD rats and Beagle dogs, respectively, blood/plasma ratios determined with LSC ranged from 0.54 to 0.67 in rats and from 0.48 to 0.64 in dogs.

Placental transfer of insulin icodec was confirmed in the rat FEED study with foetal exposure of 3-6% of maternal exposure (see section of reproductive toxicity below). No data on excretion of insulin icodec into milk were however provided. In the high-dose group of the rat PPND study 2 pups were found dead and 25 pups were euthanised of welfare reasons due to symptoms of hypoglycaemia (see section of reproductive toxicity below). This was considered due to weight loss of the dams and resulting underfeeding of the pups and not to exposure to insulin icodec via milk. Plasma concentrations of insulin icodec were detected in 2 of 64 pups on LD 11, one in the medium dose group and one in the high dose group, at levels that were markedly lower than in the dams. As oral absorption of insulin icodec is expected to be low due to its physiochemical properties, these data confirm that insulin icodec is excreted into milk of lactating rats. The extent of excretion into milk is however not known.

Metabolism

The metabolism of insulin icodec was investigated *in vitro* in hepatocytes from mice, rats, dogs, rabbits, and humans. *In vivo* metabolism of insulin icodec was studied in rats, dogs, and humans.

In vitro

Metabolic profiling following 4 hours incubation of 10 and 10000 nM [^{3}H]-Eic-insulin icodec with hepatocyte pools from male rats, female rabbits, male dogs, and male and female humans showed that the degree of metabolism was higher at the low concentration (10 nM) with low levels of unchanged substance present only in rabbit hepatocytes. Metabolite H12 represented the main metabolite produced by rat, dog, and human hepatocytes whereas metabolite H1 was the main metabolite identified in rabbit hepatocytes. At the high concentration a large part of the compound remained unchanged, ranging from 28.5% in mouse hepatocytes to 61.1% in human hepatocytes. Metabolite H12 and H1 remained as the main metabolite formed by rat, dog and human hepatocytes and rabbit hepatocytes, respectively.

In total 14 metabolites (H1-H14) were detected over the species studied. All 9 metabolites detected in human hepatocytes were present in hepatocytes from rats, dogs and/or rabbits, i.e., no unique human metabolite was formed *in vitro* by hepatocytes.

In vivo

Plasma

In plasma of rats and dogs administered a single SC dose of 75 nmol/kg (50 MBq/kg) and 18 nmol/kg (20 MBq/kg) [^{3}H]-ADO-insulin icodec, insulin icodec was the major component representing 98 and 81%, respectively, of total radioactivity. The metabolite identified in rat plasma (B$^{1-29}$-(C$_{20}$)) and the 4 most abundant of 8 metabolites detected in dog plasma (B$^{1-29}$-(C$_{20}$), B^{29}-(C$_{20}$), B$^{2-29}$-(C$_{20}$) and B$^{24-29}$-(C$_{20}$)), were characterised as products from disulphide bond reduction between the A and B chains and subsequent proteolytic cleavage of the B chain with a remaining intact C$_{20}$ fatty acid chain.

The metabolic plasma profile in humans were similar with unchanged compound representing a major part of the total exposure (92 and 85% on Day 1 and at steady state, respectively, following repeated administration of 24 mmol/kg SC once weekly for 5 weeks), a main metabolite B^{1-29}-(C_{20}) (5.6 and 11.3 % of the total measured exposure following single and repeated administration, respectively) and the minor metabolites B^{29}-(C_{20}), B^{24-29}-(C_{20}) and B^{2-29}-(C_{20}) each representing less than 3% of total exposure.

In plasma from male and female rats obtained in the 8-week toxicity study, the 3 main metabolites quantified in humans, i.e., B^{29}-(C_{20}), $B^{24\ 29}$ (C_{20}) and B^{1-29}-(C_{20}), were detected. An isomer and a deamidation product of insulin icodec were also detected and characterised.

The quantification of metabolites in humans is considered preliminary and possibly overestimated as non-labelled compound were used. Whereas no formal qualification of metabolites was performed, 3 of the 4 metabolites identified in human plasma (metabolite B^{1-29}-(C_{20}) and the minor metabolites B^{29}-(C_{20}) and $B^{24\ 29}$ (C_{20})) were detected in plasma from rats in the 8-week toxicity study. Based on this together with the lack of A-chain and expected low potential for binding to the insulin receptor, lack of alerts for genotoxicity of insulin icodec and lack of significant toxicological findings not related to the pharmacology of insulin icodec, it is agreed with the applicant that no further investigations regarding metabolites are warranted.

<u>Excreta</u>

Only a small proportion of human subjects had detectable levels of insulin icodec in urine. A similar pattern was observed in rats and dogs, following a single SC dose of 75 nmol/kg (50 MBq/kg) [^{3}H]-Eic-insulin icodec and 18 nmol/kg (20 MBq/kg) [^{3}H]-ADO-insulin icodec, respectively, for which no or a small proportion of the dose was found in urine as unchanged compound, respectively. Whereas no unchanged insulin icodec was found in faeces of rats and dogs, a large number of metabolites were detected in urine and faeces of both species and in bile of rats. The 3 most abundant metabolites in urine of dogs were characterised as products from full proteolytic cleavage and extensive β-oxidation of the C_{20} fatty acid moiety and structurally identified as B^{29}-(C_8), B^{29}-(C_6) and B^{29}-(C_4). The large number of metabolites in excreta and the identified structures of the major urine metabolites in dogs verified that insulin icodec was extensively degraded to smaller and more polar metabolites before excretion.

Excretion

Cumulative excretion of radioactivity following a single SC administration of 75 nmol/kg (50 MBq/kg) [^{3}H]-Eic-insulin icodec to rats and 18 nmol/kg (20 MBq/kg) [^{3}H]-ADO-insulin icodec to dogs showed that both urine and bile/faeces are involved in excretion of insulin icodec related material. In rats a higher part of the dose was excreted in bile/faeces (31% in faeces and 22% in urine) whereas in dogs a higher part was excreted in urine (44% in urine and 27% in faeces). The large number of metabolites detected in excreta of rats and dogs together with the identified structures of the major urine metabolites in dogs indicate that insulin icodec is excreted as smaller more polar metabolites.

Conclusion

The pharmacokinetic profile of insulin icodec is overall considered adequately assessed in relevant non-clinical species.

In plasma of rats, dogs and humans, unchanged compound was the major component. Four circulating metabolites of insulin icodec were identified in dogs and humans, and the three most abundant ones were also identified in rat plasma. Together with the *in vitro* results, which showed that all metabolites detected in human hepatocytes were present in hepatocytes from rats, dogs and/or rabbits, the metabolism data indicate that these species were relevant for the non-clinical safety studies.

High binding to albumin in plasma (more than 99% for the tested species, i.e., mouse, rat, rabbit, dog, and human) and a long $t_{1/2}$ following SC administration (25 h in rabbit, 28 h in rat, 61 h in dog and 173 h in humans) were confirmed. Whereas the $t_{1/2}$ for SC insulin icodec in the nonclinical species is shorter than in humans it is considerably longer than for human insulin which has a $t_{1/2}$ that is less than 15 minutes in rats and dogs after IV administration.

2.5.4. Toxicology

Insulin icodec is a long-acting basal insulin analogue with a clinical half-life of approximately 1 week. The molecule consists of a peptide backbone, with amino-acid changes compared to human insulin and an albumin-binding hydrophobic C20 fatty acid sidechain (coupled by acylation). It is intended for treatment of both type 1 and type 2 diabetes in adults, by once weekly subcutaneous injections.

The applicant has performed a toxicological programme in accordance with the ICH S6(R1) guideline, and at large, in line with the EMA document *"Points to Consider Document on the Non-Clinical Assessment of the Carcinogenic Potential of Insulin Analogues".*

The programme consisted of repeat-dose toxicity studies in rats of up to 52 weeks duration and dog studies of up to 26 weeks duration, as well as limited genotoxicity testing and assessment of local tolerance in rabbits and pigs. The reproductive toxicity programme was conducted in accordance with the ICH S5(R3) guideline. Pivotal studies were conducted according to good laboratory practice (GLP). Toxicokinetic evaluations were included in all pivotal repeat-dose toxicity studies and reproductive toxicity studies.

There were many observed changes in the toxicity studies, however, most of them are considered coupled to the hypoglycaemic responses and therefore related to the pharmacology of insulin or related to metabolic and endocrine compensatory mechanisms. Since signs of treatment-related systemic toxicity in the non-clinical studies are well-known sequels of insulin-induced hypoglycaemia, they are considered to be due to exaggerated pharmacodynamic rather than toxic effects and although adverse in the non-clinical setting, they are not considered to be clinically relevant in diabetic patients with well-controlled blood glucose regulation.

In several studies in rats and dogs, the dose levels of insulin icodec had to be reduced due to clinical signs of hypoglycaemia and related mortality in rats and rabbits. In general, there were no or low safety margins to clinical exposure in the toxicity studies, although more frequent dosing was used (once daily in rats and twice weekly in dogs) to somewhat compensate for the shorter half-life in rats (4-27 hours), dogs (37-83 hours) and rabbits (25 hours) compared to humans (175 hours). In all studies, the expected lowering of plasma/blood glucose levels were noted.

A safety concern with insulin icodec is hypoglycaemia and based on the hypoglycaemic risk, use of insulin icodec is currently not recommended in women who wish to become pregnant.

2.5.4.1. Single dose toxicity

Not applicable.

2.5.4.2. Repeat dose toxicity

Repeat-dose toxicity studies have been performed in healthy normo-glycaemic rats and dogs. Rat and dog are considered relevant toxicological species but treating normo-glycaemic animals with an insulin analog will result in lowering of plasma/blood glucose levels to hypoglycaemic levels.

In rats, a dose-range finding study and three repeat dose toxicity studies (8 weeks, 25 weeks, and 52 weeks) were performed. Rats were dosed once daily subcutaneously, and all studies included recovery animals except the 52-week study, which included assessment of carcinogenicity that focused on female mammary gland tumour incidences.

There were several cases of hypoglycaemia-related mortality in rats. Similar changes were seen throughout the three studies with findings including decreased plasma glucose, increased body weight/gain, increased food consumption, changes in clinical chemistry/haematology and histopathological changes in pancreas, sciatic/tibial nerve and/or skeletal muscle, adrenal glands, liver, brown fat, bone marrow, myocardial muscle and testes.

In the 52-week rat study, which included a reference group dosed with human insulin, the findings in pancreas, adipose tissue and skeletal muscle, all minimal to moderate, were only noted in insulin icodec groups and not in the human insulin reference group. It should be noted that there are differences in glucose lowering kinetics between the long-lasting insulin icodec, which gives a more persistent hypoglycaemia compared to the human insulin reference which has a half-life of about 20 min in rats, resulting in recurrent hypoglycaemia. Human insulin is therefore not an optimal comparator in this case. The applicant has provided references that support the fact that when healthy rats instead are continuously infused with human insulin, to mimic a long-lasting insulin, similar histopathological changes are also observed in the pancreas, adipose tissue, and skeletal muscle. In addition, there is a large number of publications indicating that the observed histopathological effects are seen in healthy rats in response to insulin and hypoglycaemia. All the above findings are therefore considered hypoglycaemia-related.

Dogs were dosed twice weekly subcutaneously in one 8-week study and one 26-week study, both with recovery animals. Findings included decreased blood glucose levels and effects on body weight, GI effects and liver weights, all in line with the pharmacological effect of insulin dosing to normoglycaemic dogs.

Mortalities and clinical signs

Dose reductions were needed in both species due to dose-related signs of hypoglycaemia (decreased activity, partially closed eyes and abnormal gait). A number of hypoglycaemia related mortalities/euthanasia occurred in rats, whereas no mortalities were reported in dogs.

Pancreas

Dose-dependent reversible minimal to moderate islet atrophy was observed in all studies in rats but not in dogs. It is well documented that exogenous insulin-mediated lowering of blood glucose levels results in reduced beta-cell/islet size in rats. This is therefore considered a compensatory response to the intended pharmacological effect of insulin and considered to be clinically not relevant.

Nerve effects

Partly reversible minimal to moderate axonal degeneration of the sciatic/tibial nerve was noted in mid-high dosed rats but not in dogs. This has previously been reported to occur in response to exogenous insulin in rats and axonal degeneration was also present, although at lower incidences, in rats from the reference group treated with human insulin that was included in the 52-week rat study. The nerve degeneration is

likely secondary to the insulin pharmacology effects and possibly due to energy shortage. They are considered to be not relevant to the clinical situation.

Skeletal muscle

Partly reversible, minimal to moderate degeneration/atrophy/necrosis of the myofibres in skeletal muscle in rats were noted. This was possibly connected to the denervation and was not seen in dogs. Although only noted in the insulin icodec groups and not in the human insulin reference group included in the 52-week rat study, literature data support that skeletal muscle effects arise when human insulin is continuously infused to mimic the long-lasting insulin effect achieved with insulin icodec. The skeletal muscle effects are therefore considered a known secondary effect of exogenous insulin treatment normoglycaemic rats and considered not clinically relevant.

Adipose tissue

Increased vacuolation and cell size in brown fat were seen at all dose levels in all rat studies but not in dogs. Also, increased fat content of the bone marrow was observed in the 8-week rat study in mid-high dose animals at ≥75 nmol/kg/day. Similar effects have previously been observed in rats continuously infused with human insulin and the effects are considered a sign of exaggerated pharmacology in rats and not clinically relevant.

Liver

Reversible dose-related reduction in liver weights were seen at all doses in female rats. This was coupled to decreased rarefaction in hepatocytes in rats. In dogs, reversible lower absolute and relative liver weights were noted after 26 weeks. The liver effects were most likely related to the glycogen reduction known to occur in response to insulin and are not considered relevant in the clinical situation.

Heart

In the 52-week rat study only, there was a small increase in minimal to slight myocardial fibrosis, primarily seen in the left ventricle, without obvious dose relationship, when compared to control and the human insulin reference group. Since the literature support that altered blood glucose levels can result in heart muscle effects in rats and provided that the findings were only marginally higher in incidence than controls and reference group, they are considered non-adverse.

Adrenal glands

In the 8-week rat study only, increased vacuolation changes in the zona fasciculata of the adrenal gland, was noted in mid- and high-dosed males. This is considered not clinically relevant since it could be related to the stress induced by low blood sugar levels, possibly resulting in increased glucocorticoid production.

Reproductive organs

In the 52-week rat study only, reversible minimal to severe tubular degeneration/atrophy was noted in the testis of high dosed rats. The testis findings were also present in the reference group treated with human insulin.

Clinical chemistry/haematology

In addition to lowering of plasma/blood glucose levels, there were a number of clinical chemistry changes induced in rats and dogs dosed with insulin icodec.

In rats, increased plasma urea and sodium concentrations, decreased endogenous insulin, decreased triglyceride concentrations were seen. After 52 weeks of dosing, increased creatinine increase of phosphorus and magnesium concentrations were noted. Changes in haematocrit/ haemoglobin concentrations, and slightly lowered reticulocyte counts were observed.

In dogs, decreased endogenous insulin, higher levels of triglycerides in mid- and high-group males, inorganic phosphorus (high dose males) and chloride (mid dose females) were observed together with higher albumin/globulin ratio was seen in mid-dose males.

These changes are considered consistent with compensatory effects to the blood glucose lowering effect of insulin and were fully reversible.

2.5.4.3. Genotoxicity

As laid out in ICH S6(R1), genotoxicity studies are generally not considered applicable for biotechnology-derived products such as insulin icodec. Since insulin icodec contains a C20 fatty acid sidechain derivative attached at LysB29, the applicant has performed a in silico QSAR analysis on the sidechain where no alerts for carcinogenicity, chromosome damage, genotoxicity or mutagenicity were identified.

In addition, insulin icodec was assayed for mutagenicity in five histidine-requiring strains (TA98, TA100, TA1535, TA1537 and TA102) of Salmonella typhimurium in a non-GLP screening study. No increases in revertants were noted.

In conclusion, no alerts for genotoxicity were identified for insulin icodec.

2.5.4.4. Carcinogenicity

As pointed out in ICH S6(R1), standard 2-year rat carcinogenicity *in vivo* studies are in general considered inappropriate for biotechnology-derived pharmaceuticals such as insulin icodec.

The applicant has performed a carcinogenicity assessment broadly in line with the EMA document *"Points to Consider Document on the Non-Clinical Assessment of the Carcinogenic Potential of Insulin Analogues"*.

The *in vitro* studies are described and assessed in more detail under the non-clinical pharmacology section and included determining the binding to insulin and IGF-1 receptors and the resulting down-stream signaling, metabolic effects and mitogenic effects in neoplastic and non-neoplastic cell lines. The results from the *in vitro* assessment indicate no additional concerns when compared to human insulin.

The *in vivo* assessment of the carcinogenic potential of insulin icodec was based on the repeat-dose toxicity studies with special emphasis on the 52-week study in SD rats, which included assessment of carcinogenicity focusing on female mammary gland tumours, which commonly develop in female SD rats. The study also included a reference group dosed with human insulin. Overall, the incidence of mammary gland tumours was not increased in treatment groups and the incidences were between 42% and 44% in all groups including the control and reference group.

It can be noted that no *in vivo* assessment of mammary gland cell proliferation (for example by BrdU or Ki-67 staining) was performed in the 52-week rat study. This deviates from the recommendations made in the EMA document *"Points to Consider Document on the Non-Clinical Assessment of the Carcinogenic Potential of Insulin Analogues"* where it is suggested to supplement the histopathology with cell proliferation data. The applicant has however provided a justification referring to nonclinical evidence supporting the fact that *in vivo*

mammary gland cell proliferation does not correlate with mammary gland tumours making it a poor surrogate marker for cancer development in the mammary glands of rats. It is agreed the additional value of determining *in vivo* cell proliferation in this case is questionable and the applicant's justification is accepted.

It is also acknowledged that the applicant has determined the *in vitro* mitogenic response of insulin icodec by ^{3}H-thymidine incorporation in various cell types including primary human mammary epithelial cells and a human mammary adenocarcinoma cell line. The result, which also included groups with insulin X10 (positive control) and IGF-1, do not indicate a different mitogenic potential when compared to human insulin.

In addition, throughout the toxicology programme, insulin icodec was not associated with any treatment related changes in the occurrence of hyperplastic or neoplastic lesions in rats or dogs dosed for up to 52 and 26 weeks, respectively.

Based on the above, it is concluded that insulin icodec is unlikely to hold a carcinogenic potential different from that of human insulin.

2.5.4.5. Reproductive and developmental toxicity

A reproduction and developmental toxicity programme in line with the ICH S5(R3) guideline was conducted with insulin icodec comprising studies covering fertility, embryo-foetal development and pre- and post-natal development in rats and embryo-foetal development in rabbits.

Fertility and early embryonic development (FEED) in rats

In the FEED study, rats were dosed once-daily by subcutaneous injections. Females were dosed two weeks prior to pairing until gestation day (GD) 17 with up to 60 nmol/kg/day. Males were dosed for four weeks before pairing with up to 100 nm/kg/day. The reason for the different dose schedules between males and females was based on the findings from the preliminary dose range finding study in which skeletal changes were noted at all dose levels. No safety margins to clinical exposure were achieved.

One high-dose male was euthanised due to signs of hypoglycaemia on day 48. In both sexes, the findings were consistent with the expected pharmacological effects or low plasma glucose levels and increased bodyweight/food consumption prior to pairing. A minor lower mean placental weight was observed at 60 nmol/kg/day, but values were only marginally outside the historical control range and therefore most likely not clinically relevant.

Oestrous cycle, pre-coital interval, mating performance, fertility index, pre- or post-implantation loss, foetal weight, and sex ratio were unaffected by treatment.

Dose dependent exposure was also confirmed in litters 24 hours after the last dosing on GD20 and fetal to maternal exposure ratios were in the range of 3-6%. Embryo-fetal survival and growth were unaffected by treatment. In high-dose litters, the incidence of minor fetal abnormalities (left umbilical artery and thinning of diaphragm with protrusion of liver lobe) were slightly higher than control but within the historical control data range and considered most likely not to be related to treatment. In contrast to the preliminary study, there were no clear treatment related skeletal findings.

Embryo-fœtal development (EFD) in rabbits

A preliminary dose-range finding and a pivotal embryo-foetal toxicity studies were performed in rabbits. In the preliminary study, a dose of 18 nmol/kg/day was well tolerated, while a dose of 24 nmol/mg/day was considered to exceed the maximum tolerable dose due to maternal hypoglycaemia and pre- and post-

implantation losses. Moreover, there were minor skeletal cranial abnormalities (sutural bones, fissures, and additional suture) at all dose levels in the preliminary study. In one high-dose fetus, there was a major cranial abnormality (partially fused frontal bones with frontal bump/ridge).

In the pivotal embryo-foetal toxicity study, rabbits were dosed once-daily by subcutaneous injections and there were no safety margins to clinical exposure. In mothers, there were effects related to the pharmacological effects of insulin such as low plasma glucose levels and increased food consumption.

In total four mortalities occurred. The two high-dose animals that were killed after signs of abortion (GD21/22) showed mild decrease in food consumption and only one of the animals had decreased blood glucose levels that possibly could promote abortion. The other two animals, one high-dose (killed GD13) and one mid-dose animal (killed GD11) showed signs resembling hypoglycaemia (underactivity, partially closed eyelids, unsteady muscle reaction/reduced body tone and abnormal, prostrate posture, unconscious behavior and convulsions) and had low blood glucose levels.

Litter data indicated that the number of implantation sites, the number of live young, sex ratio, number of resorptions and the extent of the pre- and post-implantation loss was not affected by treatment. No effect was determined on fetal and placental weights.

Skeletal abnormalities were noted. Single cases of scoliosis were seen at all dose levels including in control and considered incidental. There was an increase in cases of unilateral caudal shift pelvic girdle in fetuses from high dose mothers compared to control (6 vs 3). Moreover, multiple rib/thoracic vertebral was detected in a single foetus from a mid-dose mother and in two foetuses from high-dosed mother. This was not seen in any control foetus. Finally, there was an dose-dependent increase in thoracolumbar vertebra abnormalities (29 in high-dose vs 10 in control). However, since all of the above findings were within the historical control data range, the relation to treatment is uncertain.

Prenatal and postnatal development (PPND) in rats

Pre- and postnatal development was studied in rats dosed once-daily by subcutaneous injections from GD6 to lactation day (LD) 20. There were no safety margins to clinical exposure. The dose levels were reduced between GD21 to LD2 to reduce the risk of hypoglycaemia during labor and early lactation.

Exposure was confirmed in all F0 animals and was comparable on GD17 and LD11. In two F1 pups (mid and high dose), low exposure (C_{max} 200 and 1200-fold lower than mothers) was noted on day 11 of age. In all other F1 pups, no exposure was detected.

Four mothers receiving high dose (50 nmol/kg/day) were euthanised during the study course, none were lost at 20 and 35 nmol/kg/day. Two of the deaths occurred during parturition or start of lactation and were within the historical control range. The other two were euthanised during late lactation where one experienced a total litter loss on LD16. The blood glucose levels of this animal was lower than the group mean. The other mother was killed due to severe clinical signs of hypoglycaemia (abnormal gait and had limited control of their hindlimbs) on LD17. These two deaths are considered treatment related and coupled to hypoglycaemia.

In general, maternal effects were coupled to insulin pharmacology with effects of low blood glucose levels and slightly lower body weight gain during lactation. In the high dose group, there were 25 pups euthanised for welfare reasons and 4 pups were found dead in late lactation (LD 15-18). In 19/29 dead pups there were signs resembling those of hypoglycaemia (decreased activity, tremors, reduced body tone, partially closed eye lids and uncoordinated abnormal gait). 8/29 dead pups that did not show clinical signs were killed together with their mother (killed for welfare reasons) and 2/29 pups were found dead with no known reason.

There were no clinical signs or mortality during late lactation in the control group or in the groups dosed with 20 or 35 nmol/kg/day.

The dead pups were all from mothers (7 different dams in total), which had a more pronounced mean body weight loss than that of the remaining animals in the group. Moreover, the mothers of the dead pups tended to have lower blood glucose values at LD11 when compared to other dams in the same group. No pronounced effect on pup blood glucose levels were seen at LD11 in any of the dose groups but there was a tendency to somewhat lower blood glucose levels in pups of high dosed mother (-.4 to -7% of control). Low exposure was detected in a total of 2 pups. While it is uncertain to which extent insulin icodec is excreted into breast-milk, the applicant considers it unlikely that exposure through breastfeeding could result in hypoglycaemia in the pups and instead proposes that the weight loss in mothers of the affected litters had led to underfeeding of the pups. This is agreed. The lower body weight gain from day 7-18 seen in pups from high dose mothers and that 9/29 dead pups had no milk in their stomach is also supportive to the underfeeding explanation.

2.5.4.6. Toxicokinetic data

Toxicokinetic evaluations were included in all pivotal repeat-dose toxicity studies and reproductive toxicity studies, and exposure ratios relative to human exposure were estimated. In general, increases in exposure was approximately proportional to the increase in dose observed.

In rats, no clear sex differences observed were t_{max} ranged from 4-8 hours and the half-life ranged from 4-54 hours and a 2-4-fold accumulation was noted.

In dogs, terminal half-life ranged from 37-83 hours and t_{max} ranged from 4-48 hours. Female dogs tended to have slightly higher exposure (less than 20%) than male dogs and a 2-fold accumulation was observed.

2.5.4.7. Local tolerance

Local tolerance after subcutaneous injection was investigated in a pig model. Also, local tissue reaction after a single intravenous injection was characterised in rabbits. Finally, the local tolerance of the commercial product was characterised in minipigs. Local reactions were mild and comparable to that of the corresponding vehicles. The difference in response compared to sterile isotonic saline was minor. The observed inflammatory changes were mild and are considered acceptable.

Moreover, in the repeat-dose toxicity studies the local reactions observed at the injection site was comparable between control and insulin icodec dosed groups.

2.5.4.8. Other toxicity studies

Anti-drug antibodies

There were anti-drug antibodies (ADA) detected in the 8- and 26-week repeat-dose toxicity studies in rats and dogs. In the 8-week rat study, ADA was detected in the majority (78%) of the rats dosed with insulin icodec whereas 8% had antibodies in the 26-week study. In dogs, ADA were detected in 78% and 22% of the animals in the 8-and 26-weeks study, respectively.

In general, there was no clear relation to dose level and plasma glucose levels for animals with antibodies towards insulin icodec were in same range as for the antibody negative animals. Since exposure in most

animals resulted in the expected decrease in blood glucose levels, ADA formation is not considered to have significantly influenced the outcome of the studies.

ADA was also confirmed clinically, and the risk for possible cross-reactive ADA in humans is further addressed in the clinical assessment below.

Impurities

Identified product specific impurities have been non-clinically qualified in the 26-week rat study.

2.5.5. Ecotoxicity/environmental risk assessment

No environmental risk assessment has been submitted, which is acceptable given the product characteristics.

Insulin icodec is a basal insulin analogue, which is expected to be readily biodegradable and is unlikely to cause a significant risk to the environment. Consequently, the applicant is exempted from submitting ERA studies according to the EMA guideline on environmental risk assessment of medicinal products for human use.

2.5.6. Discussion on non-clinical aspects

The primary pharmacodynamic testing has focused on demonstrating that insulin icodec achieve the desired PD effects while maintaining the same biological and safety profile as human insulin. In summary, insulin icodec was shown to exert full agonist effects in the conducted biochemical and cellular studies albeit with a lower potency. Its ability to bind to albumin was reflected by the observed reduction *in vitro* in affinity in the presence of HSA. In addition, no direct or indirect signs of increased mitogenicity by insulin icodec as compared to HI was observed as based on studies of affinity to the IGF-receptor, dissociation rate from the IR or *in vitro* proliferation of primary human mammary epithelial cells and various tumour cell lines. The reduction for insulin icodec in relative affinity for the IGF-1r was stronger than for the IR, indicating the potential to maintain a desired metabolic response without increasing the relative risk for IGF-1 mediated mitogenicity during treatment with insulin icodec.

In line with a previous CHMP advice, it should be ensured that potential metabolites in the test medium, i.e., the peptide without its side chain, are evaluated for mitogenicity. The reason being that such metabolites might have a different mitogenic potential than the parent compound. However, it appears there is no need to test for metabolites in the test medium, since insulin icodec in the *in vitro* test showed less propensity for mitogenicity than human insulin. Several direct or indirect signs of reduced mitogenicity by insulin icodec were observed in comparison to HI. A lower *in vitro* proliferation in response to insulin icodec as compared to HI (0.2-2%) was demonstrated in both primary human mammary epithelial cells as well as in various tumour cell lines. Moreover, as mentioned above, insulin icodec was found to bind with less affinity to the IGF-1 receptor, as well as having a faster dissociation rate from the IR than human insulin. Furthermore, in the absence of any convincing evidence of a presence of major *in vivo* metabolites of insulin icodec, the previous suggestion of evaluation of mitogenic potential by icodec metabolites is not further pursued.

The *in vivo* potency of s.c. insulin icodec was determined, by a euglycaemic insulin clamp technique, to be approximately 200% compared to insulin glargine, in both normoglycaemic dogs and pigs, as compared to the potency of 40-50 % in rats based on an HbA1c lowering effect. No explanation was provided for this discrepancy. However, clinical data have demonstrated that s.c. insulin icodec in humans is equipotent with daily basal insulin. It was noted that the dose and not the exposure of insulin was used for the clamp model

calculations although equimolar administrations will result in different pharmacokinetics for insulin icodec and insulin glargine.

The applicant claims that GABA-ergic or thyroid hormone-related effects were absent in the *in vivo* safety pharmacology and toxicology studies and, therefore, that the *in vitro* inhibitions detected are not of clinical relevance. Although it is not specified, which findings would have been expected after GABA- or thyroid hormone-interaction *in vivo*, it is agreed not to pursue this issue further, based on the relatively high margin to the clinical C_{max} and lack of concern from clinical safety studies. Moreover, the safety pharmacology studies did not reveal any findings of concern for humans.

Insulin icodec is a basal insulin analogue, which is expected to be readily biodegradable and is unlikely to cause a significant risk to the environment. Consequently, the applicant is exempted from submitting ERA studies according to the EMA guideline on environmental risk assessment of medicinal products for human use.

2.5.7. Conclusion on the non-clinical aspects

The CHMP assessment of the non-clinical data provided for insulin icodec revealed no objections to a marketing authorisation, and the application is considered approvable from a non-clinical viewpoint.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

The application for once weekly insulin icodec includes data from 18 clinical trials in the insulin icodec clinical development programme: 6 phase 3a confirmatory efficacy and safety trials (ONWARDS 1-6), 3 phase 2 exploratory trials and 9 clinical pharmacology trials.

Figure 2. Overview of clinical development programme

Phase 3a
T2D trials, insulin naive
ONWARDS 1 (4477)[a]
ONWARDS 3 (4479)[b]
ONWARDS 5 (4481)

T2D trials, insulin experienced
ONWARDS 2 (4478)[b]: basal switch
ONWARDS 4 (4480)[b]: basal-bolus

T1D trial
ONWARDS 6 (4625)[ab]: basal-bolus

Clinical pharmacology
4314: PK/PD at SS in Caucasian T2D
4226: PK in subjects with renal impairment
4225: PK/PD at SS in Caucasian T1D
4422: PK/PD at SS in Japanese T1D
4462: Hypoglycaemia frequency and response to double/triple dose at SS in Caucasian T2D
4569: PK/PD at SS in Caucasian T2D
4570: PK in subjects with hepatic impairment
4571: PK at SS in Chinese T2D
4572: Injection region trial in Caucasian T2D

Phase 2
4383[b]: T2D, insulin naive
4465: T2D, insulin naive, titration algorithms
4466: T2D, basal switch

[a] Data from main part of trial included in the application. [b] Trial data included in population pharmacokinetics assessment.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Insulin icodec is a new insulin analogue and the pharmacokinetics should be characterised and the influence of intrinsic and extrinsic factors should be evaluated. The influence of different injection sites should also be studied.

The pharmacokinetics of insulin icodec was investigated in 9 clinical pharmacology trials, see Figure 2 and Table 1. In addition, 5 therapeutic trials were included in a population PK analysis, see Figure 2. All clinical

trials were conducted with the final formulation of insulin icodec, 700 U/mL. *In vitro* data including protein binding and metabolism was also generated.

The submitted clinical pharmacology studies are considered sufficient to characterise the PK of insulin icodec. A summary of the PK results (non-compartmental analysis) following single or multiple dosing in subjects with T1D or T2D are presented in Table 2, Table 3, Table 4 and Table 5.

Table 1. Overview of trial design of clinical pharmacology studies

Study ID Country	Type of trial	Trial design and type of control	Test drugs and route of administration	Number of subjects (FAS, M/F)	Healthy subjects or population	Duration of treatment[a]	Trial status Type of report Location
NN1436-4314 DE	PK/PD	Randomised, double-blind, double-dummy, active-controlled. single-centre, multiple-dose, dose escalation	Once weekly s.c. insulin icodec – individualised dosing Comparator: Once daily s.c. insulin degludec – individualised dosing Placebo once weekly s.c Placebo once daily s.c	50, 43/7	T2D	5 weeks	Completed CTR M 5.3.4.2
NN1436-4226 DE	PK	Single-centre, single dose, open-label, parallel group	s.c. insulin icodec – individualised dosing	58, 39/19	Healthy subjects and subjects with renal impairment	Single dose	Completed CTR M 5.3.3.3
NN1436-4225 DE	PK/PD	Randomised, 2-period crossover, single-centre, open-label, multiple-dose	Once weekly s.c. insulin icodec – individualised dosing Comparator: Once daily s.c. insulin glargine (100 U/mL)– individualised dosing	66, 56/10	T1D	8 weeks	Completed CTR M 5.3.4.2
NN1436-4422 JP	PK/PD	Randomised, single-centre, open-label, 2-period crossover, multiple-dose	Once weekly s.c. insulin icodec – individualised dosing Comparator: Once daily s.c. insulin glargine (100 U/mL)– individualised dosing	24, 14/10	T1D	8 weeks	Completed CTR M 5.3.4.2
NN1436-4462 AT	PK/PD	Randomised, single-centre, open-label, 2-period cross-over, multiple dose	Once weekly s.c. insulin icodec – individualised dosing Comparator: Once daily s.c. insulin glargine (100 U/mL) – individualised dosing	43, 31/12	T2D	6 weeks	Completed CTR M 5.3.4.2
Study ID Country	**Type of trial**	**Trial design and type of control**	**Test drugs and route of administration**	**Number of subjects (FAS, M/F)**	**Healthy subjects or population**	**Duration of treatment[a]**	**Trial status Type of report Location**
NN1436-4569 AT	PK/PD	Single-centre, open-label, one-period, multiple-dose	Once weekly s.c. insulin icodec – individualised dosing Run-in period with individualised insulin degludec dosing	46, 35/11	T2D	8 weeks	Completed CTR M 5.3.4.2
NN1436-4570 CZ, SK	PK	2-centre, single-dose, open-label, parallel-group	S.c. insulin icodec – individualised dosing	25, 12/13	Healthy subjects and subjects with hepatic impairment	Single dose	Completed CTR M 5.3.3.3
NN1436-4571 CN	PK	Single-centre, open-label, single group, multiple-dose	S.c. insulin icodec – individualised dosing Run-in period with individualised insulin degludec dosing	24, 12/12	T2D	6 weeks	Completed CTR M 5.3.3.3
NN1436-4572 DE	PK/PD	Randomised, single-centre, open-label, 3-period cross-over	S.c. insulin icodec – individualised dosing	25, 22/3	T2D	3 x single dose	Completed CTR M 5.3.1.1

Table 2. Insulin icodec first dose or single dose PK endpoints in subjects with T1D

Trial ID, report location, design	N (M/F) Race	Treatment and insulin icodec s.c. dose	Dose norm. $AUC_{Ico,0-168h,FD}$ Geom. mean (CV%) (pmol*h/L)/(U/kg)	Dose norm. $C_{max,Ico,FD}$ Geom. mean (CV%) (pmol/L)/(U/kg)	$t_{max,Ico,FD}$ Median (mean [SD]) (h)	$t_{½,Ico,FD}$ Geom. mean (CV%) (h)	$MRT_{Ico,FD}$ Geom. mean (CV%) (h)	$CL/F_{Ico,FD}$ Geom. mean (CV%) (mL/(h*kg))	$Vz/F_{Ico,FD}$ Geom. mean (CV%) (mL/kg)
4225, Trial 4225 (M 5.3.4.2), RND, OL, CO, MD	66 (56/10) Caucasian	Eight once-weekly doses. Mean (SD) at start of trial: • 1.9 (0.44) U/kg/week (all subjects)	6,503,061 (13.9)	54,403 (18.1)	18.0 (27.4 [24.8])	NA	NA	NA	NA
4422, Trial 4422 (M 5.3.4.2), RND, OL, CO, MD	24 (14/10) Japanese	Eight once-weekly doses. Mean (SD) at start of trial: • 1.7 (0.45) U/kg/week (all subjects)	6,108,460 (12.8)	52,158 (19.0)	12.0 (16.1 [6.1])	NA	NA	NA	NA

Table 3. Insulin icodec first dose or single dose PK endpoints in subjects with T2D

Trial ID, report location, design	N (M/F) Race	Treatment and insulin icodec s.c. dose	Dose norm. $AUC_{Ico,0-168h,FD}$ Geom. mean (CV%) (pmol*h/L)/(U/kg)	$AUC_{Ico,0-168h,FD}$ Geom. mean (CV%) (pmol*h/L)	Dose norm. $C_{max,Ico,FD}$ Geom. mean (CV%) (pmol/L)/(U/kg)	$C_{max,Ico,FD}$ Geom. mean (CV%) (pmol/L)	$t_{max,Ico,FD}$ Median (mean [SD]) (h)	$t_{½,Ico,FD}$ Geom. mean (CV%) (h)	$MRT_{Ico,FD}$ Geom. mean (CV%) (h)	$CL/F_{Ico,FD}$ Geom. mean (CV%) (mL/(h*kg))	$Vz/F_{Ico,FD}$ Geom. mean (CV%) (mL/kg)
4314, Trial 4314 (M 5.3.4.2), RND, DB, MD	50 (43/7) Caucasian	Five once-weekly doses. Doses at start of trial: • 2.0 U/kg/week • 3.3 U/kg/week • 4.0 U/kg/week	NA NA NA	11,848,352 (12.3) 18,874,250 (16.6) 22,504,810 (10.4)	NA NA NA	100,351 (16.1) 159,632 (24.6) 195,956 (11.2)	23.9 (30.4 [25.1]) 18.0 (23.7 [16.1]) 20.0 (24.1 [10.6])	NA NA NA	NA NA NA	NA NA NA	NA NA NA
4569, Trial 4569 (M 5.3.4.2), OL, MD	46 (35/11) Caucasian	Eight once-weekly doses. Mean (SD) at start of trial: • 2.6 (1.07) U/kg/week	6,064,501 (15.8)	NA	50,771 (22.5)	NA	21.2 (23.1 [11.7])	NA	NA	NA	NA
4571, Trial 4571 (M 5.3.3.3), OL, MD	24 (12/12) Chinese	Six once-weekly doses. Mean (SD) at start of trial: • 2.2 (0.80) U/kg/week	4,808,576 (15.9)	NA	43,076 (16.5)	NA	18.0 (21.0 [8.2])	NA	NA	NA	NA
4572, Trial 4572 (M 5.3.1.2), RND, OL, CO, SD	25 (22/3) Caucasian	Single doses.	Dose norm. $AUC_{Ico,0-168h,SD}$	$AUC_{Ico,0-inf,SD}$	Dose norm. $C_{max,Ico,SD}$	$C_{max,Ico,SD}$	$t_{max,Ico,SD}$	$t_{½,Ico,SD}$	$MRT_{Ico,SD}$	$CL/F_{Ico,SD}$	$Vz/F_{Ico,SD}$
		• 5.6 U/kg abdomen • 5.6 U/kg upper arm • 5.6 U/kg thigh	NA NA NA	69,540,984 (22.2) 71,324,215 (17.1) 68,164,713 (18.6)	NA NA NA	337,825 (23.8) 364,755 (19.6) 291,942 (24.3)	24.0 (24.1 [6.8]) 24.0 (21.9 [5.8]) 27.0 (35.3 [24.1])	150 (15.5) 150 (19.9) 153 (23.5)	211 (15.8) 209 (19.3) 226 (20.9)	0.48 (22.2) 0.47 (17.0) 0.49 (18.6)	104 (13.4) 102 (20.4) 109 (18.8)

Table 4. Insulin icodec steady state PK endpoints in subjects with T1D

Trial ID, report location, design	N (M/F) Race	Treatment and insulin icodec s.c. dose	Dose norm. $AUC_{Ico,τau,SS}$ Geom. mean (CV%) (pmol*h/L)/(U/kg)	Dose norm. $C_{max,Ico,SS}$ Geom. mean (CV%) (pmol/L)/(U/kg)	$t_{max,Ico,SS}$ Median (mean [SD]) (h)	$t_{½,Ico,SS}$ Geom. mean (CV%) (h)	$MRT_{Ico,SS}$ Geom. mean (CV%) (h)	$CL/F_{Ico,SS}$ Geom. mean (CV%) (mL/(h*kg))	$V_{SS}/F_{Ico,SS}$ Geom. mean (CV%) (mL/kg)
4225, Trial 4225 (M 5.3.4.2), RND, OL, CO, MD	66 (56/10) Caucasian	Eight once-weekly doses. Mean (SD) at end of trial: • 1.9 (0.44) U/kg/week (all subjects)	12,524,774 (23.0)	99,258 (23.2)	18.1 (21.5 [13.2])	174.6 (19.3)	268.2 (18.0)	0.479 (23.0)	128 (14.5)
4422, Trial 4422 (M 5.3.4.2), RND, OL, CO, MD	24 (14/10) Japanese	Eight once-weekly s.c. doses. Mean (SD) at end of trial: • 1.7 (0.45) U/kg/week (all subjects)	10,848,960 (10.6)	91,201 (14.7)	16.0 (5.1 [2.4])	164 (11.4)	247 (11.0)	0.553 (10.6)	137 (17.7)

Table 5. Insulin icodec steady state PK endpoints in subjects with T2D

Trial ID, report location, design	N (M/F) Race	Treatment and insulin icodec s.c. dose	Dose norm. $AUC_{Ico,τau,SS}$ Geom. mean (CV%) (pmol*h/L)/(U/kg)	$AUC_{Ico,τau,SS}$ Geom. mean (CV%) (pmol*h/L)	Dose norm. $C_{max,Ico,SS}$ Geom. mean (CV%) (pmol/L)/(U/kg)	$C_{max,Ico,SS}$ Geom. mean (CV%) (pmol/L)	$t_{max,Ico,SS}$ Median (mean [SD]) (h)	$t_{½,Ico,SS}$ Geom. mean (CV%) (h)	$MRT_{Ico,SS}$ Geom. mean (CV%) (h)	$CL/F_{Ico,SS}$ Geom. mean (CV%) (mL/(h*kg))	$V_{SS}/F_{Ico,SS}$ Geom. mean (CV%) (mL/kg)
4314, Trial 4314 (M 5.3.4.2), RND, DB, MD	50 (43/7) Caucasian	Five once-weekly doses: Dose at end of trial: • 2.0 U/kg/week • 3.3 U/kg/week • 4.0 U/kg/week	NA NA NA	26,254,425 (27.8) 37,602,218 (22.9) 46,918,670 (24.1)	NA NA NA	223,945 (22.0) 309,878 (19.3) 414,549 (21.2)	16.0 (22.2 [10.1]) 16.0 (16.9 [7.2]) 16.0 (21.0 [20.1])	238.4 (27.6) 169.9 19.8) 187.9 (20.8)	366.8 (25.1) 268.4 (17.8) 289.4 (19.3)	0.461 (26.5) 0.528 (17.8) 0.511 (19.0)	169 (28.2) 142 (13.3) 148 (13.2)
4569, Trial 4569 (M 5.3.4.2), OL, MD	46 (35/11) Caucasian	Eight once-weekly doses. Mean (SD) at end of trial: • 2.9 (1.16) U/kg/week	12,748,402 (20.0)	NA	105,822 (21.0)	282,959 (48.6)	15.1 (17.6 [6.2])	155 (15.3)	237 (13.6)	0.47 (20.0)	112 (16.5)
4571, Trial 4571 (M 5.3.3.3), OL, MD	24 (12/12) Chinese	Six once-weekly doses. Mean (SD) at end of trial: • 2.2 (0.80) U/kg/week	11,337,079 (29.9)	NA	91,554 (27.9)	191,784 (40.0)	18.0 (23.4 [13.4])	159 (22.2)	248 (22.6)	0.53 (29.9)	131 (14.5)

Analytical methods

PK data in serum is available from all studies except ONWARDS 1, 5, 4465, 4466. Three cross-validated bioanalytical methods for quantification of insulin icodec in human serum were used across the development,

with the main site being in Switzerland. A method in human urine was also validated for use in the renal impairment study 4226.

All methods were similar: insulin icodec was quantified by a specific luminescence oxygen channelling immunoassay (LOCI). LOCI is based on the proximity of two latex bead reagents: acceptor and donor beads. The donor beads are bound to an antibody specific for the B25H mutation in insulin icodec. The acceptor beads are conjugated with a monoclonal antibody recognizing human insulin. When in proximity, the photosensitiser present in the donor beads is excited to generate chemiluminescence proportional to the concentration of insulin icodec.

The immunogenicity of insulin icodec was assessed using a multi-tiered strategy including screening, confirmation, titre determination and cross-reactivity to human insulin. The neutralising potential of antidrug antibodies (ADA) was determined only in follow-up samples of studies 4384 and ONWARDS 3. ADA were analysed in all studies, except 4570 (hepatic impairment) and 4572 (injection site). In studies 4465, 4466, ONWARDS 1, and ONWARDS 5, no systematic sampling was performed, but ADA samples were planned to be collected in case of hypersensitivity reaction. These samples were to be analysed for anti-icodec IgE, anti-human insulin IgE, total IgE and tryptase, in addition to ADAs as outlined above. Generic assays were used for this purpose and an assay for anti-icodec IgE was validated using the immunoCAP IgE assay platform, using a universal level of 0.35 kUA/L as the boundary for IgE positivity.

All ADAs were analysed at the site in Switzerland, with the exception of study 4314 (at Novo Nordisk) and samples from Chinese subjects from studies 4571 and 4479/ONWARDS 3 (at a site in China). The Novo Nordisk ADA assay was able to detect ADAs from 1.696 µg/mL only.

The assays at the sites in Switzerland and China are identical (including critical reagents), but have different assay parameters, thus their results are not pooled for study 4479/ONWARDS 3. The ADA method of these assays included an acid pre-treatment step prior to PEG precipitation, followed by binding to an insulin icodec radioactive tracer, PEG precipitation and radioactivity counting in the precipitate. For confirmation, excess unlabelled insulin icodec was added, while excess human insulin was added to assess cross-reactivity. The validation at both the sites in Switzerland and in China followed current guidelines and white papers. At screening, 100 ng/mL of ADA tolerated at least 1000 nM of insulin icodec. Drug tolerance in the confirmation assay was tested at the Chinese site only. There, for 100 ng/mL of positive control, 283 nM of insulin icodec were tolerated.

A cell-based method was validated by Novo Nordisk to assess the neutralisation potential of ADAs using a commercially available cell-based functional assay (PathHunter Insulin Bioassay Kit from Eurofins DiscoverX). Monoclonal anti-insulin antibody was used as a positive control, and samples were pretreated with Glycine-HCl and PEG precipitation to increase drug tolerance. When cells from the kit are stimulated with insulin icodec amino acid backbone (0.3 nM), the insulin receptor is phosphorylated. This phosphorylation induces activation of the reporter enzyme β-gal by forcing complementation of two inactive β-gal fragments to one active β-gal form by protein-protein interaction. The β-gal enzymatic activity is hereafter measured using a chemiluminescent substrate. Neutralising effect of antibodies causes a decrease in chemiluminescent signal due to decreased insulin receptor stimulation.

Pharmacokinetic data analysis

In most clinical pharmacology studies, standard non-compartmental methods have been used. In four studies (4314, 4572, 4226 and 4570), fixed doses of insulin icodec were administered while individual doses were administered in all other studies. Since most multiple-dose trials used individualised dosing, dose-normalised

AUCIco, tau, SS and dose-normalised Cmax, Ico, SS were calculated to allow for comparison between populations and of the variation of these endpoints.

In phase 2 and phase 3 studies, pharmacokinetic data in the target population (diabetes type 1 and 2) was sampled with sparse sampling designs and analysed using a population PK (PopPK) approach as described below.

Evaluation and Qualification of Models

PopPK analysis

A PopPK analysis was performed where the objective was to investigate the effects of a number of covariates on insulin icodec exposure at steady state.

A pooled dataset was used for the PopPK analysis including 5 studies in diabetes patients where PK was collected using a sparse sampling design. In total, the dataset for the PopPK analysis included 6939 PK observations from 1244 patients.

The covariates that were explored are listed in Table 6 (categorical covariates) and Table 7 (continuous covariates).

Table 6. Summary of categorical covariates in the population PK dataset

Category	Group	4383	4478	4479	4480	4625	Total
All	N	123 (9.9%)	260 (20.9%)	290 (23.3%)	284 (22.8%)	287 (23.1%)	1244 (100%)
Age group	18<= to <65 years	83 (67.5%)	143 (55%)	207 (71.4%)	185 (65.1%)	265 (92.3%)	883 (71%)
	65<= to <75 years	39 (31.7%)	98 (37.7%)	73 (25.2%)	90 (31.7%)	19 (6.6%)	319 (25.6%)
	Elderly (75<= years)	1 (0.8%)	19 (7.3%)	10 (3.4%)	9 (3.2%)	3 (1%)	42 (3.4%)
Ethnicity	NOT HISPANIC OR LATINO	113 (91.9%)	245 (94.2%)	200 (69%)	233 (82%)	277 (96.5%)	1068 (85.9%)
	HISPANIC OR LATINO	10 (8.1%)	15 (5.8%)	76 (26.2%)	51 (18%)	10 (3.5%)	162 (13%)
	NOT REPORTED	-	-	14 (4.8%)	-	-	14 (1.1%)
Race	WHITE	108 (87.8%)	158 (60.8%)	178 (61.4%)	180 (63.4%)	227 (79.1%)	851 (68.4%)
	ASIAN	8 (6.5%)	86 (33.1%)	78 (26.9%)	91 (32%)	51 (17.8%)	314 (25.2%)
	BLACK OR AFRICAN AMERICAN	6 (4.9%)	11 (4.2%)	9 (3.1%)	13 (4.6%)	9 (3.1%)	48 (3.9%)
	OTHER	-	3 (1.2%)	11 (3.8%)	-	-	14 (1.1%)
	AMERICAN INDIAN OR ALASKA NATIVE	-	2 (0.8%)	-	-	-	2 (0.2%)
	NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1 (0.8%)	-	-	-	-	1 (0.1%)
	NOT REPORTED	-	-	14 (4.8%)	-	-	14 (1.1%)
Chinese	Non-Chinese	123 (100%)	260 (100%)	220 (75.9%)	284 (100%)	287 (100%)	1174 (94.4%)
	Chinese	-	-	70 (24.1%)	-	-	70 (5.6%)

| Japanese | Non-Japanese | 123 (100%) | 209 (80.4%) | 290 (100%) | 240 (84.5%) | 255 (88.9%) | 1117 (89.8%) |
| | Japanese | - | 51 (19.6%) | - | 44 (15.5%) | 32 (11.1%) | 127 (10.2%) |

For the analysis, the race groups 'American Indian or Alaska Native', 'Native Hawaiian or Other Pacific Islander', and 'Other' as well as subjects with unreported race were pooled with the 'White' race group, and subjects with unreported ethnicity were pooled with the 'Not Hispanic or Latino' ethnicity group.

Table 7. Summary of continuous covariates in the population PK dataset

Category	Group	4383	4478	4479	4480	4625	Total
All	N	123 (9.9%)	260 (20.9%)	290 (23.3%)	284 (22.8%)	287 (23.1%)	1244 (100%)
Sex	M	68 (55.3%)	160 (61.5%)	183 (63.1%)	151 (53.2%)	162 (56.4%)	724 (58.2%)
	F	55 (44.7%)	100 (38.5%)	107 (36.9%)	133 (46.8%)	125 (43.6%)	520 (41.8%)
Antibody level	Negative AB	22 (17.9%)	76 (29.2%)	64 (22.1%)	79 (27.8%)	61 (21.3%)	302 (24.3%)
	1st quartile	31 (25.2%)	58 (22.3%)	87 (30%)	84 (29.6%)	88 (30.7%)	348 (28%)
	2nd quartile	31 (25.2%)	49 (18.9%)	57 (19.6%)	48 (16.9%)	52 (18.1%)	237 (19%)
	3rd quartile	11 (8.9%)	37 (14.2%)	51 (17.6%)	39 (13.7%)	54 (18.8%)	192 (15.4%)
	4th quartile	28 (22.8%)	40 (15.4%)	31 (10.7%)	34 (12%)	32 (11.1%)	165 (13.3%)
Population	Type 2 diabetes	123 (100%)	260 (100%)	290 (100%)	284 (100%)	-	957 (76.9%)
	Type 1 diabetes	-	-	-	-	287 (100%)	287 (23.1%)
Age (years)	Mean (SD)	59.9 (8.1)	62.4 (9.7)	57.7 (10.2)	59.6 (10)	43.9 (14)	56.1 (12.9)
	Range	[33-75]	[26-86]	[26-78]	[19-80]	[18-82]	[18-86]
Body weight (kg)	Mean (SD)	89.4 (16.4)	83.6 (18.4)	85.9 (20)	85.7 (17.7)	78.6 (17.7)	84.1 (18.6)
	Range	[50.7-123.1]	[43.9-136.8]	[43.5-151.4]	[49-136.7]	[39.6-160.3]	[39.6-160.3]
BMI (kg/m2)	Mean (SD)	31 (4.9)	29.5 (5.2)	29.9 (5.2)	30.6 (5)	26.9 (5)	29.4 (5.3)
	Range	[17.8-40.4]	[16.9-40.5]	[16.6-41.1]	[18.1-41.2]	[16.6-46.6]	[16.6-46.6]
Albumin (g/dL)	Mean (SD)	4.6 (0.3)	4.5 (0.3)	4.5 (0.3)	4.4 (0.3)	4.4 (0.3)	4.5 (0.3)
	Range	[3.9-5.3]	[3.6-5.3]	[3.6-5.3]	[3.2-5.4]	[3.5-5.2]	[3.2-5.4]

Th PK observations included in the PopPK dataset are plotted vs time since randomisation in Figure 3.
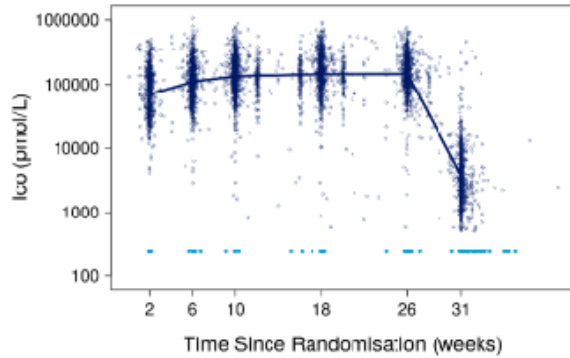
Figure 3. Insulin icodec concentration data versus time since randomisation.
Dark blue points indicate individual values above LLOQ. Light blue points indicate individual values below LLOQ (plotted at LLOQ/2). Lines indicate geometric mean. N=1244. Ico: Insulin icodec

The analyses were carried out in NONMEM version 7.3 using the first-order conditional estimation method with interaction. For the structural model, a one-compartment model with first-order absorption and elimination was used to describe insulin icodec PK. To ensure identifiability of the model with the sparsely sampled data, kA was fixed to 0.175/h, in line with previous PopPK results from trial NN1436-4314.

For the covariate analysis, a confirmatory full model approach was used as proposed by Hu et al in 2008 (Hu C, Zhou H. An improved approach for confirmatory phase III population pharmacokinetic analysis. J Clin Pharmacol. 2008;48(7):812-22) and 2011 (Hu C, Zhang J, Zhou H. Confirmatory analysis for phase III population pharmacokinetics. Pharm Stat. 2011;10(1):14-26). Age, body weight, race, sex, antibody titre (i.e. ADA), albumin and disease type (type 1 vs 2 diabetes) were explored on CL/F in the covariate analysis. Body weight was also included on V/F.

The model checking and validation included standard goodness-of-fit plots and a prediction-corrected visual predictive check (pcVPC) as illustrated for the full model in Figure 4.
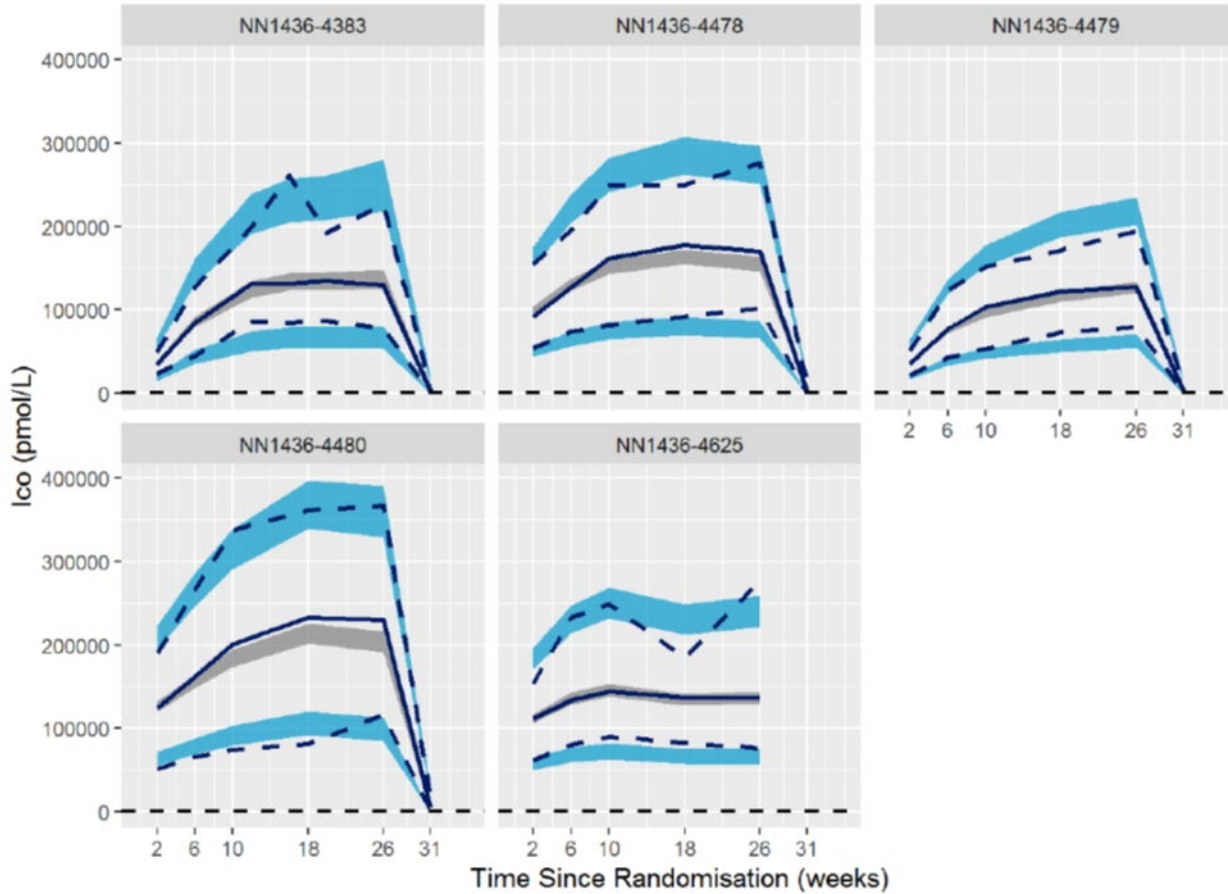
Figure 4. Full model Prediction-corrected VPC
Data are observed (lines) and simulated (shaded areas, n=1000, 95% CI) medians and 5th and 95th concentration percentiles vs. time since randomisation, stratified by trial. Ico: Insulin icodec.

The full model, where all investigated covariate effects were included simultaneously, was successfully estimated and the precision of the estimated parameters was good, except for the albumin exponent on CL/F where the estimate was close to zero and relative standard error (RSE) therefore high (Table 8).

Table 8. Full population PK model: Parameter estimates

Parameter	Unit	Estimate	95% CI	RSE (%)	IIV (% CV)	Shrinkage (%)
Absorption rate constant (kA)	1/h	0.175	Fixed	Fixed	NA	NA
Clearance (CL/F)	L/h	0.045	0.0434 - 0.0466	1.78	19.5	14.3
Volume of distribution (V/F)	L	9.79	9.57 - 10	1.17	25.5	26.9
Age group covariate on CL/F (65-74 years/18-64 years)	NA	0.956	0.929 - 0.983	1.43	NA	NA
Age group covariate on CL/F (>=75 years/18-64 years)	NA	0.905	0.863 - 0.947	2.35	NA	NA
Body weight exponent on CL/F	NA	0.732	0.651 - 0.812	5.61	NA	NA
Ethnicity covariate on CL/F (Hispanic/Non-Hispanic)	NA	1.02	0.978 - 1.06	1.95	NA	NA
Race covariate on CL/F (Black/White)	NA	0.922	0.865 - 0.979	3.16	NA	NA

Race covariate on CL/F (Chinese/White)	NA	1.01	0.968 - 1.06	2.24	NA	NA
Race covariate on CL/F (Japanese/White)	NA	0.985	0.949 - 1.02	1.87	NA	NA
Race covariate on CL/F (Other Asian/White)	NA	0.937	0.892 - 0.983	2.46	NA	NA
Sex covariate on CL/F (Male/Female)	NA	1	0.976 - 1.03	1.33	NA	NA
Antibody group covariate on CL/F (1st quartile/Negative AB)	NA	1.01	0.976 - 1.04	1.53	NA	NA
Antibody group covariate on CL/F (2nd quartile/Negative AB)	NA	0.999	0.967 - 1.03	1.64	NA	NA
Antibody group covariate on CL/F (3rd quartile/Negative AB)	NA	0.943	0.907 - 0.979	1.95	NA	NA
Antibody group covariate on CL/F (4th quartile/Negative AB)	NA	0.828	0.789 - 0.868	2.45	NA	NA
Albumin exponent on CL/F	NA	0.25	0.0269 - 0.474	45.6	NA	NA
Population covariate on CL/F (Type 1 diabetes/Type 2 diabetes)	NA	0.862	0.831 - 0.892	1.8	NA	NA
Body weight exponent on V/F	NA	0.703	0.597 - 0.808	7.64	NA	NA
Proportional Error	% CV	27.7	NA	NA	NA	11

The impact of covariates on exposure was assessed using the full model, with all investigated covariate effects included simultaneously, and presented in a forest plot (Figure 5). The most important, and only potentially clinically relevant, covariate for predicting exposure was body weight, with exposure decreasing with increasing body weight.
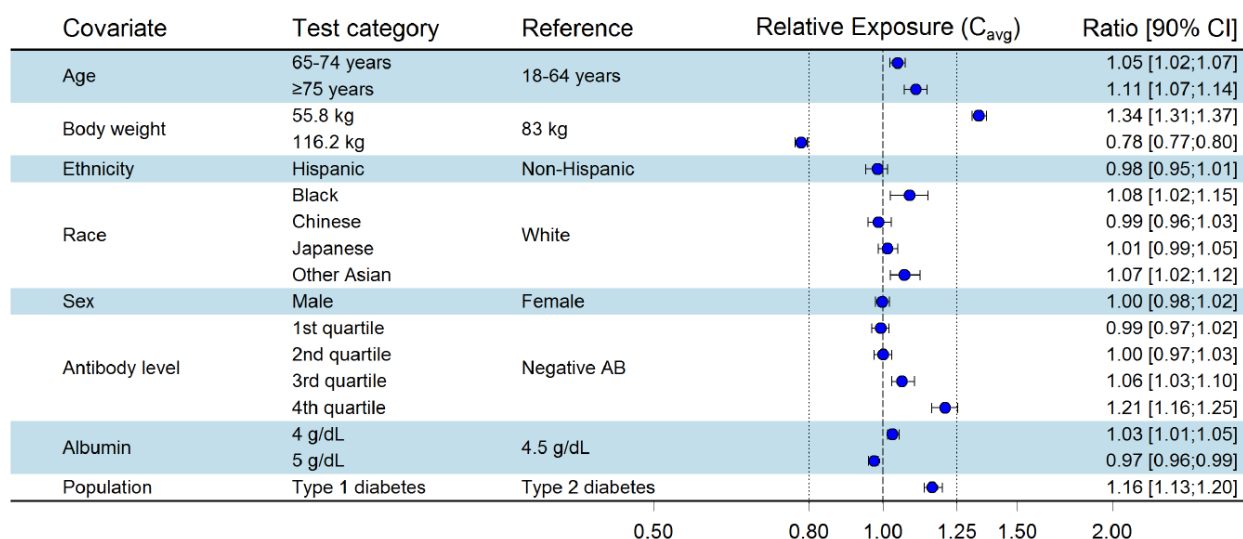
Data are steady-state, dose-normalised C_{avg} relative to a reference subject profile. The forest plot and column to the right show means and 90% CI of relative exposure. Body weight and albumin test categories represent the 5th and 95th percentiles in the data. Vertical lines represent the [0.80; 1.25]-limits. Note: The inclusion of albumin and population as covariates was not pre-specified in the modelling analysis plan, and the analysis is thus formally a *post-hoc* analysis.

Figure 5. Forest plot of covariate effect on insulin icodec exposure using the full model

Absorption

The primary objective of the study NN1436-4572 was to compare pharmacokinetic properties of single dose subcutaneously administered insulin icodec when administered in abdomen, upper arm and thigh in subjects with type 2 diabetes. The PK results are presented in Table 3. Subcutaneous single dose administration of insulin icodec in the thigh, the abdomen and the upper arm resulted in comparable total exposure (AUCIco,0-inf) across injection sites. The maximum concentration of insulin icodec was slightly higher after administration in the abdomen and the upper arm compared to the thigh, with a ratio of 1.17 and 1.24, respectively.

Distribution

The volume of distribution for insulin icodec was estimated in the PopPK analysis (Table 8). The volume of distribution was estimated to 9.78 L.

Several *in vitro* studies were performed to evaluate the binding of insulin icodec in plasma and to serum albumin and the degree of plasma protein binding was >99%.

Elimination

The elimination was quantified as part of the PopPK analysis where apparent clearance was estimated to 0.0453 L/h in the typical patient with estimated IIV of 19.6 %CV. The elimination half-life in a typical patient was 6.24 days, according to the PopPK analysis.

Metabolism: In vitro incubation studies in human hepatocytes resulted in nine metabolites and all of them were detected also in other species and hence no unique human metabolites were identified. Metabolism by insulin degrading enzyme were evaluated *in vitro* with human insulin as comparator resulting in a slower rate of proteolytic degradation for insulin icodec compared to human insulin. When comparing cleavage specificity, 9 of the 12 identified cleavage sites were the same in both insulins indicating similar proteolytic degradation of insulin icodec to that of human insulin. Exploratory analysis of *in vivo* serum samples from study 4314 was performed and four metabolites were structurally identified in serum. Insulin icodec and the three quantified plasma metabolites, B1-29, B24-29 and B29, accounted for 85.3, 11.3, 0.74 and 2.64% of the total AUC0-168h, respectively.

Dose proportionality and time dependencies

Dose proportionality for insulin icodec was demonstrated between doses of 2.0, 3.3 and 4.0 U/kg/week in subjects with T2D in study 4314. Also results from studies 4225, 4422, 4569 and 4571 supports dose proportionality.

Time dependency was not studied specifically in any study. In study 4314, AUC0-168h following single-dose was compared to AUC0-168h at steady-state following multiple dose and the mean accumulation ratio for insulin icodec was approximately 2.0 for AUC across all dose groups.

Immunogenicity

ADA were analysed in all studies, except 4570 (hepatic impairment) and 4572 (injection site). In studies 4465, 4466, ONWARDS 1, and ONWARDS 5, no systematic sampling was performed, but ADA samples were planned to be collected in case of hypersensitivity reaction. Immunogenicity was in a similar range in early and late clinical studies, with up to 57% of subjects positive at baseline, and up to 77% of treatment emergent ADAs. The majority of the ADAs were also cross-reactive towards human insulin. The number of

subjects who developed treatment-induced or treatment-boosted antibodies across the concerned trials is presented in Table 9.

Table 9. Development of treatment-induced and treatment-boosted antibodies

	Tested (N)	Treatment-induced (N)	Treatment-boosted (N)
ONWARDS 2	262	142 (54.2%)	29 (11.1 %)
ONWARDS 3 RoW [a]	243	187 (77.0%)	4 (1.6%)
ONWARDS 3 China [a]	47	33 (70.2%)	1 (2.1%)
ONWARDS 4	288	118 (41.0%)	55 (19.1%)
ONWARDS 6	288	94 (32.6%)	106 (36.8%)
Trial 4383 [a]	123	101 (82.1%)	0

Note: [a]in insulin naïve subjects no pre-existing antibodies and therefore no treatment-boosted antibodies were expected. Treatment-induced antibodies are defined as cases in which subjects were negative at baseline and positive at any time after treatment initiation. Treatment-boosted antibodies are described as cases in which subjects were positive at baseline and experienced a titre increase by at least 4-fold at-any time during the trial.

The relationship between anti-insulin icodec antibody titres and pharmacokinetic properties of insulin icodec as assessed by popPK analysis in 5 confirmatory trials (trials 4383, 4478, 4479, 4480, and 4625) is presented in Figure 6. Overall, PK properties were similar between groups, with a trend towards higher exposure with higher ADA titres. The effect is not considered clinically relevant as relative exposure (C_{avg}) was inside the 0.8-1.25 interval when compared to ADA-negative subjects.
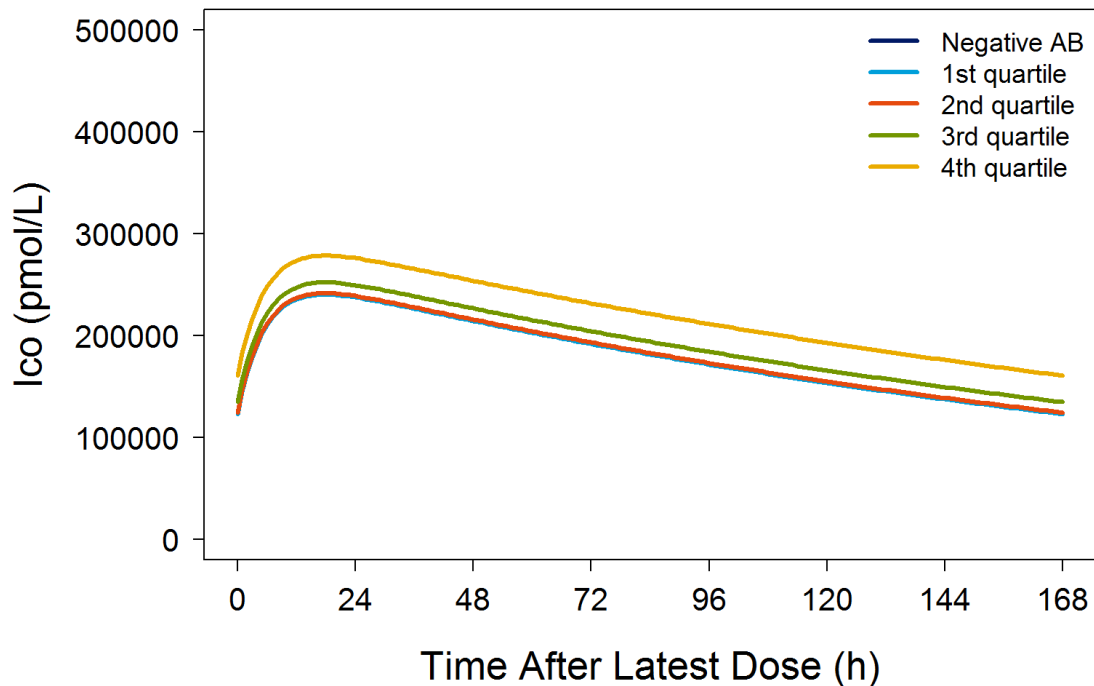
Figure 6. Model-derived concentration-time profiles from the population PK analysis by quartiles of peak anti-insulin icodec antibody titre Notes: Model-derived concentration time profiles corresponding to the median end-of-treatment dose for the subjects included in the population PK analysis. Abbreviations: h = hours.

In both study ONWARDS 3 (RoW) and study 4383, 13% of the ADA positive samples were also positive for neutralising antibodies. The majority of neutralising antibody positive samples had ADA titres in the 3rd or 4th quartile.

Target population

The PK in T1D and T2D population were evaluated in several clinical pharmacology studies and the results from non-compartmental analysis from all studies are presented in Table 2, Table 3, Table 4 and Table 5. In most of the studies individualised doses were administered and dose-adjusted AUC and Cmax were reported for comparison. No conclusion could be made regarding differences between the two populations from these data.

The population pharmacokinetic analysis included Type 1 and Type 2 patients and are thus relevant for describing the PK in the target population. The population PK model predicted that Type 1 patients had 16% (90%CI: 13-20%) higher exposure than Type 2 patients (Figure 3).

Variability between individuals was quantified in the population PK analysis where the inter-individual variability in CL/F was 19.5 %CV (Table 8).

Within-subject variability was evaluated in trial 4569 using individual, titrated doses in Caucasian subjects with T2D. Mean within-subject variability in exposure from week to week (measured as CV%) was assessed at steady state and the variability of the last three doses was 5.90% (N = 42) for total exposure and the CV% was 8.25% (N = 42) for maximum concentration.

The time to reach steady-state was 3-4 weeks in T2D and 2-3 weeks in T1D when initiating insulin icodec without a one-time additional dose. The time to steady state was comparable for trials 4314, 4569 and 4571 when using the same definition and method for estimation of clinical steady state.

Special populations

Sex, race and age were explored as covariates during the population PK analysis and were not identified to be clinically significant covariates (Figure 2).

Weight was tested as a covariate in the PopPK analysis where total body weight in the population PK dataset had a mean weight (SD) of 84.1 kg and ranged from 39.6-160.3 kg (Table 11). Weight was identified as both a statistically and clinically significant covariate for the PK of insulin icodec (included on CL/F and V/F). The model predicted that the insulin icodec exposure increased with increasing body weight (Figure 3).

Table 10. Number of subjects with PK observations in different age groups including elderly subjects

Trial	Age 18-64 years	Age 65-74 years	Age 75-84 years	Age >85 years	Total
Clinical pharmacology trials					
4314	50	0	0	0	50
4226	48	10	0	0	58
4225	66	0	0	0	66
4422	24	0	0	0	24
4462	33	10	0	0	43
4569	29	17	0	0	46
4570	20	5	0	0	25
4571	24	0	0	0	24
4572	16	9	0	0	25
Total	310	51	0	0	361
Phase 2 and 3 trials used for insulin icodec population PK analysis					
4383	83	39	1	0	123
4478	144	99	17	2	262
4479	207	73	10	0	290
4480	188	91	9	0	288
4625	266	19	3	0	288
Total	888	321	40	2	1251
Clinical pharmacology, and phase 2 and 3 trials used for insulin icodec population PK analysis					
Total	1198	372	40	2	1612

Renal impairment:

The pharmacokinetic properties of insulin icodec in subjects with various degrees of renal impairment (normal, mild, moderate, severe, ESRD) were investigated in a single-centre, open-label, parallel-group, single dose trial (study NN1436-4226). The PK results are presented in Table 11 and Figure 2. Total exposure (AUCico, 0-840h, SD) increased with impaired renal function, for moderate and severe impairment, total exposure was 22-26 % higher compared to subjects with normal renal function. For subjects with ESRD and mild impairment, total exposure was 11-12 % higher when comparing to subjects with normal renal function. Cmax for the subjects with impaired renal function was comparable to that of subjects with normal renal function.

Table 11. Pharmacokinetic endpoints for insulin icodec in subjects with different levels of renal impairment

Trial ID, report location, design	N (M/F) Race	Treatment and insulin icodec s.c. dose	AUC$_{Ico,0-168h,SD}$ Geom. mean (CV%) (pmol*h/L)	C$_{max,Ico,SD}$ Geom. mean (CV%) (pmol/L)	t$_{max,Ico,SD}$ Median (mean [SD]) (h)	t$_{½,Ico,SD}$ Geom. mean (CV%) (h)	MRT$_{Ico,SD}$ Geom. mean (CV%) (h)	CL/F$_{Ico,SD}$ Geom. mean (CV%) (mL/(h*kg))	Vz/F$_{Ico,SD}$ Geom. mean (CV%) (mL/kg)
4226, Trial 4226 (M 5.3.3.3), OL, PG, SD	58 (39/19) *Renal:* Normal: 12 Mild: 12 Moderate: 12 Severe: 12 ESRD: 10	Single doses. • 1.5 U/kg normal • 1.5 U/kg mild • 1.5 U/kg moderate • 1.5 U/kg severe • ESRD	17,390,878 (14.3) 19,888,308 (9.8) 21,366,414 (8.2) 19,857,044 (36.6) 18,590,836 (16.2)	84,704 (17.1) 90,707 (14.6) 91,100 (24.9) 76,893 (48.1) 80,426 (18.4)	15.0 (22.8 [18.6]) 15.0 (15.5 [1.7]) 21.0 (27.0 [16.9]) 21.1 (28.3 [16.5]) 18.1 (29.3 [26.0])	139.4 (11.2) 160.1 (9.0) 169.1 (7.6) 178.1 (18.6) 170.6 (9.0)	204.8 (10.4) 231.2 (6.8) 248.5 (9.6) 260.8 (17.2) 244.6 (8.5)	0.507 (14.2) 0.442 (9.8) 0.408 (8.2) 0.437 (36.8) 0.466 (15.6)	102 (8.7) 102 (9.4) 99 (9.9) 112 (45.1) 115 (16.5)

Notes: Full analysis set. **Abbreviations:** GFR = glomerular filtration rate, SD = single dose.

Figure 7. AUCIco vs. GFR for insulin icodec in subjects with different levels of renal impairment

A scatter plot of AUCI287,0-840h,SD versus albumin at baseline is provided in Figure 8. There was no obvious association between baseline albumin and AUCI287, 0-840h, SD in subjects from different renal function groups.
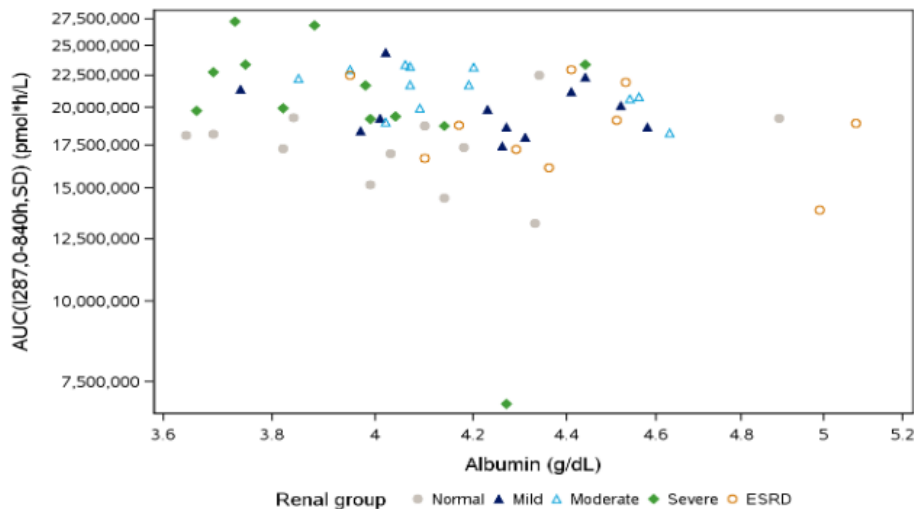
Figure 8. AUCI287,0-840h,SD against serum albumin at baseline - scatter plot - log scale – full analysis set

Hepatic impairment:

The pharmacokinetic properties of insulin icodec in subjects with various degrees of hepatic impairment (normal, mild, moderate, severe) were investigated in a two-centre, single-dose, open-label, parallel-group trial (study NN1436-4570). The PK results are presented in Table 12. Based on total concentrations, severe hepatic impairment did not affect the AUC or Cmax of insulin icodec. AUC and Cmax were slightly increased (13-15%) in subjects with mild and moderate hepatic impairment compared to subjects with normal hepatic function.

Table 12. Pharmacokinetic endpoints for insulin icodec in subjects with different levels of hepatic impairment

Trial ID, report location, design	N (M/F) Race	Treatment and insulin icodec s.c. dose	$AUC_{Ico,0-168h,SD}$ Geom. mean (CV%) (pmol*h/L)	$C_{max,Ico,SD}$ Geom. mean (CV%) (pmol/L)	$t_{max,Ico,SD}$ Median (mean [SD]) (h)	$t_{½,Ico,SD}$ Geom. mean (CV%) (h)	$MRT_{Ico,SD}$ Geom. mean (CV%) (h)	$CL/F_{Ico,SD}$ Geom. mean (CV%) (mL/(h*kg))	$Vz/F_{Ico,SD}$ Geom. mean (CV%) (mL/kg)
4570, Trial 4570 (M 5.3.3.3), OL, PG, SD	25 (12/13) *Hepatic:* Normal: 6 Mild: 6 Moderate: 6 Severe: 7	Single doses. • 1.5 U/kg normal • 1.5 U/kg mild • 1.5 U/kg moderate • 1.5 U/kg severe	16,871,624 (8.6) 18,084,678 (18.4) 18,676,172 (15.1) 15,695,274 (18.6)	78,614 (13.4) 82,632 (24.1) 80,417 (27.8) 73,230 (19.8)	22.5 (21.0 [5.0]) 17.9 (18.5 [5.2]) 25.5 (29.0 [16.2]) 27.0 (26.5 [7.2])	134 (12.3) 134 (7.1) 148 (14.5) 161 (6.8)	197 (10.6) 192 (5.7) 214 (14.9) 223 (8.3)	0.52 (9.5) 0.50 (20.4) 0.47 (14.8) 0.56 (17.3)	101 (12.0) 96 (14.3) 102 (22.9) 130 (19.6)

The serum albumin concentrations in subjects with severe hepatic impairment was generally lower than that of the other three groups at baseline. The mean measured serum albumin concentration at baseline was:

• Normal hepatic function: 4.25 g/dL
• Mild hepatic impairment: 4.06 g/dL
• Moderate hepatic impairment: 3.82 g/dL
• Severe hepatic impairment: 3.36 g/dL

A scatter plot of AUCIco,0-inf,SD versus serum albumin concentration at baseline is shown in Figure 9. There was no association between baseline albumin and AUCIco,0-inf,SD in subjects from different hepatic groups (0.286 [-0.102; 0.674]95%CI, p-value = 0.1389).
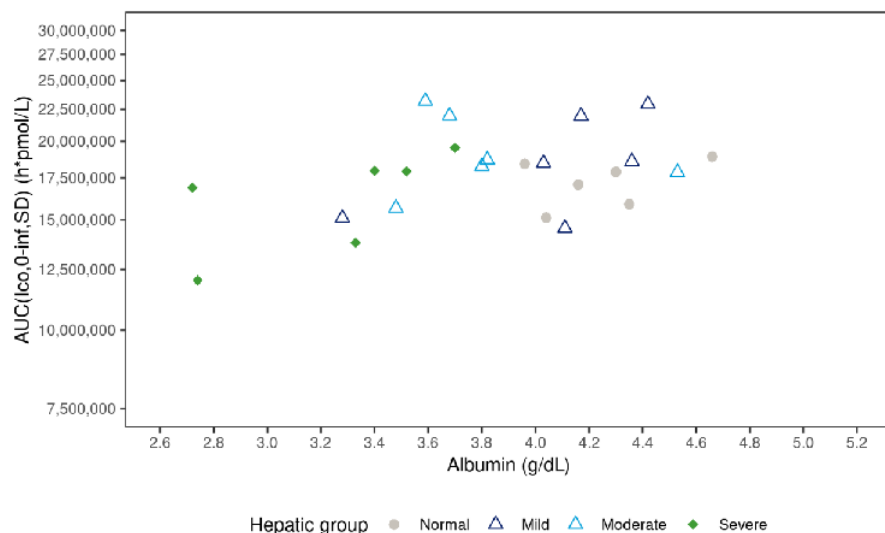
Figure 9. AUCIco, 0-inf, SD against serum albumin at baseline - scatter plot - semi-log scale - full analysis set

Pharmacokinetic interaction studies

Insulin icodec is primarily metabolised by proteolytic degradation. Further, insulins are generally not described as inhibitors or inducers of human CYP enzymes and there is no indication that insulin icodec will interact with CYP enzymes. No CYP enzyme inhibition or induction (*in vitro* or *in vivo*) studies were submitted.

Based on results from *in vitro* displacement experiments using palmitate it may be concluded that there is a low likelihood that free fatty acids binding to albumin will affect the binding of insulin icodec to HSA. The potential of insulin icodec to competitively displace albumin-bound drugs and the propensity of being displaced are considered to be very low as the concentration of insulin icodec is significantly lower in human plasma (<1300 nM, with an average of 266 nM) compared to the albumin concentration (600 µM)). The theoretical argument, in addition to the study performed, points towards the fact that protein binding interactions are unlikely for insulin icodec.

2.6.2.2. Pharmacodynamics

Insulin icodec is a novel long-acting insulin analogue developed to cover the basal insulin requirements for a full week with a once-weekly subcutaneous (s.c.) injection. Insulin icodec is intended for treatment of diabetes mellitus in adults.

Mechanism of action

Insulin icodec is a modified insulin that binds to the insulin receptor and results in the same pharmacological effect as insulin. A slow and steady glucose-lowering effect of insulin icodec is driven by albumin binding as well as reduced insulin receptor binding and clearance. The extended half-life of insulin icodec reflects a depot of insulin icodec in the circulation and in the interstitial compartment, from which insulin icodec is slowly and continuously released and binds specifically to the insulin receptor.

There was no obvious association between serum albumin and AUC in subjects with different degrees of renal or hepatic impairment, respectively.

Primary and secondary pharmacology

The development programme investigating the pharmacodynamic profile of insulin icodec is in general considered adequate. The trials investigating PD properties were trial 4314 (euglycaemic clamp, 3 fixed dose levels), trial 4569 (euglycaemic clamp), trial 4572 (euglycaemic clamp; different injection regions) and trial 4462 (hypoglycaemic clamp) in T2DM subjects and trial 4225 (euglycaemic clamp) and trial 4422 (euglycaemic clamp; Japanese population) in T1DM subjects (Table 13).

Table 13. Overview of trials in the clinical pharmacology programme investigating the pharmacodynamic profile

Trial ID	Population	Trial design	Dosing	Comparator
4314	T2D Caucasian	RND, DB, MD	Fixed dose	IDeg
4569	T2D Caucasian	OL, MD	Individualised	-
4462	T2D Caucasian	RND, OL, CO, MD	Individualised	IGlar
4572	T2D Caucasian	RND, OL, CO, SD	Fixed dose	-
4225	T1D Caucasian	RND, OL, CO, MD	Individualised	IGlar
4422	T1D Japanese	RND, OL, CO, MD	Individualised	IGlar

CO = crossover; DB = double blinded; IDeg = insulin degludec; IGlar = insulin glargine; MD = multiple dose; OL = open label;

PG = parallel group; RND = randomised; SD = single dose; T1D = type 1 diabetes; T2D = type 2 diabetes.

The partial glucose-lowering effect of insulin icodec was evaluated using euglycaemic clamps. In trials 4314, 4569, 4225, and 4422, standard glucose infusion rate endpoints were derived from glucose infusion rate profiles obtained following dosing at steady state with insulin icodec. Twenty-four-hour clamps, hence covering the total daily dosing interval, were made for the once-daily comparator arm in trials 4225, 4422, and 4314. In trial 4569, two 24-hour clamps and one 36-hour clamp were conducted.

Besides euglycaemic clamps carried out to evaluate glucose lowering effect of insulin icodec across the entire once-weekly dosing interval, clamps were performed in trial 4572 to evaluate whether injection region affected pharmacodynamic properties of insulin icodec. In trial 4572, three euglycaemic clamps per subject were carried out; one per s.c. injection region. Clamps were carried out during the period where maximal glucose-lowering effect was expected (36-60 hours after dosing).

The predefined clamp target was 5.5 mmol/L in trial 4314 (T2DM subjects), 7.7 mmol/L in trials 4569 and 4572 (T2DM subjects) and 6.7 mmol/L in trial 4225 and 4422 (T1DM subjects) (Table 14).

Table 14. Overview of euglycaemic clamps

Trial	Population	Clamp type	Clamp target
4569	T2D	Manual	7.5 mmol/L (135 mg/dL)
4314	T2D	ClampArt	5.5 mmol/L (100 mg/dL)
4572	T2D	ClampArt	7.5 mmol/L (135 mg/dL)
4225	T1D	ClampArt	6.7 mmol/L (120 mg/dL)
4422	T1D	STG-55	6.7 mmol/L (120 mg/dL)

In multiple-dose trials with euglycaemic clamps (trials 4314, 4569, 4225, and 4422), model-based interpolation was applied to obtain GIR profiles covering a full week at steady-state. Using the serum insulin icodec concentration data and the GIR data from the trials, PK-PD models were developed, and interpolation was performed to obtain an individual full-week steady-state GIR profile for each subject by using the post-hoc estimates of the model parameters for the individual subjects.

The hypoglycaemia frequency and the counter-regulatory response to controlled hypoglycaemia induced by insulin icodec and insulin glargine after multiple doses in subjects with T2DM was investigated using a hypoglycaemic glucose clamp in trial 4462.

Steady-State Pharmacodynamic Properties

The steady-state pharmacodynamic properties of insulin icodec in subjects with T2DM were investigated in trials 4569 and 4314.

Subjects with type 2 diabetes

Trial 4569

Trial 4569 was a single-centre, open-label, multiple-dose trial with no comparator. The total trial duration of the individual subjects participating in the trial was 17 weeks and included a 3-week screening period, a 1-week run-in period with once daily insulin degludec and an 8-week treatment period with once-weekly insulin icodec. Mean dose at steady state was 2.9 U/kg/week (range: 1.5-5.6 U/kg/week). Pharmacodynamic properties were investigated during 3 euglycaemic clamps (target 7.5 mmol/L) during steady state covering 3.5 of the 7 days dosing interval: 1) 36-hour clamp conducted 0-36 hours after insulin icodec dose, 2) 24-hour clamp conducted 40-64 hours after insulin icodec dose and 3) 24-hour clamp conducted 144-168 hours after insulin icodec dose.

Glucose-lowering effect

Glucose-lowering effect was evaluated where subjects were individually titrated with insulin icodec. The GIR profiles for all three clamps together with the model-derived data for a full week in shown in Figure 10. The model-based approach used to derive the predictions is described below under "*Relationship between plasma concentration and effect*". Median time to GIR_{max} was 46.5 hours for insulin icodec.

Figure 10. Full-week mean steady-state glucose infusion rate (GIR) profile for insulin icodec in subjects with T2DM (PK/PD modelling)
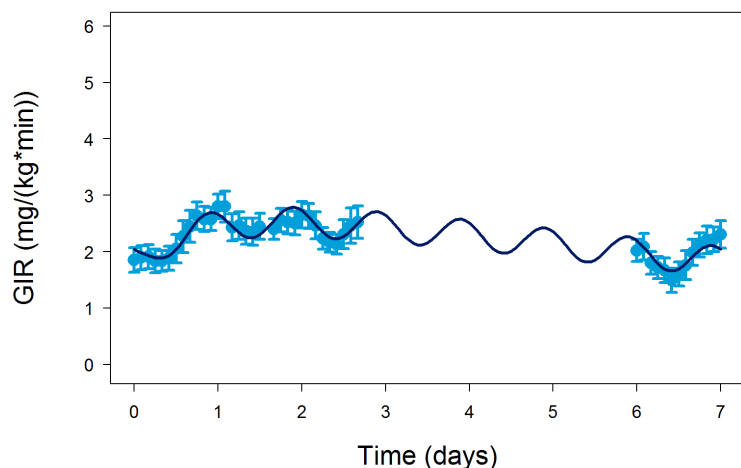
Points and error bars are mean and 95% confidence interval of individual GIR profiles (pooled across the three steady-state weeks). Line is mean of individual model-predicted GIR profiles (for one steady-state week).

The glucose-lowering effect of insulin icodec seems to be distributed fairly evenly within the dosing interval of one week. The applicant argues that the fluctuations in GIR are most likely due to diurnal variation in insulin sensitivity with a decreased insulin sensitivity during night, leading to less glucose-lowering effect overnight.

Duration of action

Blood glucose profiles during the clamp covering the last 24 hours of the weekly dosing interval in trial 4569 could be kept at target and no escapes were observed in the end of the clamp period. Duration of action in T2DM patients implies to be extended beyond 168 hours for insulin icodec. Mean individual blood glucose profiles showed blood glucose values evenly distributed above and below the clamp target of 7.5 mmol/L (Figure 11).

Figure 11. Individual blood glucose profiles during steady state during last 24-hours period of a dosing interval (144-168 hours after dosing) in Caucasian subjects with T2DM
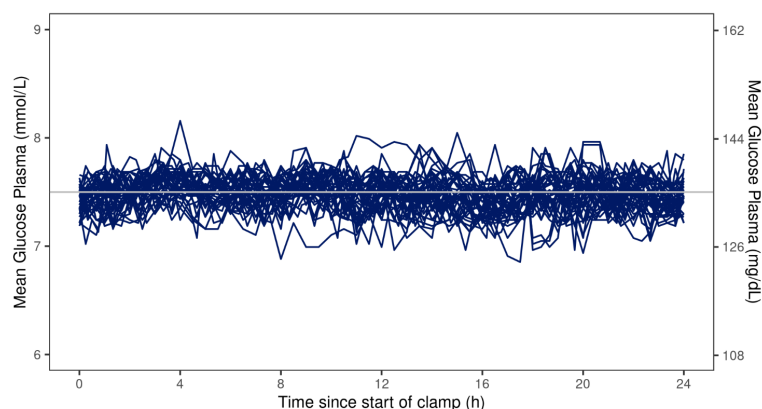
Trial 4314

Trial 4314 was a randomised, double-blind (within cohort), double-dummy, multiple-dose, active-controlled trial. Insulin degludec was used as a comparator. The main trial objective was to investigate safety of insulin

icodec. The secondary objectives were to evaluate insulin icodec PK and PD properties. Frequent BG measurements were carried out throughout the trial period as a safety precaution. Clamp target level of 5.5 mmol/L (100 mg/dL ±20 %). The following 3 dose levels of insulin icodec were planned to be investigated: 12, 20 and 28 nmol/kg; however, the dose for cohort 3 was reduced to 24 nmol/kg as it could not be ruled out that the planned dose of 28 nmol/kg would be too high for some individuals. The treatment period lasted for 5 weeks (35 days). The steady state PD response was assessed during two 24-hour euglycaemic glucose clamps after dosing on day 30 and on day 35.

Glucose-lowering effect

The 24-hour mean smoothed GIR profiles for insulin icodec and insulin degludec on day 2 (day 30) and day 7 (day 35) of the dosing interval are depicted in Figure 12. The observed mean GIR response at steady state increased for insulin icodec with 20 nmol/kg and 24 nmol/kg compared to 12 nmol/kg insulin icodec. The mean smoothed GIR profiles from 4314 did not show a dose-response. Based on the mean 24-hour profiles for day 30 and day 35, the mean glucose infusion rate showed highest response at 20 nmol/kg dose. Because of recruitment challenges, the eligibility criteria were updated to allow subjects on insulin therapy in combination with metformin to participate in the trial. Of the 9 subjects with metformin as concomitant medication, 7 subjects were in the insulin icodec (24 nmol/kg) group, and 2 subjects were in the insulin degludec group. Thus, the difference in the inclusion criteria between cohorts led to differences in the trial populations, with subjects being likely more insulin resistant in the high-dose cohort (24 nmol/kg dose – 4.0 U/kg/week) compared to the middle-dose cohort (20 nmol/kg dose –3.3 U/kg/week). Because of these issues in trial 4314, trial 4569 was performed in parallel with the phase 3 programme to generate PK and PD data for insulin icodec in T2DM at steady state using individualised doses. In conclusion, no safety issues were identified in trial 4314.

Figure 12. PD - GIR, smoothed - mean profiles – insulin icodec and IDeg - day 30 and day 35 – full analysis set
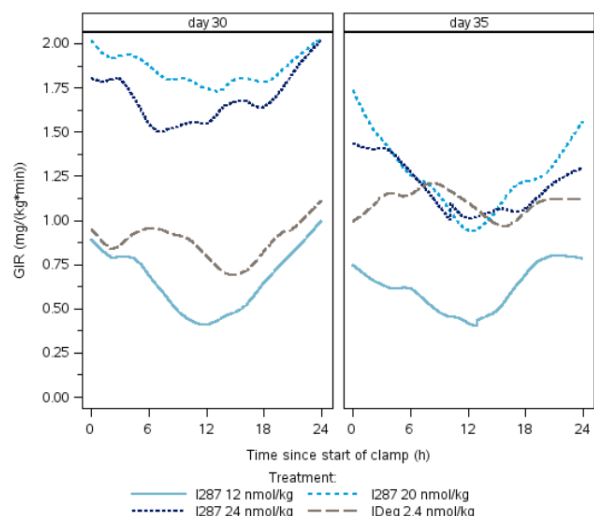
Subjects with type 1 diabetes

Trial 4225

The steady-state pharmacodynamic properties of insulin icodec in Caucasian subjects with T1DM were investigated in trial 4225. The trial was a single-centre, randomised, 2-period crossover, open-label, multiple-dose trial evaluating insulin icodec administered once-weekly for eight weeks (mean dose for sufficiently-dosed subjects: 2.0 U/kg/week; range 1.2-3.2 U/kg/week) and insulin glargine administered once-daily for two weeks (mean dose for sufficiently-dosed subjects: 0.29 U/kg/day; range 0.2-0.5 U/kg/day). The individual doses were optimised during a run-in period where the basal insulin dose for each subject was titrated to achieve pre-breakfast SMPG within glycaemic target of 4.4-7.2 mmol/L (80-130 mg/dL). The partial pharmacodynamic properties of insulin icodec were measured in 2 euglycaemic clamps (6.7 mmol/L [120 mg/dL]) during steady state covering more than 2 days of the 7 days dosing interval: 1) 36-hour clamp conducted 16-52 hours after insulin icodec dose and 2) 30-hour clamp conducted 138-168 hours after insulin icodec dose. The first clamp covered the expected maximum glucose-lowering period, while the second clamp included the end of the dosing interval thus evaluating duration of action.

Glucose-lowering effect

The glucose-lowering effect of insulin icodec across the one-week dosing interval was assessed by pharmacodynamic modelling. GIR profiles for both clamps together with the model-derived data for a full week in shown in Figure 13. The model-based approach used to derive the predictions is described below under "*Relationship between plasma concentration and effect*". Median time to GIR_{max} was 46 hours for insulin icodec.

Figure 13. Full-week mean steady-state GIR profile for insulin icodec in Caucasian subjects with T1DM (PK/PD modelling)
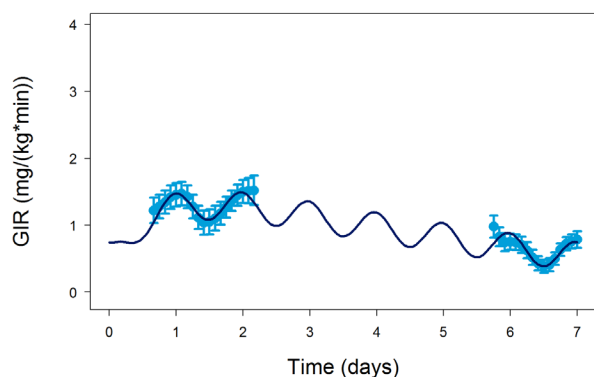

Includes sufficiently-dosed subjects. Line is mean of individual model-predicted GIR profiles. Points and error bars are mean and 95% confidence interval of individual smoothed GIR profiles.

As for T2DM subjects, the fluctuations in GIR for T1DM subjects are most likely due to diurnal variation in insulin sensitivity with a decreased insulin sensitivity during night. The PD profile obtained in T1DM subjects differs slightly compared to the PD profile observed in T2DM subjects. In T1DM subjects, the glucose-lowering effect of insulin icodec was distributed less evenly within the dosing interval of one week.

Duration of action

During review of the clamp profiles, it became clear that some of the T1DM subjects did not meet the predefined clamp conditions in one or more of the clamps. According to the study report, 15 subjects (23%;

15/64) were insufficiently dosed and did not meet the predefined clamp conditions. Data only from sufficiently dosed T1DM subjects was presented.

Molar dose ratio

The molar dose ratio was estimated to be 1.03 [0.74; 1.44]$_{95\%CI}$ in Caucasian T2DM subjects, thus similar glucose-lowering effect of insulin icodec and insulin degludec was obtained when the two products were administered at identical molar doses. The molar dose ratio was estimated to be slightly higher (1.19 [1.00; 1.43]$_{95\%CI}$) when comparing the glucose-lowering effect of insulin icodec with insulin degludec in T1DM subjects. However, in general insulin icodec could be considered to be equipotent to both insulin glargine and insulin icodec.

Injection regions

Subcutaneous injections in thigh, abdomen, or upper arm

Trial 4572

The glucose-lowering effect of insulin icodec when injected s.c. in different regions of the body was investigated in trial 4572. The trial was a single-centre, randomised, open-label, three-period cross-over trial. To measure the glucose-lowering effect of insulin icodec when administered s.c. in thigh, abdomen, and upper arm in subjects with T2DM, a euglycaemic clamp was performed (clamp target: 7.5 mmol/L [135 mg/dL]). The partial glucose-lowering effect (measured as GIR) was measured from 36 to 60 hours after dosing covering the expected maximum glucose-lowering period (Figure 14).

Figure 14. Smoothed mean GIR profiles for different injection regions in Caucasian subjects with T2DM
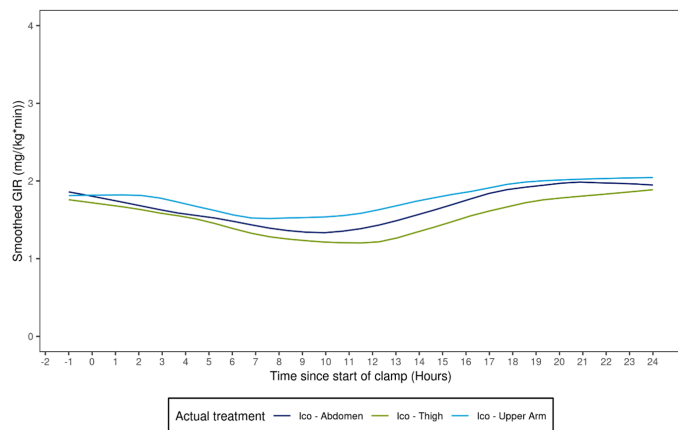
Descriptive statistics for GIR measured 36-60 hours after a single s.c. dose of insulin icodec into the thigh, abdomen and upper are presented in Table 15.

Table 15. Insulin icodec PD endpoints – summary – full analysis set

	Ico - Abdomen	Ico - Upper Arm	Ico - Thigh
Number of profiles	23	22	22
AUCGIR(36-60h,SD) (mg/kg)			
N	23	22	22
Geometric mean (CV%)	2,130 (51.6)	2,391 (39.6)	1,961 (51.3)
Median	1,896	2,484	1,899
Min ; Max	806 ; 5,922	907 ; 5,212	521 ; 5,679

Total exposure of insulin icodec after a single dose (AUCIco,0-inf,SD - primary endpoint) was comparable across injection regions (Table 16).

Table 16. Insulin icodec primary endpoint AUCIco,0-inf,SD – statistical analysis – full analysis set

	FAS	N	Estimate	95% CI	p-value
AUC(Ico,0-inf,SD) (h*pmol/L)					
Geometric mean (LSMean)					
Ico - Abdomen	24	24	69,854,393		
Ico - Upper Arm	24	23	70,965,451		
Ico - Thigh	23	23	68,335,757		
Injection region ratio					
Abdomen/Thigh			1.02	[0.96 ; 1.09]	0.4729
Upper arm/Thigh			1.04	[0.98 ; 1.10]	0.1621
Abdomen/Upper arm			0.98	[0.93 ; 1.05]	0.6103

Maximum concentrations after single dose and for predicted steady state (Cmax, Ico, SD and Cmax, Ico, SS, model) were higher in abdomen and upper arm compared to thigh. The estimated injection region ratios were:

- Abdomen/thigh:
  single dose 1.17 [1.07; 1.29]95%CI, p-value = 0.0016
  steady state 1.11 [1.03; 1.19]95%CI, p-value = 0.0035

- Upper arm/thigh:
  single dose 1.24 [1.14; 1.35]95%CI, p-value = <0.0001
  steady state 1.16 [1.10; 1.23]95%CI, p-value = <0.0001

- Abdomen/upper arm:
  single dose 0.94 [0.86; 1.03]95%CI, p-value = 0.2051
  steady state 0.95 [0.89; 1.02]95%CI, p-value = 0.2439

The differences in predicted maximum insulin icodec concentrations between abdomen/thigh and upper arm/thigh at steady state were lower than the difference shown in maximum insulin icodec concentration after single-dose administration, indicating that the observed differences are not clinically relevant.

Hypoglycaemia frequency and response in subjects with type 2 diabetes

Trial 4462

Trial 4462 was a randomised, single-centre, open-label, two-period cross-over multiple dose trial in subjects with T2DM. Subjects started with a run-in period of 3-28 days on once-daily insulin glargine to establish and optimise the individual basal insulin glargine dose (SMPG target: 4.4-7.2 mmol/L [80-130 mg/dL]). At steady state, double and triple doses of insulin icodec or insulin glargine were administered, and hypoglycaemia was

induced 44 hours (insulin icodec) or 7 hours (insulin glargine) after dosing. This corresponded to the expected time of maximum glucose-lowering effect for each insulin.

Hypoglycaemia frequency

The proportion of individuals that experienced clinically significant hypoglycaemia (PG_{nadir}<3.0 mmol/L [<54 mg/dL]) was 39.5% vs. 35.7% for insulin icodec vs. insulin glargine following double dose and 52.6% vs. 70.0% for insulin icodec vs. insulin glargine following triple dose. The proportion of individuals with PG_{nadir}≤2.5 mmol/L (≤45 mg/dL) after double dose was 4.7% vs. 7.1% for insulin icodec vs. insulin glargine and 2.6% vs. 25.0% for insulin icodec vs. insulin glargine after triple dose (Figure 15).

Figure 15. Proportion of individuals with clinically significant hypoglycaemia after double and triple dose
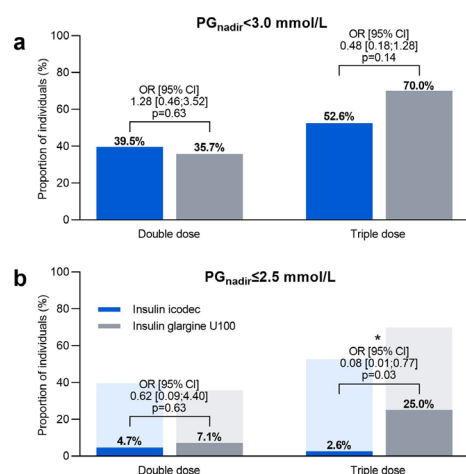
Recovery from hypoglycaemia

During recovery from hypoglycaemia at a constant glucose infusion rate of 5.5 mg kg^{-1} min^{-1}, it took on average 29 min and required on average 111-139 mg/kg of glucose to restore PG from PG nadir to 5.5 mmol/L (100 mg/dL) for insulin icodec compared to 22 min and required on average 115-116 mg/kg of glucose to restore PG from PG nadir to 5.5 mmol/L for insulin glargine. Slightly more plasma glucose was needed to increase plasma glucose from nadir to 5.5 mmol/l for insulin icodec (139 mg/kg) compared to insulin glargine (111 mg/kg) for the second dose, but the amount of glucose needed to recover from PG nadir was comparable for insulin icodec (116 mg/kg) and insulin glargine (115 mg/kg) for the triple dose. However, it is difficult to compare groups regarding the need for glucose administration as the safety monitoring/observation period was different for insulin icodec and insulin glargine, in relation to time of dosing.

Double and triple doses of once-weekly insulin icodec did not lead to an apparent increased risk of clinically significant hypoglycaemia compared with once-daily insulin glargine. Time to recover from hypoglycaemia (to restore PG from PG nadir to 5.5 mmol/L) was slightly longer for insulin icodec (29 min) compared with insulin glargine (22 min). During the safety monitoring period, rapidly absorbable carbohydrate or iv glucose was administered if the PG concentration declined to <4.4 mmol/L in the period after insulin glargine or insulin icodec overdosing.

In trial 4462, the hypoglycaemic clamp was performed in T2DM subjects to investigate the counter-regulatory response to controlled hypoglycaemia induced by insulin icodec or insulin glargine. There was a greater increase in the counter-regulatory hormone response with insulin icodec compared to insulin glargine for

adrenaline, the most important counter-regulatory hormone, following a triple dose at PG 3.0 mmol/L (2.54 [1.69; 3.82]). In addition, cortisol concentration was greater at PG mmol/L (2.54 [1.69; 3.82]) and at PG nadir (1.80[1.09; 2.97]) following a triple dose.

<u>Genetic differences in PD response</u>

Data does not indicate any obvious clinically relevant differences between Japanese and Caucasian subjects. However, the PD profile for insulin icodec in Japanese and Caucasian subjects should be interpreted with caution since this is a comparison between trials using different techniques.

Relationship between plasma concentration and effect

Exposure-response relationships were explored for GIR using model-based exposure-response analyses for Type 1 and Type 2 diabetes patients in studies 4225 (Type 1 diabetes patients) and 4569 (Type 2 diabetes patients), respectively. The objective was to evaluate the glucose-lowering effect of insulin icodec over a full week at steady-state in Type 1 and 2 patients in studies 4225 and 4569.

For study 4225, GIR data were obtained from the 36-hour and 30-hour euglycaemic clamps performed at steady-state. The analysis included 3430 PK observations from 65 subjects and 6505 PD observations from 49 subjects.

For study 4569, obtained in the three euglycaemic clamps performed at steady-state the analysis included 2269 PK observations from 46 subjects and 7011 PD observations from 42 subjects.

Similar methodology was used to evaluate the exposure-response relationship in GIR for studies 4225 and 4569. A sequential population PK-PD modelling approach was applied, where the serum insulin icodec concentration data was first used to develop a PK model, which was used to assess the approach to steady-state. The models were evaluated using standard diagnostic plots including visual predictive checks (VPCs).

Trial 4225

The structural part of the final PK model was a one-compartment model with first-order absorption and first-order elimination (Table 17). A VPC for the final Study 4225 PK model is shown in Figure 16.

Table 17. Parameter estimates from the final Study 4225 PK model

Parameter	Estimate	CI95.lower	CI95.upper	pct.RSE	IIV.pct.CV	Shrinkage.pct
KA [1/h]	0.186	0.162	0.209	6.54	54.7	1.76
CL/F [L/h/kg]	0.000494	0.000472	0.000516	2.26	19	0.0000000001
V/F [L/kg]	0.113	0.109	0.117	1.7	13.2	2.14
Antibody status on CL/F (Negative/Positive)	1.01	0.956	1.07	2.86		
Exponent for effect of antibody titre on CL/F (for antibody positive)	-0.0758	-0.128	-0.0235	35.2		
Add. Error [pmol/L]	3140					2.72
Prop. Error [% CV]	10.6					2.72
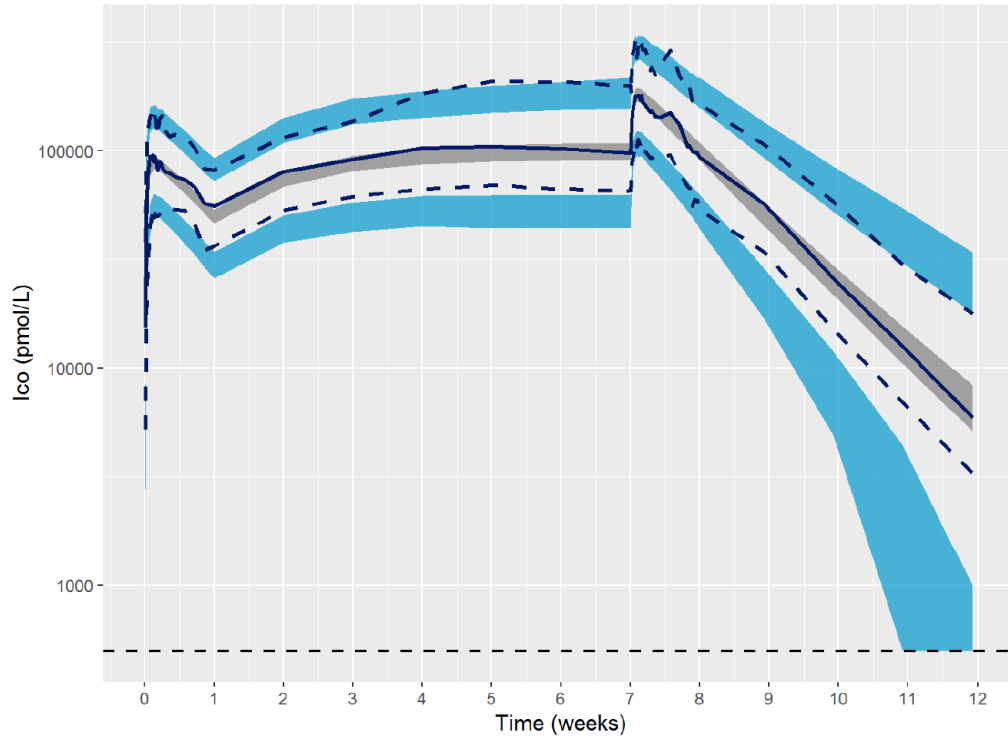
08-okt-2020 15:15 E:/Project/NN1436/NN1436-4225/current/Scripts/05_PK_ModelEvaluation_VPC.R

Data are observed values (lines) and 95% CIs (shaded areas, n=1000) of simulated values for the median and the 5th and 95th concentration percentiles versus time.

Figure 16. Visual predictive check for the final Study 4225 PK model

The structural part of the final PD model consisted of an effect compartment for insulin action turnover, and a direct link between insulin action and GIR, and it was parameterised in terms of a turnover parameter (p2) and an insulin sensitivity parameter (SI). Diurnal variation in GIR was modelled by an additive sinusoidal term with a fixed period of 24 hours, parameterised in terms of an amplitude parameter (AMP) and a phase shift parameter (PHASE). Finally, a threshold parameter (THRESH) was introduced to reflect that, in a euglycaemic clamp setting in subjects with type 1 diabetes, the insulin action that is needed to keep blood glucose at the clamp target is not measurable as a GIR>0. The parameters of the final PD model are shown in Table 18. A VPC of the final PD model is shown in Figure 16.

Table 18. Parameter estimates from the final Study 4225 PD model

Parameter	Estimate	CI95.lower	CI95.upper	pct.RSE	IIV.pct.CV	Shrinkage.pct
P2 [1/h]	0.119	0.0928	0.145	11.3	224	14
SI [(mg/kg/min)/nM]	0.0116	0.0104	0.0127	5.15	24.9	0.0000000001
AMP [mg/kg/min]	0.238	0.207	0.27	6.72	43.5	5.26
PHASE	1.73	1.55	1.92	5.51	77.9	0.17
THRESH [mg/kg/min]	0.726	0.634	0.819	6.47		
Add. Error [mg/kg/min]	0.193					1.36

Data are observed values (lines) and 95% CIs (shaded areas, n=1000) of simulated values for the median and the 5th and 95th smoothed GIR percentiles versus time.

Figure 17. Visual predictive check of the final Study 4225 PD model

Using the individual PK and PD parameters, interpolation was performed to obtain an individual full-week steady-state GIR profile for each subject. Using these profiles, a mean full-week steady-state GIR profile was plotted in Figure 12.

Trial 4569

The structural part of the final PK model was a one-compartment model with first-order absorption and first-order elimination (Table 19). A VPC of the final Study 4569 model is shown in Figure 18.

Table 19. Parameter estimates from the final Study 4569 PK model

Parameter	Estimate	CI95.lower	CI95.upper	pct.RSE	IIV.pct.CV	Shrinkage.pct
KA [1/h]	0.207	0.184	0.23	5.75	38.6	3.66
CL/F [L/h/kg]	0.000489	0.000462	0.000516	2.83	16.6	0.0000000001
V/F [L/kg]	0.117	0.11	0.123	2.96	19.7	0.158
Antibody status on CL/F (Negative/Positive)	1.13	1.07	1.19	2.74		
Exponent for effect of antibody titre on CL/F (for antibody positive)	-0.0369	-0.0583	-0.0155	29.6		
Add. Error [pmol/L]	3420					2.89
Prop. Error [% CV]	10.1					2.89
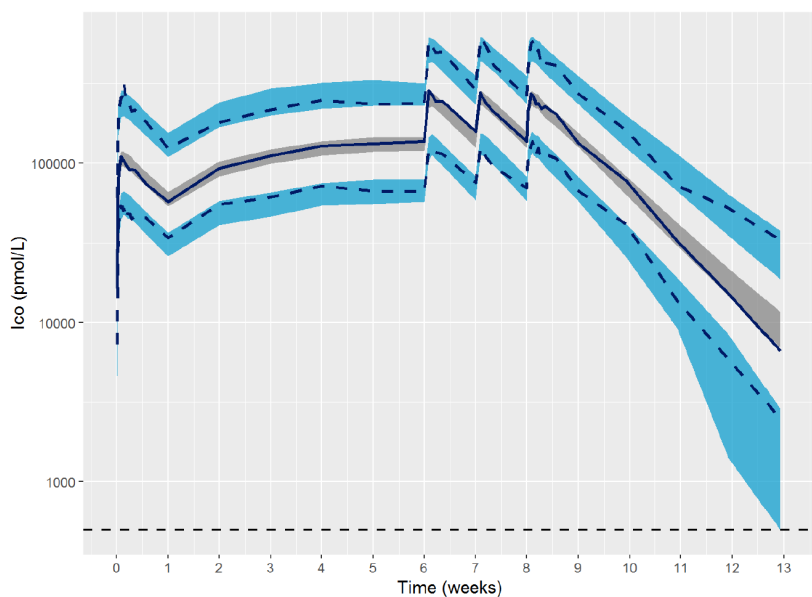
Data are observed values (lines) and 95% CIs (shaded areas, n=1000) of simulated values for the median and the 5th and 95th concentration percentiles versus time.

Figure 18. Visual predictive check for the final Study 4569 PK model

The structural part of the final PD model consisted of an effect compartment for insulin action turnover, and a direct link between insulin action and GIR, and it was parameterised in terms of a turnover parameter (p2) and an insulin sensitivity parameter (SI). Diurnal variation in GIR was modelled by an additive sinusoidal term with a fixed period of 24 hours, parameterised in terms of an amplitude parameter (AMP) and a phase shift parameter (PHASE). The parameters of the final PD model are shown in Table 20. A VPC for the final Study 4569 model is shown in Figure 19.

Table 20. Parameter estimates from the final Study 4569 PD model

Parameter	Estimate	CI95.lower	CI95.upper	pct.RSE	IIV.pct.CV	Shrinkage.pct
P2 [1/h]	0.0585	0.0326	0.0844	22.6	453	6.7
SI [(mg/kg/min)/nM]	0.0108	0.00873	0.013	9.97	61.3	0.0000000001
AMP [mg/kg/min]	0.27	0.223	0.317	8.86	55.5	10.2
PHASE	2.13	1.91	2.35	5.28	77.9	1.21
Add. Error [mg/kg/min]	0.413					1.08
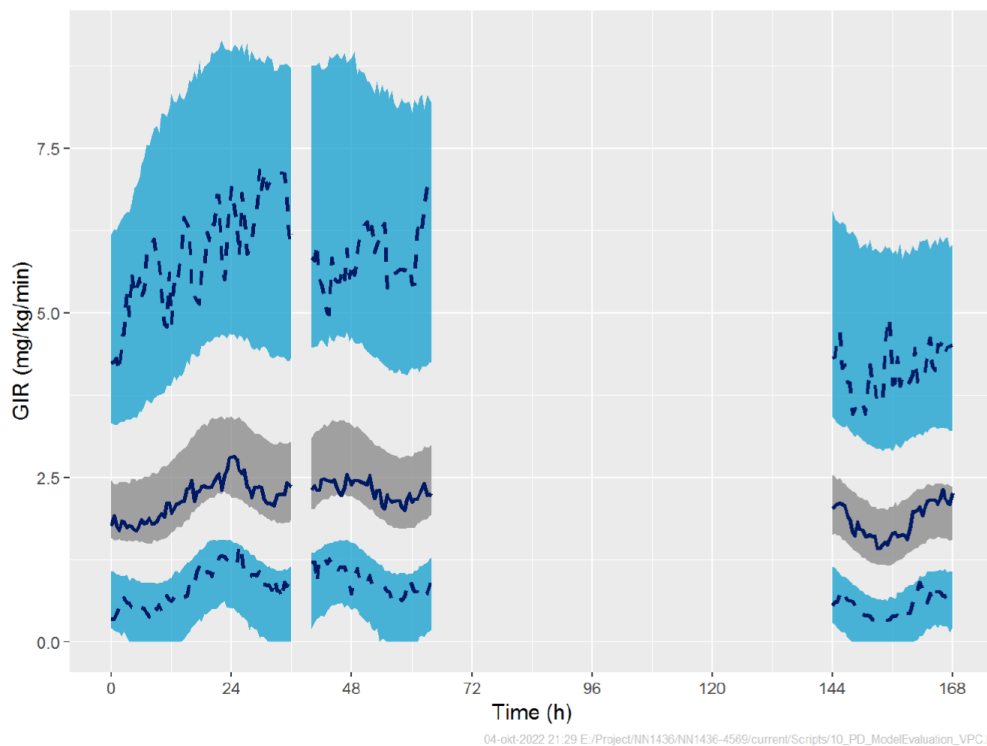
04-okt-2022 21:29 E:/Project/NN1436/NN1436-4569/current/Scripts/10_PD_ModelEvaluation_VPC.R

Data are observed values (lines) and 95% CIs (shaded areas, n=1000) of simulated values for the median and the 5th and 95th GIR percentiles versus time.

Figure 19. Visual predictive check for the final Study 4569 PD model

The predicted interpolation of the GIR profile where no data were available are shown as a mean full-week steady-state GIR profile in Figure 19.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Methods

Bioanalysis

The bioanalytical methods were addressed in the CHMP scientific advice EMA/CHMP/SAWP/302624/2018. Most points raised were addressed by the applicant in the validation. An issue that was insufficiently addressed is whether the same batches of reference standard/critical reagents were used in validation and study sample analysis. The applicant clarified that every new batch of critical reagents was qualified before use.
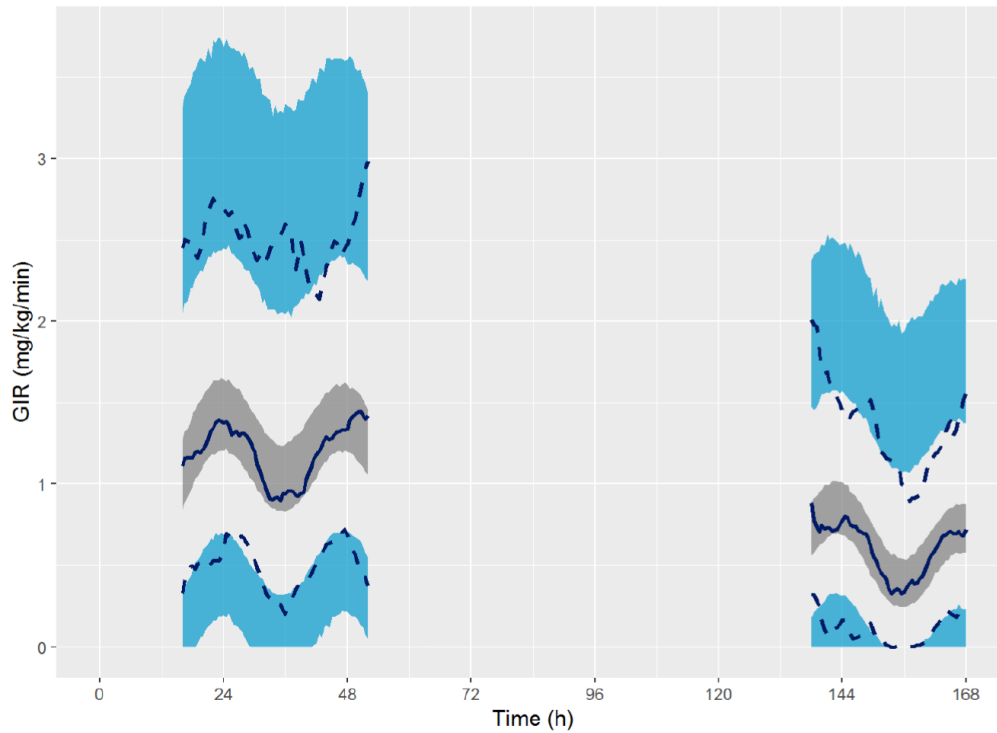
Only the two amendments to the validation report 321497 400098-202993-PMV at the Chinese site were included in the dossier, with the initial validation missing. Based on the summaries, the methods seem validated, including a cross-validation and parallelism. The applicant provided the missing validation report, and clarified that the amendment 01, included in the initial submission, was indeed the initial validation, after correction of an error not taking into account purity. The method is thus adequately validated.

Validation of all methods with available validation reports was performed following current guidelines and shows that the methods are adequately validated, including cross-validation between the methods. Study sample analysis was adequate.

Immunogenicity

There are multiple issues with the Novo Nordisk assay for ADAs, starting with a low sensitivity, compared to the currently required 100 ng/mL. It could thus be considered that positive ADA samples in study 4314 are reliable, however, a proportion of the negative ADA samples would likely result in a positive signal if measured in the assays at the sites in Switzerland and China. Due to the difference in sensitivity, results should not directly be compared to other studies.

The lack of data on the neutralising potential has been addressed in CHMP scientific advice EMA/CHMP/SAWP/302624/2018 and EMA/CHMP/SAWP/221272/2020. It was deemed acceptable if positive antibodies did not affect relevant PK, efficacy and safety tests. High titre ADA have an effect on PK. Additionally, the incidence of ADAs, both against insulin icodec and cross reactive against human insulin is high, thus it would have been relevant to characterise the neutralising potential of the ADAs, based on the received scientific advice. During the procedure, the applicant provided data on the neutralisation potential of anti-insulin icodec antibodies, showing that 13% of ADA positive subjects had neutralising antibodies.

The assays used in case of hypersensitivity are considered fit for purpose.

The ADA methods at the Swiss and Chinese sites were adequately validated following current guidelines and white papers. The selection of cut points in the validation and study sample analysis were adequate. Drug tolerance in the screening assay was sufficient for use in clinical studies, were steady state concentrations were generally between 200 and 300 nM and Cmax up to 500 nM, thus well below the limit of 1000 nM for 100 ng/mL of positive control. The extent of drug tolerance testing was higher in the validation at the

Chinese site, where drug tolerance was tested also for the confirmation assay. There, for 100 ng/mL of positive control, 283 nM of insulin icodec were tolerated, which could result in some samples with low ADA levels being wrongly confirmed negative.

It was unclear if the drug tolerance at confirmation is similar in the ADA method at the Swiss site that was used for the majority of studies, in particular considering that the insulin icodec concentration in the confirmation assay was changed in the add-on validation. The applicant reviewed the insulin icodec concentration in the ADA samples, both in a by subject and by sample level. It is agreed that the by patient level is most relevant. On a sample level, 4.51% of samples had concentrations higher than 283 nM insulin icodec (the established drug tolerance limit in the confirmation assay at the Chinese site) and were found ADA negative either at screening or confirmation. On a subject level, 3 subjects had samples with concentrations >283 nM insulin icodec, with one previously identified as ADA positive. Thus there were only two subjects (0.21%) that should be considered inconclusive. Overall, it is agreed that these results are unlikely to affect the general conclusions on immunogenicity induced by insulin icodec, which is high.

Absorption

Subcutaneous single dose administration of insulin icodec in the thigh, the abdomen and the upper arm in study NN1436-4572 resulted in comparable total exposure ($AUC_{Ico,0-inf}$) across injection sites. The maximum concentration of insulin icodec was slightly higher after administration in the abdomen and the upper arm compared to the thigh, with a ratio of 1.17 and 1.24, respectively. The slightly higher Cmax is not considered clinically relevant.

No bioequivalence trials were required as all clinical trials submitted in the application were conducted with the to-be-marketed 700 U/mL formulation.

Distribution

Using the PopPK analysis to determine the volume of distribution is considered reasonable.

Several *in vitro* studies were performed to evaluate the binding of insulin icodec in plasma and to serum albumin. In humans as well as in relevant animal species, the degree of binding was >99%. The bound fraction of insulin icodec to human serum albumin correlated well with the bound fraction to proteins in human plasma, suggesting that insulin icodec mainly binds to albumin in human plasma.

Elimination

The half-life of insulin icodec of about one week, which is reported in the SmPC is in line with the PopPK-based results.

Metabolism: In vitro incubation studies in human hepatocytes resulted in nine metabolites and all of them were detected also in other species and hence no unique human metabolites were identified. The identified metabolites are not considered to possess any pharmacological action. *In vivo* serum samples from study 4314 were analysed with an exploratory UPLC-MS for analysis of circulating metabolites from insulin icodec. Four metabolites of insulin icodec were structurally identified in serum from human subjects with type 2 diabetes following multiple s.c. dosing of insulin icodec (trial 4314). Insulin icodec and the three quantified plasma metabolites, B1-29, B24-29 and B29, accounted for 85, 11, 0.74 and 2.6% of the total AUC0-168h, respectively. The quantification of metabolites *in vivo* is considered preliminary and possibly overestimated

since non-labelled compound were used and pooled plasma samples from a few timepoints. Based on the studies performed, degradation of insulin icodec are expected to be similar to that of human insulin and no further studies are warranted.

Immunogenicity

Increasing ADA titre leads to increased exposure, however the effect of antibody titre on the PK of insulin icodec does not appear to lead to any clinically significant changes compared to antibody negative patients. Analyses stratified by nAb status were also provided for efficacy parameters such as HbA1c or weekly insulin dose, without alarming trends. It is agreed that efficacy does not seem substantially affected by the presence of nAbs.

Antibody titre was explored as a covariate during the population PK analysis. Generally, a population PK approach is considered valid to explore the influence of antibody titre on the PK profile. In this case the peak antibody titre was tested as a time-constant covariate which could be considered a limitation; a more mechanistic implementation is to include antibody titre as a time-varying covariate (provided that antibody titre was measured at a sufficient number of time-points throughout the studies included in the population PK analysis). However, the current implementation is considered sufficient to conclude that the effect of antibody titre do not appear to be clinically relevant.

Given the extent of immunogenicity, it is considered relevant to describe this in the SmPC. The applicant proposed such a text for SmPC section 5.2 highlighting the effect of ADA on PK. The text is acceptable.

Target population

The PK in T1D and T2D populations were evaluated in several clinical pharmacology studies with non-compartmental analysis. No conclusion could be made regarding differences between the two populations from these data. However, the population PK results indicated a 16% higher plasma exposure in T1D compared to T2D patients, which is not considered clinically relevant at steady-state.

Pharmacokinetics of insulin icodec was evaluated in the target population (Type 1 and 2 diabetes patients) using a population PK approach where the objective was to investigate the effects of a number of covariates on insulin icodec exposure at steady state. The objectives outlined for the PopPK part appear overall relevant. The PopPK model is considered to have low impact in the current procedure, as it is used for descriptive purposes only where it will support SmPC statements in section 5.2 related to special populations where no dedicated clinical study exists (e.g., weight, age, sex).

The PopPK was developed on a dataset including 1244 patients with Type 1 and 2 diabetes, respectively, including a total of 6939 observations, from studies with sparse type PK sampling schedules. The data exclusions were limited to rather few samples which is acceptable. The available covariates for the population PK analysis and their distribution appear overall reasonable.

The population PK analysis used a condensed model development which appears overall reasonable, considering that the full model gave an acceptable description of the observed data (Figure 2). The choice of structural model was a one-compartment model with first-order absorption and elimination was informed by previous population PK models (results not shown), which is considered acceptable.

The kA parameter was fixed based on previous analyses but was estimated as part of a sensitivity analysis. This was done since no study with rich PK sampling was included in the population PK analysis. This approach is considered acceptable.

The model diagnostics included standard goodness-of-fit plots as well as pcVPCs which is considered reasonable. Forest plots were generated to assess the clinical impact of various covariates, which is considered a reasonable approach.

The covariate analysis consisted of a full model approach. When using this type of full model approach, it is important to demonstrate that the covariates have reasonable correlation. No covariate pairs included in the final PopPK model had high correlation, which is acceptable.

All covariates were explored on CL/F whereas only body weight was included on V/F. No covariates were explored on KA which is reasonable since KA was fixed. Exploring all covariates on CL/F could be acceptable since this is considered the most crucial parameter.

The parameter estimates were overall reasonable and with reasonable precision, apart from the coefficient of albumin on CL/F which had quite high RSE (Table 8).

According to the pcVPC stratified by study the median was slightly underpredicted in studies 4480 and 4478 (Figure 2). Of note, studies 4480 and 4478 are the only studies only including insulin-experienced patients which could imply that there is an underlying PK difference between insulin-naïve and experienced patients. Nevertheless, the full model was able to give an overall reasonable description of the data which is acceptable.

Several covariates were included in the full model including covariates, which are not considered statistically significant based on the confidence intervals overlapping the null value. The forest plots confirmed the observation that body weight is an influential covariate which agrees with other insulin products. Other covariates that appeared to have an influence on the model predictions were antibody group where 3rd + 4th quartile led to higher exposure compared to antibody negative patients as well as disease type where Type 1 diabetes patients had higher exposure than Type 2 diabetes patients. Overall, the covariate analysis is considered acceptable and it provides useful information on covariate influence on insulin icodec exposure.

In addition to dedicated clinical pharmacology study in diabetes patients, insulin icodec PK was characterised using population PK analysis in studies with sparse PK sampling, including Type 1 and Type 2 diabetes patients. During the covariate analysis the disease type (Type 1 vs Type 2 diabetes) was explored as a covariate on CL/F. Disease type was identified as a statistically significant covariate (the 95% confidence interval did not overlap with the null value) on CL/F and the model predicted that the exposure is approximately 16% higher in Type 1 than Type 2 diabetes patients. This information is considered useful, but as stated by the applicant, is not considered clinically relevant.

In summary, a few limitations have been identified with the PopPK model as described above. However, the population PK model is considered overall acceptable as such and an updated population PK model is not needed.

No statement on inter-individual variability is included in the SmPC, which could is considered reasonable since the dose of insulin icodec is titrated in each individual patient. Thus, information on inter-individual variability will be less useful compared to the variability within an individual.

Special populations

Sex was explored as a covariate during the population PK analysis and was neither identified to be a statistically nor a clinically significant covariate.

Exploring race as a covariate during the population PK analysis is considered acceptable. Chinese and Japanese were not identified as statistically or clinically significant covariates, which is agreed. The Other Asian category and black race were identified as statistically significant covariates but not clinically significant covariates, which is agreed.

Body weight was identified as a clinically significant covariate for the PK of insulin icodec PK. This finding is in line with other insulin-containing products. Although it is considered clinically significant, the applicant has not proposed any information in the SmPC to describe this finding, which is considered acceptable since the dose of insulin icodec is to be set individually in all patients irrespective of the body weight.

Body weight, which is considered an important covariate was included in the model using a power model. Body weight was explored using estimated coefficients as well as fixing the coefficients to literature values of 0.75 for CL/F and 1 for V/F, which did not seem to alter any conclusion from the model.

Exploring age as a covariate during the population PK analysis is considered a reasonable approach. Age was identified as a statistically but not clinically significant covariate, which is agreed.

Renal impairment: Total exposure (AUC) increased with impaired renal function. For individuals with moderate and severe renal impairment total exposure was 22-26% higher compared to subjects with normal renal function. The slightly increased AUC for subjects with moderate and severe renal impairment is not considered clinically relevant considering that the product is individually titrated. Measuring of unbound concentrations would have been preferable considering the high degree of protein binding of insulin icodec (>99%). However, there was no obvious association between serum albumin and AUC in subjects from different renal function groups and the use of total concentrations is therefore acceptable.

Hepatic impairment: Based on total concentrations, severe hepatic impairment did not affect the AUC or Cmax of insulin icodec. AUC and Cmax were slightly increased (13-15%) in subjects with mild and moderate hepatic impairment compared to subjects with normal hepatic function. The small increase in total exposure was not considered clinically relevant. Measuring of unbound concentrations would have been preferable considering the high degree of protein binding of insulin icodec (>99%). However, there was no obvious association between serum albumin and AUC in subjects from different hepatic impairment groups and the use of total concentrations is therefore acceptable.

Pharmacodynamics

Insulin icodec is a modified insulin that binds to the insulin receptor and results in the same pharmacological effect as insulin. The extended half-life of insulin icodec is due to strong but reversible binding to albumin. Insulin icodec occupies less than 0.05% of albumin. Thereby a depot of essentially inactive insulin icodec is formed throughout the circulation and the interstitial compartment, from which insulin icodec is slowly and continuously released. The slow and steady glucose-lowering effect is due to reversible albumin binding, reduced insulin receptor binding and receptor-mediated clearance from the circulating insulin icodec depot. There was no obvious association between serum albumin and AUC in subjects with different degrees of renal or hepatic impairment, respectively.

The steady-state PD properties of insulin icodec were investigated in **trials 4569** and **4314** in T2DM subjects and in **trial 4225** and **4422** (Japanese population) in T1DM subjects. Euglycaemic glucose clamp setting for insulin icodec was not performed over the whole dosing interval of one week as this was not feasible. Instead, shorter clamps covering the onset, peak effect, and end of dosing interval were performed. The periods in between were covered with PK/PD modelling. The approach is considered appropriate and is in line with the advice.

In **trials 4569** and **4225**, steady state data showed fluctuations in GIR for both T2DM and sufficiently dosed T1DM subjects. According to the applicant, this is most likely due to diurnal variation in insulin sensitivity with a decreased insulin sensitivity during night, leading to less glucose-lowering effect overnight.

The main trial objective in trial **4314** was to investigate safety of insulin icodec. Results showed that insulin icodec was well-tolerated. In T2DM subject (**trial 4569**), the glucose-lowering effect of insulin icodec seems to be distributed fairly evenly within the dosing interval of one week. Duration of action was estimated during the euglycaemic clamp covering the end of the weekly dosing interval (the last 24 hours) and implies to be extended beyond 168 hours for insulin icodec. No escapes were observed in the end of the clamp period.

In T1DM subjects (**trial 4225**), however, the glucose lowering effect of insulin icodec was less evenly distributed during the week. The daily contribution to the GIR effect varied between 8-20%, compared to 12-15% in T2DM subjects. Duration of action was estimated during the euglycaemic clamp covering the last 30 hours. However, data only from sufficiently dosed T1DM subjects was presented. Data from insufficiently dosed subjects (15/63; 23%) showed no or little glucose infusion and the glucose levels rose markedly above the predefined clamp target of 6.7 mmol/L. The individual dose for glucose control with a once-weekly insulin may not be sufficient to obtain an effective GIR-reading during the clamp in T1DM subjects. Therefore, the approach of overdosing in clamp trials is not feasible for safety reasons with once-weekly insulins after repeated dosing for several weeks. This is acknowledged.

In **trials 4569** and **4225**, fluctuations were observed in GIR in both T2DM and T1DM population. Accordingly, the hypoglycaemia rate was increased in the first 4 days post-injection compared to days 5 to 7 of the dosing interval in T1DM and T2DM patients. The applicant argues that the underlying cause of the observed fluctuations in GIR is the diurnal variation of insulin sensitivity. However, it must be noted that stress and rebound hyperglycaemic episodes experienced frequently by diabetic subjects may be also responsible for the observed fluctuations in GIR.

Data from **trial 4422** in T1DM subjects, comparing the PD profile for insulin icodec in Japanese and Caucasian, should be interpreted with caution since this is a comparison between trials using different techniques. However, the data does not indicate any obvious clinically relevant differences between Japanese and Caucasian subjects.

In **trial 4462**, the hypoglycaemic clamp was performed in T2DM subjects to investigate the counter-regulatory response to controlled hypoglycaemia induced by insulin icodec or insulin glargine. There was a greater increase in the counter-regulatory hormone response with insulin icodec compared to insulin glargine for adrenaline, the most important counter-regulatory hormone, following a triple dose at PG 3.0 mmol/L (2.54 [1.69; 3.82]). In addition, cortisol concentration was greater at PG mmol/L (2.54 [1.69; 3.82]) and at PG nadir (1.80[1.09; 2.97]) following a triple dose. The hypoglycaemic clamp did not reveal any attenuation of the counter-regulation in response to hypoglycaemia with insulin icodec as compared to insulin glargine. Double and triple doses of once-weekly insulin icodec did not lead to an apparent increased risk of clinically significant hypoglycaemia compared with once-daily insulin glargine, and the time to develop hypoglycaemia

and time to recover from hypoglycaemia seemed to be comparable. During the safety monitoring period, rapidly absorbable carbohydrate or iv glucose was administered if the PG concentration declined to <4.4 mmol/L in the period after insulin glargine or insulin icodec overdosing. Slightly more plasma glucose was needed to increase plasma glucose from nadir to 5.5 mmol/l for insulin icodec (139 mg/kg) compared to insulin glargine (111 mg/kg) for the second dose, but the amount of glucose needed to recover from PG nadir was comparable for insulin icodec (116 mg/kg) and insulin glargine (115 mg/kg) for the triple dose. However, it is difficult to compare groups regarding the need for glucose administration as the safety monitoring/observation period was different for insulin icodec and insulin glargine, in relation to time of dosing. The applicant was in the advice encouraged to consider conducting a similar trial in T1DM patients who in general are more vulnerable to hypoglycaemia. A similar trial in T1DM patients has not been performed.

In trial 4462, counter-regulatory hormone secretion to triple dose of *insulin icodec* was notable regarding adrenaline, noradrenaline and cortisol as compared to findings observed with the comparator.

In trial 4572, the influence of different injection regions on the PD profile was investigated. Similar PD profiles during the time period (from 36 to 60 hours after dosing) seemed to be obtained irrespective of injection sites; however, a slight difference in AUC was observed. The largest difference in AUC was seen between "upper arm" (AUC $_{GIR\ mean}$ 2391) and "thigh" (AUC $_{GIR\ mean}$ 1961). The differences in predicted maximum insulin icodec concentrations between abdomen/thigh and upper arm/thigh at steady state were lower than the difference shown in maximum insulin icodec concentration after single-dose administration, indicating that the observed differences are not clinically relevant. The proposed SmPC text advice to switch injection sites within the same region is endorsed.

The molar dose ratio was estimated to be 1.03 [0.74; 1.44]$_{95\%CI}$ in T2DM subjects, thus similar glucose-lowering effect of insulin icodec and insulin degludec was obtained when the two products were administered at identical molar doses. The molar dose ratio was estimated to be slightly higher (1.19 [1.00; 1.43]$_{95\%CI}$) when comparing the glucose-lowering effect of insulin icodec with insulin degludec in T1DM subjects. However, in general insulin icodec is equipotent to insulin glargine and insulin degludec. One unit of insulin icodec corresponds to one unit of insulin glargine (100 units/mL) and 1 unit of insulin degludec. This may be extrapolated to other insulin analogues and human insulin.

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

Pharmacokinetics-pharmacodynamics

Model-based exposure-response analyses were performed to describe the relationship between insulin icodec in plasma and GIR. This was done for multiple studies in the clinical development programme whereas the most important studies for the exposure-response modelling are studies 4225 and 4569 since these included both PK and GIR sampling at steady state in Type 1 and 2 patients, respectively. Hence, no assessment of the other modelling of GIR is included in this report.

The objective for the model-based exposure-response analyses is considered relevant. Using a model-based approach to describe GIR profile across a whole week at steady state is a reasonable approach. Clamp studies were performed in multiple subjects at steady-state at the beginning and end of the insulin icodec dosing interval. Hence, data are not collected throughout the whole dosing interval which is due to practical

limitations of clamp studies. The impact of this modelling is mainly for descriptive purposes and is thus not of high impact per se.

The database used to develop PK and PKPD models included a considerable amount of PK and GIR data, which is considered acceptable.

A sequential approach was used to develop the PKPD model where a PK model was developed first followed by development of a PK model. The individual PK parameters from the PK model was used to describe the PK profile in each subject wen developing the PD model. This is considered an acceptable approach. Relevant diagnostics were used to assess the model fit. No formal covariate analysis was performed which is considered acceptable since covariates were explored in a separate population PK analysis.

The developed PK and PKPD models had overall reasonable parameter estimates and RSEs. According to the VPCs for PK and GIR, the models gave acceptable description of the observed data. For Study 4569, model can be considered fit-for-purpose for interpolating the GIR curve between days ~2.5 – 6 (i.e. the predictions included in Figure 19).

For Study 4569 there was a sign of model misspecification in one of the standard goodness-of-fit plots (observations vs typical predictions, data not shown), which could imply that clinical trial simulations for scenarios outside the setting of Study 4569 may be inaccurate. The model may need to be revised to resolve the model misspecification in the standard goodness-of-fit plots if the model is used e.g., to extrapolate/predict any unstudied scenario in case of a future regulatory application. Since the model is considered fit-for-purpose for descriptive purposes, this issue will not be pursued further.

Predictions were performed with the final PD model to interpolate the GIR profile for time-points where no GIR data were available, which is considered a reasonable approach.

2.6.4. Conclusions on clinical pharmacology

The pharmacokinetics have been characterised for insulin icodec and the influence of intrinsic and extrinsic factors have been evaluated. Also, the influence of different injection sites has been studied.

The pharmacodynamic characteristics of insulin icodec have been investigated and the PD profile obtained by PKPD modelling. The PKPD modelling appears acceptable. Fluctuations in glucose infusion rate for insulin icodec is most likely due to diurnal variation in insulin sensitivity with a decreased insulin sensitivity during night. In T2DM subjects, the steady-state PD properties of insulin icodec in T2DM subjects were investigated in trials 4569 and 4314. In T2DM subjects, about 23% of the subjects were insufficiently dosed and did not meet the predefined clamp conditions. Data only from sufficiently dosed T1DM subjects was presented. The applicant argues that the approach of overdosing in clamp trials is not feasible for safety reasons with once-weekly insulin in T1DM subjects. This is acknowledged.

2.6.5. Clinical efficacy

The evaluation of efficacy is based on the results of the six therapeutic trials in the phase 3a ONWARDS programme. Five phase 3 studies with a treat-to target design (ONWARDS 1-6). ONWARDS 5 included an approach to mimic a clinical practice setting with fewer dedicated visits and routine assessment left to the treating physician (Table 21). The exploratory phase 2 trials 4383, 4465 and 4466 are discussed in the section on dose-response studies below).

Table 21. Key trial design features for phase 3a trials – ONWARDS 1-6

Trial Name (Trial ID)	Duration (weeks)[a]	N (FAS/SAS)[b]	Population	Screening HbA$_{1c}$ level	Pre-trial insulin treatment	Insulin icodec starting dose	Basal insulin comparator (starting dose)	Blinding	Action to non-insulin anti-diabetic treatment	Stratification
ONWARDS 1 (4477)	78 (52[c])	984/984	T2D	7.0-11.0%	Insulin naïve	70 U	Insulin glargine (10 U)	Open label	To be continued at pre-trial levels, except SU and glinides which were to be discontinued	None
ONWARDS 2 (4478)	26	526/525	T2D	7.0-10.0%	Basal only	Total daily basal insulin dose before randomisation x 7 + additional dose[d]	Insulin degludec (according to label)	Open label	To be continued at pre-trial levels, except SU and glinides which were to be discontinued[e]	None
ONWARDS 3 (4479)	26	588/587	T2D	7.0-11.0%	Insulin naïve	70 U	Insulin degludec (10 U)	Double blind	To be continued at pre-trial levels, except SU and glinides which were to be reduced by ~50% at the discretion of the investigator	Stratified according to region and SU or glinide use (yes/no)
ONWARDS 4 (4480)	26	582/582	T2D	7.0-10.0%	Basal-bolus	Total daily basal insulin dose before randomisation x 7 + additional dose[d]	Insulin glargine[f] (according to label)	Open label	To be continued at pre-trial levels, except SU and glinides which were to be discontinued[e]	None
ONWARDS 5 (4481)[j]	52	1085/1080	T2D	>7.0%	Insulin naïve	70 U	Basal insulin analogues[g] (according to label)	Open label	Subjects were asked to reduce SUs and glinides by ~50% at the discretion of the investigator	None
ONWARDS 6 (4625)	52 (26[c])	582/582	T1D	<10%	Basal-bolus	Total daily basal insulin dose before randomisation x 7 + additional dose[d,h]	Insulin degludec[f] (according to label)	Open label	Not applicable for T1D	Stratified according to pre-trial basal insulin treatment[i] and HbA$_{1c}$ at screening (<8% or ≥ 8%)

2.6.5.1. Dose response study(ies)

No formal dose-response studies were performed. The selection of doses and titration for the phase 3a trials was based on data from one of the PK/PD trial 4314 and the three phase 2 trials 4383, 4465 and 4446.

Dose selection and titration

The explorative phase 2 trials 4383, 4465 and 4466 were conducted in T2DM subjects to investigate the effect on glycaemic control and safety of insulin icodec compared to daily basal insulin, and to evaluate starting dose and dose titration. Starting dose of 70 U for insulin icodec was used. Titration of trial product in the trials was to be based on the 3 pre-breakfast SMPG values measured on two days prior to titration and on the day of the contact (Table 22).

Table 22. Key trial design features for phase 2 trials

Trial ID	Duration (weeks)	N (FAS)	Treatment arms	Population	Screening HbA$_{1c}$ level	Pre-trial anti-diabetic treatment	Blinding	Stratification
4383	26	247	2 treatment arms (randomised 1:1): • insulin icodec once weekly s.c. and placebo once daily • insulin glargine once daily s.c. and placebo once weekly Starting doses were 70 U for insulin icodec and 10 U for insulin glargine. Insulin icodec/weekly placebo titration: • +28 U if mean SMPG was above 7.0 mmol/L (>126 mg/dL) • +14 U if mean SMPG was 6.1-7.0 mmol/L (109-126 mg/dL) • -14 U if lowest SMPG was 3.0-3.8 mmol/L (54-69 mg/dL) • -28 U if lowest SMPG was below 3.0 mmol/L (<54 mg/dL) Insulin glargine/daily placebo titration • as above but with ±4 and ±2 U, respectively.	Insulin naïve, T2D	7.0-9.5%	Metformin ± DPP4i	Double blind	Stratified according to DPP4i use (yes/no)

Trial ID	Duration (weeks)	N (FAS)	Treatment arms	Population	Screening HbA$_{1c}$ level	Pre-trial anti-diabetic treatment	Blinding	Stratification

4465	16	205	4 treatment arms (randomised 1:1:1:1):
			Insulin icodec once weekly s.c., with a starting dose of 70 U, and titrated according to titration algorithms:
			• A: +21 U if mean SMPG was above 7.2 mmol/L (>130 mg/dL)
			   -21 U if lowest SMPG was below 4.4 mmol/L (<80 mg/dL)
			• B: +28 U if mean SMPG was above 7.2 mmol/L (>130 mg/dL)
			   -28 U if lowest SMPG was below 4.4 mmol/L (<80 mg/dL)
			• C: +28 U if mean SMPG was above 6.0 mmol/L (>108 mg/dL)
			   -28 U if lowest SMPG was below 3.9 mmol/L (<70 mg/dL)
			
			Insulin glargine once daily s.c., with a starting dose of 10 U, and titrated according to titration algorithm:
			• D: +4 U if mean SMPG was above 7.2 mmol/L (>130 mg/dL)
			   -4 U if lowest SMPG was below 4.4 mmol/L (<80 mg/dL)
				Insulin naïve, T2D	7.0-10.0%	Metformin ± DPP4i ± SGLT2i	Open label	Stratified according to SGLT2i use (yes/no)

4466	16	154	3 treatment arms (randomised 1:1:1): Insulin icodec once weekly s.c. using either of two different approaches for switching from pre-trial basal insulin: • unit-to-unit switch *without* a one-time additional dose • unit-to-unit switch *with* a one-time additional 100% dose Insulin glargine U100 once daily s.c., with a starting dose equal to pre-trial basal insulin (reduced by 20% if the subject prior to randomisation received insulin glargine U300 or a twice-daily regimen with any basal insulin analogue) Insulin icodec titration: • +28 U if mean SMPG was above 7.2 mmol/L (>130 mg/dL) • -28 U if lowest SMPG was below 4.4 mmol/L (<80 mg/dL) Insulin glargine titration: • +4 U if mean SMPG was above 7.2 mmol/L (>130 mg/dL) • -4 U if lowest SMPG was below 4.4 mmol/L (<80 mg/dL)	Basal treated, T2D	7.0-10.0%	Basal insulin (once or twice daily) + metformin ± DPP4i ± SGLT2i	Open label	Stratified according to pre-trial insulin treatment and SGLT2i use (yes/no)

Based on the data from the clinical pharmacology trial 4314, the starting dose of 70 U (7 times the starting dose of daily insulin) in insulin naïve T2DM subjects was evaluated in trials 4383 and 4465.

In **trial 4383** was designed to investigate the effect on glycaemic control and safety compared to insulin glargine. The primary endpoint was the reduction in HbA$_{1c}$ from baseline to end of treatment. Reduction in FPG, mean weekly insulin dose and time in range 3.9-7.8 mmol/L were supportive secondary endpoints. No difference between treatment arms with regards to reductions in HbA1c and FPG was noted. Time spent in glycaemic target range 3.9-7.8 mmol/L (exploratory endpoint) was improved with insulin icodec compared to insulin glargine. Weekly insulin dose was lower with insulin icodec. More hypoglycaemic events during titration were noted.

In **trial 4465** was designed to compare insulin icodec versus insulin glargine using three different titration algorithms: arm A (±21 U if SMPG below or above 4.4-7.2 mmol/L, arm B (±28 U if SMPG below or above 4.4-7.2 mmol/L and arm C (±28 U if SMPG below or above 3.9-6.0 mmol/L). The primary endpoint was the time in range 3.9-10.0 mmol/L (%) measured by CGM during the last two weeks of treatment. In treatment

arm A, the glycaemic response (time in range, HbA$_{1c}$ decrease, FPG and weekly insulin dose) was comparable for insulin icodec and insulin glargine. In arm B and C, insulin icodec had statistically significantly more time in range (arm B) and larger reduction in HbA$_{1c}$ and FPG, respectively (arm C) compared to insulin glargine. However, arm A had lower rates of level 2 and 3 hypoglycaemic events compared to arm B and C.

Trial 4466, was designed to compare two different switch approaches for insulin icodec versus insulin glargine. The primary endpoint was the time in range 3.9-10.0 mmol/L (%) measured by CGM during the last two weeks of treatment. From the fasting SMPG profiles, a glycaemic slip was observed in the insulin icodec arm without the one-time additional dose, but not in the arm with a one-time additional 100% insulin icodec dose. The rate of level 2 and 3 hypoglycaemic episodes was comparable between the insulin icodec + one-time additional 100% dose and the insulin glargine group and was lower in the insulin icodec group without one-time additional dose.

Rationale for the titration algorithm and chosen starting doses

The trial **4465** supported dose adjustments of ± 20 U and a glycaemic target of 4.4-7.2 mmol/L (80-130 mg/dL) to be selected for the ONWARDS trials.

The trial **4383** was undertaken to confirm the starting dose of 70 U for insulin icodec in insulin naïve subjects.

Trial **4466** evaluated the starting dose for T2DM patients previously on basal insulin (basal switch) or on basal-bolus regimen. Given the risk of hypoglycaemic events with an additional 100% dose, a conservative approach was applied. A one-time additional 50% dose was selected for the first administration of insulin icodec in the therapeutic studies for T2DM subjects previously on basal or basal-bolus regimen (ONWARDS 2 and 4, respectively). In T1DM patients, a one-time additional 100% dose was chosen for patients with HbA$_{1c}$ ≥8% at screening to reduce the risk of hyperglycaemic events and DKA in T1DM patients. In order not to increase the risk of hypoglycaemic episodes at the beginning of the study, a one-time additional 50% insulin icodec dose was applied in subjects with HbA$_{1c}$ <8% at baseline or if insulin glargine U300 or twice daily basal insulin had been received prior to randomisation.

2.6.5.2. Main study(ies)

The efficacy of once weekly insulin icodec has been investigated in six confirmatory studies, of which five trials in T2DM patients (ONWARDS 1-5) and one trial in T1DM patients (trial 4625). All studies were open-label, except for one T2DM study (ONWARDS 3), which was double-blinded with a double dummy design. The efficacy was evaluated in insulin naïve T2DM patients (ONWARDS 1 and 3), in T2DM patients previously treated with basal insulin (ONWARDS 2) and in T2DM and T1DM patients previously treated with basal-bolus insulin (ONWARDS 4 and 6).

All trials applied a treat-to-target design, except for ONWARDS 5, which was designed to mimic a clinical practice setting with fewer dedicated visits and routine assessment left to the treating physician. ONWARDS 5 was a study in insulin naïve T2DM patients where insulin icodec was used together with a dosing guide application under investigation. The dosing guide application provided automated dose guidance to subjects randomised to insulin icodec.

An overview of the confirmatory ONWARDS trials (Figure 20).

Figure 20. Overview of the confirmatory ONWARDS trials

	T2D	**T1D**
Insulin naïve	**ONWARDS 1** *vs* insulin glargine **ONWARDS 3** *vs* insulin degludec **ONWARDS 5** with DoseGuide *vs* daily basal insulin in a clinical practice setting	
Basal switch	**ONWARDS 2** *vs* insulin degludec	
Basal-bolus	**ONWARDS 4** *vs* insulin glargine	**ONWARDS 6** *vs* insulin degludec

Methods

Trials in T2DM patients

Trial 4477 (ONWARDS 1) – 78 weeks (52 w+26 w), insulin naïve T2DM subjects, open-label

ONWARDS 1 consisted of two treatment periods: a 52-week main part and a 26-week extension part. It was a randomised (1:1), open label, active-controlled, parallel-group, multicentre, multinational, treat-to-target trial. A total of 984 insulin naïve subjects with T2DM in need of insulin initiation were randomised. The trial was comparing the effect and safety of once weekly insulin icodec and once daily insulin glargine 100 units/mL, both in combination with non-insulin anti-diabetic treatment (excluded sulfonylureas and glinides), in insulin naïve subjects with type 2 diabetes.

Trial 4479 (ONWARDS 3) – 26 weeks, insulin naïve T2DM subjects, double blind

ONWARDS 3 was a 26-week, randomised (1:1), stratified, double blind, double dummy, active-controlled, parallel-group, multicentre, multiregional, treat-to-target trial.   A total of 588 insulin naïve subjects with T2DM in need of insulin initiation were randomised. Randomisation was stratified according to region (Asia, North America, South America, Europe) and treatment with SU or glinides (yes/no). The trial was comparing the effect and safety of once weekly insulin icodec and once daily insulin degludec 100 units/mL, both in combination with non-insulin anti-diabetic drugs (sulphonylureas and glinides reduced by approximately 50%), in insulin naïve subjects with type 2 diabetes.

ONWARDS 5 (trial 4481) – 52 weeks, insulin naïve T2DM subjects, open-label

ONWARDS 5 was a 52-week, randomised (1:1), open label, parallel-group, active-controlled, multicentre, multinational trial with **elements to mimic a clinical practice setting**. A total of 1,085 insulin naïve subjects with T2DM in need of insulin initiation were randomised. **Effectiveness** and safety of once weekly insulin icodec used with DoseGuide versus once daily basal insulin analogues (insulin glargine U100, U300 or insulin degludec U100), both in combination with non-insulin anti-diabetic drugs (sulphonylureas and glinides reduced by approximately 50%), in an insulin naïve type 2 diabetes population in a clinical practice setting.

The Dosing guidance application was a Software as medical device, which calculated and provided automated dose guidance to subjects randomised to insulin icodec. The DoseGuide System consisted of the DoseGuide App for subjects and the DoseGuide Portal for investigators, both integrated with the DoseGuide Cloud, where the dose recommendations were calculated. The DoseGuide System utilised measurements from a BG meter via Bluetooth as well as injection history and pre-breakfast fasting SMPG provided by the subject. The investigator was to set up the subject profile in the DoseGuide Portal according to the titration guidance, as specified in the protocol. The subject was to request and receive dose recommendations in the DoseGuide App.

Trial 4478 (ONWARDS 2) – 26 weeks, T2DM subjects (basal switch), open-label

ONWARDS 2 was a 26-week, randomised (1:1), open label, active-controlled, parallel-group, multicentre, multinational, treat-to-target trial. A total of 526 basal insulin treated subjects with T2DM were randomised. The trial was comparing the effect and safety of once weekly insulin icodec and once daily insulin degludec, both with and without non-insulin anti-diabetic drugs (excluded sulphonylureas and glinides), in subjects with type 2 diabetes treated with basal insulin.

Trial 4480 (ONWARDS 4) – 26 weeks, T2DM subjects (basal bolus), open-label

ONWARDS 4 was a 26-week, randomised (1:1), open label, active-controlled, parallel-group, multicentre, multinational, treat-to-target trial. A total of 582 basal-bolus treated subjects with T2DM were randomised. The trial was comparing the effect and safety of once weekly insulin icodec and once daily insulin glargine 100 units/mL, both in combination with bolus insulin with or without non-insulin anti-diabetic drugs (excluded sulphonylureas and glinides), in subjects with type 2 diabetes on a basal-bolus regimen.

Trial in T1DM patients

ONWARDS 6 (trial 4625)– 52 weeks (26 w + 26 w), T1DM subjects (basal bolus), open-label

ONWARDS 6 consisted of two treatment periods: a 26-week main part and a 26-week extension part. It was a randomised (1:1), stratified, open label, active-controlled, parallel-group, multicentre, multinational, treat-to-target trial. A total of 582 basal-bolus treated subjects with T1DM were randomised. Randomisation was stratified by pre-trial basal insulin regimen and HbA$_{1c}$ at screening. The trial was comparing the efficacy and safety of once weekly insulin icodec compared to once daily insulin degludec 100 units/mL, both in combination with insulin aspart, in adults with T1DM.

Study Participants

In insulin naïve patients in ONWARDS 1 and 3, the HbA$_{1c}$ limits were 7.0–11.0%. A slightly lower upper limit of HbA$_{1c}$ of 10.0% was applied for subjects previously on basal insulin or basal-bolus regimen. In T1DM patients, the HbA1c limit was <10.0%. In ONWARDS 5 there was no upper limit on the HbA$_{1c}$ value at screening. All T2DM subjects were allowed to maintain current treatment with non-insulin anti-diabetic drugs at the same dose level, except for glinides or sulphonylureas. Pre-trial treatment with all non-insulin anti-diabetic drugs was allowed to be maintained at the same dose level, except for glinides or sulphonylureas. To minimise the risk of hypoglycaemia, treatment with glinides or sulphonylureas was to be discontinued (ONWARDS 1, 2 and 4) or reduced by approximately 50% (ONWARDS 3 and 5) at randomisation. Patients with severe renal impairment (eGFR <30 ml/min/1.73m^2) were excluded from the studies (Table 23). Overall, inclusion and exclusion criteria are considered adequate.

The **exclusion criteria** precluded enrolment of subjects with concomitant conditions which could jeopardise the safety of the subjects or compliance with the protocol. This was to safeguard subjects, and to avoid compromising trial validity and confounding of trial results (Table 24). In ONWARDS 5, there was fewer exclusion criteria and less frequent site visits than the other ONWARDS trials.

Table 23. Overview of inclusion criteria across the ONWARDS trials

	OW1	OW2	OW3	OW4	OW5	OW6
General						
Informed consent obtained before any trial-related activities	X	X	X	X	X	X
Male or female of at least 18 years of age[a]	X	X	X	X	X	X
HbA$_{1c}$ limits:						
7.0–10.0% (53–85.8 mmol/mol)		X		X		
7.0–11.0% (53−96.7 mmol/mol)	X		X			
Above 7.0% (53 mmol/mol)					X	
Below 10% (85.8 mmol/mol)						X
Diabetes history at screening						
Diagnosed with T1D ≥ 1 year						X
Diagnosed with T2D ≥ 180 days	X	X	X	X	X	
Intensification with insulin is indicated to achieve glycaemic target (4.4-7.2 mmol/L [80-130 mg/dL]) at the discretion of the treating investigator					X	
Anti-diabetic treatment at screening:						
Insulin naïve	X		X		X	
Once or twice daily basal insulin ≥ 90 days		X				
Basal[b]-bolus insulin regimen				X[c]		X[d]
Stable dose(s) for ≥ 90 days of OAD monotherapy, OAD combination therapy, or injectable GLP-1 RA	X	X[e]	X	X[e]	X	
Body mass index (BMI):						
BMI ≤ 40.0 kg/m^2	X	X	X	X		

Table 24. Overview of exclusion criteria across the ONWARDS trials

	OW1	OW2	OW3	OW4	OW5	OW6
Known or suspected hypersensitivity to trial product(s) or related products.	X	X	X	X	X	X
Previous participation in the trial. Participation is defined as signed informed consent.	X	X	X	X	X	X
Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate	X	X	X	X		X

	OW1	OW2	OW3	OW4	OW5	OW6
contraceptive method (adequate contraceptive measures as required by local regulation or practice).					X	
Participation in any clinical trial of an approved or non-approved investigational medicinal product within 90 days before screening.[a]	X	X	X	X	X	X
Any disorder, except for conditions associated with type 2 diabetes mellitus[b], which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol.[c]	X	X	X	X	X	X
Myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischaemic attack within 180 days prior to the day of screening.	X	X	X	X		X
Chronic heart failure classified as being in New York Heart Association (NYHA) Class IV at screening.	X	X	X	X		X
Planned coronary, carotid or peripheral artery revascularisation.	X	X	X	X		X
Renal impairment with estimated glomerular filtration rate (eGFR) value of eGFR < 30 ml/min/1.73m^2 at screening by central laboratory analysis.	X	X	X	X		X
Impaired liver function, defined as alanine aminotransferase (ALT) ≥ 2.5 times or bilirubin >1.5 times upper normal limit at screening by central laboratory analysis.	X	X	X	X		X
Inadequately treated blood pressure defined as systolic ≥180 mmHg or diastolic ≥110 mmHg at screening.	X	X	X	X		X
Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within 90 days prior to the day of screening.	X	X	X	X		X
Anticipated initiation or change in concomitant medications (for more than 14 consecutive days) known to affect weight or glucose metabolism (e.g. treatment with orlistat, thyroid hormones, or corticosteroids)	X	X	X	X		X
Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 90 days prior to screening or in the period between screening and randomisation. Pharmacological pupil-dilation is a requirement unless using a digital fundus photography camera specified for non-dilated examination.	X	X	X	X		X
Presence or history of malignant neoplasm (other than basal or squamous cell skin cancer, in-situ carcinomas of the cervix, or in situ prostate cancer) within 5 years prior to the day of screening.	X	X	X	X		X
Any episodes of diabetic ketoacidosis according to medical records within 90 days prior to screening	X	X	X	X		
Anticipated change in lifestyle affecting glucose control	X	X	X	X		
Known hypoglycaemic unawareness as indicated by the investigator according to Clarke's questionnaire question		X		X		X
Recurrent severe hypoglycaemic episodes within the last year as judged by the investigator		X		X		X

Treatments

In the ONWARDS trials, insulin icodec was to be injected subcutaneously once weekly on the same day each week, at any time of the day. The comparator (insulin glargine or insulin degludec) was to be injected subcutaneously once daily at any time of the day, but at the same time every day throughout the trial. Insulin aspart was to be injected subcutaneously with main meals 2-4 times per day in ONWARDS 4 and 6.

The subcutaneous injections could be into the thigh, upper arm, or abdomen in the open-label trials. In ONWARDS 3, which was double-blind, insulin icodec (and weekly placebo) were injected into the left thigh and insulin degludec (and daily placebo) were injected into the right thigh.

Insulin icodec is formulated as a 4200 nmol/mL solution equivalent to 700 U/mL and filled in 3 mL cartridges for the clinical trials. The PDS290 pre-filled pen-injector was used for administration of insulin icodec, insulin degludec and daily/weekly placebo, while SoloStar pre-filled pen-injector was used for administration of insulin glargine.

Starting dose

For insulin naïve subjects with T2DM, the starting dose of insulin icodec was defined by the protocol to be 70 U. For T2DM subjects previously on basal insulin or basal-bolus regimen, the starting dose of insulin icodec was their total daily basal dose multiplied by 7 (rounded off to the nearest 10 U) and for the first administration they received a one-time additional dose. The one-time additional dose was applied to avoid glycaemic slip during the first weeks of treatment (Table 25). The starting dose of the comparator was 10 U in ONWARDS 1 and 3 and not specified but in accordance with local label for ONWARDS 2, 4 and 6. Switch from previous bolus insulin was done unit-to-unit per meal in ONWARDS 4 and 6.

Table 25. Starting dose of insulin icodec in the ONWARDS trials

	Population	Starting dose insulin icodec
ONWARDS 1	T2D, insulin naïve	70 U
ONWARDS 2	T2D, basal only	Total daily basal insulin dose x 7 + one-time additional 50% dose
ONWARDS 3	T2D, insulin naïve	70 U (also for weekly placebo)
ONWARDS 4	T2D, basal-bolus	Total daily basal insulin dose x 7 + one-time additional 50% dose
ONWARDS 5	T2D, insulin naïve	70 U
ONWARDS 6	T1D, basal-bolus	HbA$_{1c}$ <8% (64 mmol/mol) or subjects who received insulin glargine U300 or twice daily basal insulin prior to randomisation: Total daily basal insulin dose x 7 + one-time additional 50% dose HbA$_{1c}$ ≥ 8% (64 mmol/mol): Total daily basal insulin dose x 7 + one-time additional 100% dose

Basal insulin dose titration

The investigator was to adjust insulin icodec and basal insulin comparators once weekly (ONWARDS 2-4 and 6) or according to trial schedule (ONWARDS 1). According to the protocol there was no titration of insulin icodec at week 2 in ONWARDS 2, 4 and 6. The titration of the basal insulins was based on the three preceding pre-breakfast SMPG values (i.e., pre-breakfast SMPG values measured on the two days prior to titration and on the day of contact) (Table 26). In ONWARDS 5, this titration algorithm was built into the Dosing guidance system, and the Dosing guidance application provided insulin icodec dose recommendations.

If the Dosing guidance system was temporarily suspended, titration of insulin icodec could be done according to Table 26.

Table 26. Titration algorithms for insulin icodec and comparators

Pre-breakfast self-measured plasma glucose (SMPG)			Dose adjustment insulin icodec	Dose adjustment insulin degludec or insulin glargine
Value to use	mmol/L	mg/dL	U	U
Lowest of the SMPG values	<4.4	<80	−20	−3
Mean of the SMPG values	4.4–7.2	80–130	0	0
	>7.2	>130	+20	+3

Bolus insulin

Insulin aspart was used as bolus insulin in ONWARDS 4 with T2DM subjects and in ONWARDS 6 with T1DM subjects.

Missed dose

Changing the dosing day by up to 3 days if necessary was allowed in all ONWARDS trials except for ONWARDS 6 (T1DM subjects). If an insulin icodec dose was missed for ≤3 days after the planned dosing day, subjects should inject the planned dose as soon as possible and perform control self-measured plasma glucose (SMPG) measurement. If the dose was missed for >3 days after the planned dosing day, the subject should await the next planned day-of-injection. While awaiting the next planned dose, subjects in ONWARDS 6 should perform frequent SMPG measurements to closely monitor their glycaemic control and adjust bolus doses, if needed.

Objectives

The *primary objective* for the phase 3a trials was to demonstrate the effect on glycaemic control of once weekly insulin icodec compared to a daily basal insulin in the specific diabetes population investigated. This included comparison of the change in HbA$_{1c}$ from baseline to end of treatment with the comparator to a non-inferiority margin of 0.3%.

The *secondary objective* of the ONWARDS trials was to compare parameters of safety with once weekly insulin icodec versus a daily basal insulin. In some ONWARDS trials, the secondary objective also concerned additional parameters: parameters of glycaemic control and patient reported outcomes (PROs).

The objectives of the trials are adequate. The design of non-inferiority with a margin of 0.3% is considered appropriate and in line with the given advice and current CHMP diabetes guideline.

The *estimand* was defined as the treatment difference between insulin icodec and daily basal insulin comparator of the change in HbA$_{1c}$ from baseline to week 26 (ONWARDS 2, 3, 4 and 6) or week 52 (ONWARDS 1) for all randomised subjects, irrespective of adherence to randomised treatment and changes to anti-diabetic background medication. Hence, the treatment policy strategy was applied to the intercurrent events of 1) treatment discontinuation or 2) initiation of bolus treatment lasting for more than 2 weeks in bolus-naïve subjects (ONWARDS 1, 2, and 3).

The treatment policy approach is in line with the given advice. The change in HbA1c at the end of the trial is the appropriate choice of primary outcome. Intercurrent events are of particular importance. The efficacy

results of the ITT population can be considered conservative as long as treatment discontinuation is mainly due to AEs, withdrawal of consent or otherwise.

Outcomes/endpoints

Change from baseline in HbA$_{1c}$ was the primary endpoint in all ONWARDS trials. All other endpoints were supportive secondary endpoints, except time in range 3.9-10.0 mmol/L (70-180 mg/dL) in ONWARDS 1, where it was a confirmatory secondary endpoint (Table 27). Multiple testing procedure was in place for the confirmatory key secondary endpoint in ONWARDS 1. Other secondary endpoints are not corrected for multiplicity.

Table 27. Primary and secondary endpoints in ONWARDS trials

	OW1	OW2	OW3	OW4	OW5	OW6
Change from baseline in:						
HbA$_{1c}$	P	P	P	P	P	P
FPG	S	S	S	S		S
Time spent in range (%) week 22 to 26[a]						
Time in target range 3.9-10.0 mmol/L (70–180 mg/dL)	C	S		S		S
Time spent < 3.0 mmol/L (54 mg/dL)	S	S		S		S
Time spent > 10.0 mmol/L (180 mg/dL)	S	S		S		S
Number of hypoglycaemic events						
Number of level 2 hypoglycaemic episodes	S	S	S	S	S	S
Number of level 3 hypoglycaemic episodes	S	S	S	S	S	S
Number of level 2 or 3 hypoglycaemic episodes	S	S	S	S	S	S
Number of nocturnal level 2 or 3 hypoglycaemic episodes						S
Mean weekly insulin dose week 24 to 26[b]	S	S	S	S		S
Change in body weight	S	S	S	S		S
Patient reported outcomes (PROs)						
Change from baseline in DTSQ score		S			S	S
Trim-D compliance domain score					S	
Time from baseline to treatment discontinuation or intensification					S	

C = confirmatory secondary endpoint; P: primary endpoint; S = supportive secondary endpoint;

Notes: [a] week 48 to 52 for ONWARDS 1; [b] week 50 to 52 for ONWARDS 1.

Sample size

In all the ONWARDS studies (1-6), the primary hypothesis to be tested was that insulin icodec is non-inferior to daily basal insulin comparator in change from baseline to week 26 *or* week 52 in HbA1c using a non-inferiority margin of 0.3%. Common for all studies was that the sample size was determined in order to have at least 90% power for declaring non-inferiority for the specified estimand and the primary full analysis set.

The standard deviation was assumed to be 1.0% based on earlier study experiences for all studies but for ONWARD 5 where the standard deviation was assumed to be 1.3% based on an expectation that the standard deviation for HbA1c after 52 weeks was to be elevated compared to a strict treat-to-target randomised controlled trial.

For ONWARDS 1 and, specifically ONWARDS 5, additional considerations were made, and these were also the two studies that had been planned with the largest sample sizes. Based on the assumptions and considerations made for each study separately, the planned sample size for ONWARDS 1 was 970 (1:1), for ONWARDS 2, 520 (1:1), for ONWARDS 3 and 4, 580 (1:1), for ONWARDS 5, 1.096 (1:1) and for ONWARDS 6, 580 (1:1).

In the CHMP scientific advice (EMA/CHMP/SAWP/221272/2020) it was pointed out that besides the fact that only one study had been planned in a T1D population, the proposed sample size was considered limited.

Randomisation and blinding (masking)

In all six phase 3 studies, subjects were centrally randomised 1:1 through the use of IWRS to receive either insulin icodec or daily basal insulin. The comparator in ONWARDS 1 and 4 was insulin glargine U100 and in ONWARDS 2, 3 and 6, insulin degludec U100. In ONWARDS 5, subjects randomised to the control arm was to receive either insulin glargine U100, insulin glargine U300 or insulin degludec U100. The daily basal insulin analogue that a subject was to receive if randomised to the control arm was to have been selected by the investigator prior to randomisation as per standard of care. This was expected and hence, is endorsed.

Only two studies used a stratified randomisation. In ONWARDS 3, the stratification factors were region (Asia, North America, South America, Europe) and treatment with sulphonylureas (SU) or glinides (yes/no). In ONWARDS 6, the stratification factors were pre-trial basal insulin treatment (either twice daily/insulin glargine U300 or once daily) and HbA1c (either <8% or ≥ 8%) at screening.

All the ONWARDS studies were open label except for study ONWARDS 3, which was to be performed under double-blind conditions using double-dummy technique. In ONWARDS 3, randomised treatments were to be packed blinded and were to be visually identical:

- Once weekly insulin icodec or once weekly placebo, 3 mL PDS290 pre-filled pen-injector
- Once daily insulin degludec or once daily placebo, 3 mL PDS290 pre-filled pen-injector

Subjects were to receive once weekly insulin icodec and once daily placebo or once daily insulin degludec and once weekly placebo. The main reason for the ONWARDS 3 double-blind design was to ensure collection of blinded safety data. According to instructions, insulin icodec was to be administered in the left thigh and insulin degludec was to be administered in the right thigh. Thus, this approach may have led to unintentional unblinding of treatments in case of apparent differences in local reactions between placebo and active treatment.

Statistical methods

The statistical evaluations were based on pre-specified analyses for each trial individually, with common statistical principles implemented across the phase 3a (ONWARDS) studies. Study-specific separate statistical analysis plans have been provided within the submission. All SAPs except for the ONWARDS 6 SAP had been amended: once (ONWARDS 1, 3 and 5), twice (ONWARDS 4) or three times (ONWARDS 2). Overall, no concerns are raised. No interim analysis had been planned in any of the studies.

For the studies with an extension, reporting was to be split into a main phase and an extension phase, where the results of the main phase could be reported before last subject last visit. To preserve trial integrity during the extension phase, dissemination of results from the main phase was initially to be limited to communication internally and with regulatory authorities.

Primary estimand

The primary estimand was the 'treatment policy estimand' defined as the treatment difference between insulin icodec and the comparator in change in HbA1c from baseline to week 26 or 52 for all randomised subjects, irrespective of adherence to randomised treatment and changes to anti-diabetic background medication. In the CHMP scientific advice (EMA/CHMP/SAWP/221272/2020), the proposed estimand derived from the ITT principle was supported.

Analysis population and definition of in-trial-period

Analyses of efficacy was based on the full analysis set (FAS), defined to include all randomised subjects analysed according to randomised treatment.

The **in-trial period** was used for all **efficacy** evaluations in line with the treatment policy estimand. It was defined as the time from randomisation until:

- The last direct subject-site contact;

- Withdrawal for subjects who withdrew their informed consent;

- The last subject-investigator contact as defined by the investigator for subjects who are lost to follow-up (i.e., possibly an unscheduled phone visit);

- Death for subjects who died before any of the above.

Analyses of primary and secondary efficacy endpoints

In all trials, the upper limit of the 95% confidence interval for the mean difference of the primary endpoint, change in HbA1c from baseline, was to be compared to the pre-specified non-inferiority margin of 0.3%.

The primary endpoint was planned and have been analysed using an analysis of covariance (ANCOVA) model including treatment, stratification factor(s) (ONWARDS 3 and 6), personal CGM device use (y/n) (ONWARDS 2 and 4) and region as fixed effects and HbA1c baseline value as covariate (where baseline was available).

Secondary continuous endpoints, except for time spent below range <3.0 mmol/L, were to be analysed using the same model as described for the primary endpoint.

Time spent below range <3.0 mmol/L (TBR) was analysed using a negative binomial regression model with a log-link function, and the logarithm of the number of recorded measurements as offset. The model included the same fixed factors as specified for the ANCOVA model.

Binary assessments were analysed using a logistic regression model with the same fixed factors as specified for the ANCOVA model and the applicable baseline value as covariate.

All hypotheses were tested at a 5%, 2-sided significance level. Presentation of results from a statistical analysis was to include the estimated mean treatment difference, or ratio, presented together with a two-sided 95% confidence interval and the corresponding two-sided p-value.

Missing data

A similar multiple imputation approach was used irrespective of study. The distinction below pertains the difference in intercurrent events.

ONWARDS 1-3

Missing HbA1c at the week 26/52 visit (regardless of treatment completion status) was to be handled using multiple imputation from trial participants, who had discontinued their randomised treatment or initiated bolus insulin treatment for more than 2 weeks prior to the week 26/52 visit and had a measurement at the week 26/52 visit.

ONWARDS 4-6

Missing HbA1c at the week 26/52 visit (regardless of treatment completion status) was to be imputed using multiple imputation from trial participants, who had discontinued their randomised treatment prior to the week 26/52 visit and had a measurement at the week 26/52 visit.

In case the amount of data for the imputation model was insufficient for meaningful imputation, the imputation model was either simplified (primary endpoint in ONWARDS 2 and 3) or replaced by a return-to-baseline imputation approach (primary endpoint in ONWARDS 4) or by imputation based on the subjects in the comparator arm who had completed the treatment (confirmatory secondary endpoint in ONWARDS 1).

Sensitivity analysis

For the primary endpoint, a two-dimensional tipping point analysis was performed where subjects having imputed HbA1c measurement at the week 26/52 visit were assumed to have a worse outcome in the insulin icodec arm and a better outcome in the basal insulin analogue arm compared to what was imputed in the primary analysis by adding or subtracting values Δi to the imputed HbA1c values before analysing the data. The value of Δi varied independently in the two treatment arms. The non-inferiority margin of 0.3% was among the Δi values investigated.

Multiple testing procedure

In order to control the overall Type I error at a 5% level, two-sided, a hierarchical testing procedure had been defined. A few hypotheses, denoted confirmatory, were to be adjusted for multiplicity and were only to tested if the primary hypothesis had been confirmed. Any subsequent confirmatory secondary hypotheses were tested only if all preceding hypotheses had been confirmed. All hypotheses were tested at a 5%, 2-sided significance level.

Figure 21. Confirmatory statistical testing hierarchy in ONWARDS trials
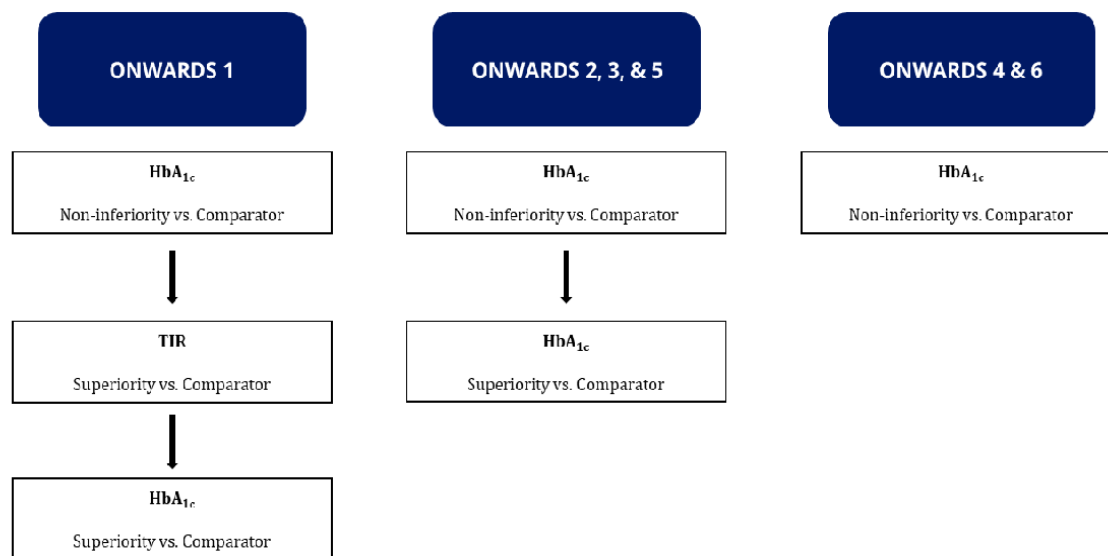
Abbreviation: HbA1c = glycated haemoglobin; TIR = time in range

Results

Participant flow

The phase 3a (ONWARDS) programme included 4,347 subjects in the full analysis set, of which 2,170 subjects were exposed to insulin icodec (1,880 subjects with T2DM and 290 subjects with T1DM) (Table 28).

Table 28. Subject disposition - summary

	OW 1	OW 2	OW 3	OW 4	OW 6	OW 5
Screened	1,192	635	737	746	655	1,250
Screen failures	176	103	121	146	62	120
Withdrawn prior to randomisation	32	6	28	18	11	45
Randomised	984	526	588	582	582	1,085
Exposed	Ico (n=492) D (n=492)	Ico (n=262) D (n=263)	Ico (n=293) D (n=294)	Ico (n=291) D (n=291)	Ico (n=291) D (n=291)	Ico (n=542) D (n=538)
Permanent discontinuation of trial product						
Not withdrawn from trial during the treatment period	Ico (n=7) D (n=5)	Ico (n=4) D (n=6)	Ico (n=7) D (n=3)	Ico (n=2) D (n=4)	Ico (n=7) D (n=1)	Ico (n=20) D (n=4)
Withdrawn from trial during the treatment period	Ico (n=10) D (n=7)	Ico (n=3) D (n=4)	Ico (n=6) D (n=8)	Ico (n=15) D (n=18)	Ico (n=11) D (n=8)	Ico (n=39) D (n=46)
Withdrawal from trial	Ico (n=10) D (n=7)	Ico (n=3) D (n=5)	Ico (n=6) D (n=8)	Ico (n=16) D (n=18)	Ico (n=11) D (n=8)	Ico (n=45) D (n=50)
Completed week 52						
Completed without permanent discontinuation of trial product	Ico (n=475) D (n=479)	Ico (n=256) D (n=253)	Ico (n=281) D (n=283)	Ico (n=274) D (n=269)	Ico (n=272) D (n=283)	Ico (n=483) D (n=493)
Completed without permanent discontinuation of trial product	Ico (n=7) D (n=3)	Ico (n=4) D (n=6)	Ico (n=5) D (n=7)	Ico (n=6) D (n=13)	Ico (n=5) D (n=2)	Ico (n=13) D (n=3)
Full analysis set (FAS)	Ico (n=492) D (n=492)	Ico (n=263) D (n=263)	Ico (n=294) D (n=294)	Ico (n=291) D (n=291)	Ico (n=290) D (n=292)	Ico (n=542) D (n=543)

Recruitment

All studies were global multi-centre studies and included a relevant portion of patients from Europe.

Trial 4477 (ONWARDS 1)

Trial 4477 was conducted in 12 countries. A total of 143 sites screened subjects and 140 sites randomised subjects in <u>North America</u>: USA (n=55), <u>Europe</u>: Croatia (n=4), Italy (n=5), Poland (n=8), Slovakia (n=7), Spain (n=5) and United Kingdom (n=11), <u>Asia</u>: Israel (n=5), Japan (n=14) and Russia n=14) and India (n=9) and <u>Central America</u>: Mexico (n=3).

Trial 4478 (ONWARDS 2)

Trial 4478 was conducted in 9 countries. A total of 71 sites screened subjects and 71 sites randomised subjects in <u>North America</u>: USA (n=26), <u>Europe</u>: Bulgaria (n=4), Germany (n=6), Poland (n=3), Portugal (n=6) and Ukraine (n=4), <u>Asia</u>: Japan (n=9) and Republic of Korea (n=7) and <u>South Africa</u> (n=6).

Trial 4479 (ONWARDS 3)

Trial 4479l was conducted in 11 countries. A total of 92 sites screened subjects and 89 sites randomised subjects in <u>North America</u>: USA (n=27), Canada (n=13), <u>Europe</u>: Austria (n=3), Czech Republic (n=6), Denmark (n=4) and France (n=8), <u>Asia</u>: China mainland (n=13) and Taiwan (n=5), <u>South America</u>: Argentina (n=4), Brazil (n=4) and <u>Central America</u>: Mexico (n=2).

Trial 4480 (ONWARDS 4)

Trial 4480 was conducted in 9 countries. A total of 83 sites screened subjects and 83 sites randomised subjects in <u>North America</u>: USA (n=30), <u>Europe</u>: Belgium (n=5), Italy (n=6), Netherlands (n=5), Romania (n=6) and <u>Asia</u>: India (n=9), Japan (n=9), Russia (n=10) and <u>Central America</u>: Mexico (n=3).

Trial 4481 (ONWARDS 5

Trial 4481 was conducted in 7 countries. A total of 182 sites screened subjects and 176 sites randomised subjects in <u>North America</u>: USA (n=80), Canada (n=34), <u>Europe</u>: Germany (n=14), Greece (n=12), Hungary (n=12), Poland (n=10) and Turkey (n=14).

Trial 4625 (ONWARDS 6)

Trial 4265 was conducted in 12 countries. A total of 99 sites screened subjects and 99 sites randomised subjects in <u>North America</u>: USA (n=29), Canada (n=5), <u>Europe</u>: Austria (n=6), Germany (n=8), Italy (n=5), Netherlands (n=4), Spain (n=4) and Turkey (n=7) and United Kingdom (n=8) and <u>Asia</u>: India (n=6), Japan (n=7) and Russia (n=10).

Conduct of the study

The statistical analysis plan was amended in all trials but ONWARDS 6; however, no substantial protocol amendment was made in any of the trials.

The protocol deviations in the trials are considered not to seriously affect the assessment of the results.

The ONWARDS studies were more or less run in parallel. They were initiated during 2020 or 2021 and completed during 2022, i.e., during the COVID-19 pandemic. According to the applicant, the ONWARDS studies were only minimally impacted by COVID-19.

Baseline data

The study populations were representative for the target population and balanced between the study groups with regards to HbA1c, FPG and severity of disease. A total of 180 patients >75 years were included in the trials. The subjects with T1DM (ONWARDS 6) were generally younger than the subjects with T2DM. In ONWARDS 6, 7.6% of the subjects were ≥65 years, while in the trials with a T2DM population it was between 30-44% were aged 65 years or more. About 47% of T1DM subjects and 24-48% of T2DM subjects. Asian subjects contributed to 21-37% of the study population in all studies except for the RWE trial ONWARDS 5 (4%) (Table 29 and Table 30).

The pretrial treatments with regards to insulin reflects the current treatment practice and was well balanced between groups. The T2DM groups were balanced with regards to non-insulin anti-diabetic treatment, except for a slight imbalance regarding treatment of SGLT-2 inhibitors (40% vs 32% for insulin icodec vs IDeg) and GLP-1 agonists (22% vs 16% for insulin icodec vs IDeg) in ONWARDS 3 and treatment of SU (9.6% vs 5.5% for insulin icodec vs IGlar) in ONWARDS 4. However, treatment with sulphonylureas was discontinued before study entry in ONWARDS 4. Treatment of metformin was used by 84-92% of insulin naïve subjects and basal switch subjects and by 66% of basal-bolus T2DM patients (Table 31).

Table 29. Demographics and baseline characteristics - full analysis set, ONWARDS trials

	ONWARDS 1	ONWARDS 3	ONWARDS 5	ONWARDS 2	ONWARDS 4	ONWARDS 6
Number of subjects	984	588	1085	526	582	582
Sex, N (%)						
N	984 (100.0)	588 (100.0)	1085 (100.0)	526 (100.0)	582 (100.0)	582 (100.0)
Male	558 (56.7)	369 (62.8)	622 (57.3)	302 (57.4)	304 (52.2)	337 (57.9)
Female	426 (43.3)	219 (37.2)	463 (42.7)	224 (42.6)	278 (47.8)	245 (42.1)
Age (years)						
N	984	588	1085	526	582	582
Mean (SD)	59.0 (9.9)	58.1 (10.0)	59.3 (10.5)	62.5 (9.1)	59.8 (10.0)	44.2 (14.1)
Median	60.0	58.0	60.0	63.0	61.0	44.0
Min ; max	27.0 ; 84.0	26.0 ; 81.0	27.0 ; 94.0	26.0 ; 86.0	19.0 ; 85.0	18.0 ; 82.0
Age group, N (%)						
N	984 (100.0)	588 (100.0)	1085 (100.0)	526 (100.0)	582 (100.0)	582 (100.0)
>=18 - <65 years	665 (67.6)	411 (69.9)	722 (66.5)	294 (55.9)	373 (64.1)	538 (92.4)
>=65 - <75 years	278 (28.3)	158 (26.9)	304 (28.0)	198 (37.6)	188 (32.3)	38 (6.5)
>=65 years	319 (32.4)	177 (30.1)	363 (33.5)	232 (44.1)	209 (35.9)	44 (7.6)
>=75 years	41 (4.2)	19 (3.2)	59 (5.4)	34 (6.5)	21 (3.6)	6 (1.0)
Race, N (%)						
N	984 (100.0)	588 (100.0)	1085 (100.0)	526 (100.0)	582 (100.0)	582 (100.0)
White	650 (66.1)	354 (60.2)	971 (89.5)	298 (56.7)	370 (63.6)	448 (77.0)
Black or African American	27 (2.7)	15 (2.6)	52 (4.8)	23 (4.4)	21 (3.6)	11 (1.9)
Asian	274 (27.8)	165 (28.1)	47 (4.3)	196 (37.3)	188 (32.3)	123 (21.1)
Other	33 (3.4)	23 (3.9)	14 (1.3)	9 (1.7)	2 (0.3)	0
Missing	0	31 (5.3)	1 (0.1)	0	1 (0.2)	0
Ethnicity, N (%)						
N	984 (100.0)	588 (100.0)	1085 (100.0)	526 (100.0)	582 (100.0)	582 (100.0)
Not Hispanic or Latino	878 (89.2)	393 (66.8)	989 (91.2)	494 (93.9)	476 (81.8)	562 (96.6)
Hispanic or Latino	106 (10.8)	164 (27.9)	95 (8.8)	32 (6.1)	105 (18.0)	20 (3.4)
Missing	0	31 (5.3)	1 (0.1)	0	1 (0.2)	0
Region, N (%)						
N	984 (100.0)	588 (100.0)	1085 (100.0)	526 (100.0)	582 (100.0)	582 (100.0)
Europe	471 (47.9)	142 (24.1)	557 (51.3)	167 (31.7)	205 (35.2)	275 (47.3)
North America	220 (22.4)	149 (25.3)	528 (48.7)	139 (26.4)	133 (22.9)	191 (32.8)
South America	41 (4.2)	152 (25.9)	0	0	66 (11.3)	0
Africa	0	0	0	50 (9.5)	0	0
Asia	252 (25.6)	145 (24.7)	0	170 (32.3)	178 (30.6)	116 (19.9)
BMI (kg/m^2)						
N	984	588	1084	526	582	582
Mean (SD)	30.1 (4.9)	29.6 (5.1)	32.8 (7.0)	29.3 (5.0)	30.3 (5.0)	26.5 (4.8)
Median	29.9	28.8	31.5	29.0	30.2	26.0
Min ; max	15.4 ; 40.3	16.6 ; 41.1	17.7 ; 85.6	16.9 ; 40.6	18.1 ; 41.2	16.2 ; 46.6
BMI (kg/m^2), N (%)						
N	984 (100.0)	588 (100.0)	1085 (100.0)	526 (100.0)	582 (100.0)	582 (100.0)
<25	167 (17.0)	110 (18.7)	105 (9.7)	110 (20.9)	91 (15.6)	240 (41.2)
>=25 - <30	335 (34.0)	230 (39.1)	313 (28.8)	197 (37.5)	191 (32.8)	220 (37.8)
Missing	0	0	1 (0.1)	0	0	0
>=30 - <35	308 (31.3)	146 (24.8)	311 (28.7)	132 (25.1)	192 (33.0)	87 (14.9)
>=35	174 (17.7)	102 (17.3)	355 (32.7)	87 (16.5)	108 (18.6)	35 (6.0)

Table 30. Baseline diabetes characteristics - full analysis set, ONWARDS trials

	ONWARDS 1	ONWARDS 3	ONWARDS 5	ONWARDS 2	ONWARDS 4	ONWARDS 6
Number of subjects	984	588	1085	526	582	582
HbA1c (%)						
N	984	588	1084	526	582	582
Mean (SD)	8.5 (1.0)	8.5 (1.1)	8.9 (1.6)	8.1 (0.8)	8.3 (0.9)	7.6 (0.9)
Median	8.3	8.4	8.5	8.0	8.2	7.6
Min ; max	6.6 ; 12.8	6.7 ; 11.6	6.3 ; 16.3	6.4 ; 11.0	6.6 ; 12.9	5.1 ; 10.1
HbA1c, N (%)						
N	984 (100.0)	588 (100.0)	1085 (100.0)	526 (100.0)	582 (100.0)	582 (100.0)
<8%	358 (36.4)	217 (36.9)	346 (31.9)	251 (47.7)	237 (40.7)	378 (64.9)
>=8%	626 (63.6)	371 (63.1)	738 (68.0)	275 (52.3)	345 (59.3)	204 (35.1)
Missing	0	0	1 (0.1)	0	0	0
HbA1c (mmol/mol)						
N	984	588	1084	526	582	582
Mean (SD)	69.1 (11.0)	69.6 (11.6)	74.0 (17.0)	65.4 (8.5)	67.2 (9.6)	59.7 (10.3)
Median	67.2	68.3	69.4	63.9	66.1	59.6
Min ; max	48.6 ; 116.4	49.7 ; 103.3	45.4 ; 154.7	46.5 ; 96.7	48.6 ; 117.5	32.2 ; 86.9
FPG (mmol/L)						
N	954	574	N/A	517	567	563
Mean (SD)	10.3 (2.8)	10.1 (2.8)	N/A	8.4 (2.5)	9.4 (3.3)	9.7 (4.1)
Median	9.9	9.5	N/A	8.2	8.9	9.0
Min ; max	4.1 ; 22.6	4.5 ; 24.3	N/A	2.9 ; 18.7	3.1 ; 24.2	2.2 ; 27.7
FPG (mg/dL)						
N	954	574	N/A	517	567	563
Mean (SD)	185.5 (50.3)	181.4 (50.4)	N/A	151.5 (44.3)	169.8 (59.0)	175.7 (73.1)
Median	178.4	171.2	N/A	147.8	160.4	162.2
Min ; max	73.9 ; 407.3	81.1 ; 437.9	N/A	52.3 ; 337.0	55.9 ; 436.1	39.6 ; 499.2
Duration of diabetes (years)						
N	984	588	1085	526	582	582
Mean (SD)	11.5 (6.7)	11.3 (6.6)	11.9 (7.3)	16.7 (8.1)	17.1 (8.4)	19.5 (13.0)
Median	10.8	10.6	11.2	15.5	16.5	17.2
Min ; max	0.5 ; 41.3	0.0 ; 40.7	0.2 ; 51.5	0.7 ; 51.3	0.6 ; 59.6	1.1 ; 62.5
Duration of diabetes (years), N (%)						
N	984 (100.0)	588 (100.0)	1085 (100.0)	526 (100.0)	582 (100.0)	582 (100.0)
<10 years	441 (44.8)	274 (46.6)	471 (43.4)	102 (19.4)	117 (20.1)	157 (27.0)
>=10 years	543 (55.2)	314 (53.4)	614 (56.6)	424 (80.6)	465 (79.9)	425 (73.0)
eGFR (mL/min/1.73m^2)						
N	984	587	1084	526	582	582
Mean (SD)	85.5 (18.9)	90.8 (18.9)	88.1 (20.7)	80.6 (19.3)	81.9 (20.4)	97.8 (19.2)
Median	88.0	95.0	92.0	84.0	84.0	98.0
Min ; max	26.0 ; 148.0	32.0 ; 140.0	17.0 ; 135.0	32.0 ; 140.0	33.0 ; 149.0	36.0 ; 161.0
Renal function (eGFR, mL/min/1.73m^2), N (%)						
N	984 (100.0)	588 (100.0)	1085 (100.0)	526 (100.0)	582 (100.0)	582 (100.0)
Normal (>=90)	446 (45.3)	358 (60.9)	618 (57.0)	203 (38.6)	250 (43.0)	387 (66.5)
Mild impairment (>=60 - <90)	436 (44.3)	185 (31.5)	345 (31.8)	243 (46.2)	241 (41.4)	181 (31.1)
Moderate impairment (>=30 - <60)	101 (10.3)	44 (7.5)	113 (10.4)	80 (15.2)	91 (15.6)	14 (2.4)
Severe impairment (<30)	1 (0.1)	0	8 (0.7)	0	0	0
Missing	0	1 (0.2)	1 (0.1)	0	0	0
Hepatic function, N (%)						
N	984 (100.0)	588 (100.0)	1085 (100.0)	526 (100.0)	582 (100.0)	582 (100.0)
Normal	928 (94.3)	570 (96.9)	1044 (96.2)	498 (94.7)	552 (94.8)	566 (97.3)
Impaired	2 (0.2)	0	8 (0.7)	0	4 (0.7)	1 (0.2)
Missing	54 (5.5)	18 (3.1)	33 (3.0)	28 (5.3)	26 (4.5)	15 (2.6)
Personal CGM device use, N (%)						
N	984 (100.0)	588 (100.0)	1085 (100.0)	526 (100.0)	582 (100.0)	582 (100.0)
Yes	0	0	0	23 (4.4)	102 (17.5)	0
No	0	0	0	503 (95.6)	480 (82.5)	0
Not Collected	984 (100.0)	588 (100.0)	1085 (100.0)	0	0	582 (100.0)

Table 31. Anti-diabetic non-insulin background medication at screening - full analysis set

	ONWARDS 1		ONWARDS 3		ONWARDS 5		ONWARDS 2		ONWARDS 4	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Number of subjects	984		588		1085		526		582	
Metformin	885	(89.9)	530	(90.1)	998	(92.0)	440	(83.7)	385	(66.2)
SGLT-2i	359	(36.5)	214	(36.4)	474	(43.7)	173	(32.9)	168	(28.9)
GLP-1 RA	175	(17.8)	112	(19.0)	306	(28.2)	137	(26.0)	71	(12.2)
Injectable	171	(17.4)	112	(19.0)	296	(27.3)	136	(25.9)	71	(12.2)
Oral	4	(0.4)	0		9	(0.8)	1	(0.2)	0	
DPP-4i	347	(35.3)	156	(26.5)	306	(28.2)	128	(24.3)	83	(14.3)
SU	446	(45.3)	260	(44.2)	439	(40.5)	114	(21.7)	44	(7.6)
Alpha-glucosidase inhibitor	45	(4.6)	38	(6.5)	6	(0.6)	28	(5.3)	18	(3.1)
Thiazolidinediones	49	(5.0)	45	(7.7)	45	(4.1)	21	(4.0)	18	(3.1)
Glinides	26	(2.6)	11	(1.9)	13	(1.2)	19	(3.6)	2	(0.3)

Numbers analysed

The primary efficacy analysis population in all studies was the full analysis population (FAS) including all randomised subjects. This is agreed. In general, drop-out rates were low and balanced between the groups. A large proportion of patients completed the trials without permanent discontinuation of trial product (93-97% in the confirmatory trials and 90% in the RWE trial) (Table 32).

Only 3 subjects (1 subject in ONWARDS 4 and 2 subjects in ONWARDS 5) discontinued treatment due to lack of efficacy of insulin icodec. In ONWARDS 1-4, less than 11% made any changes in their anti-diabetic treatment, of which slightly more subjects in the daily basal insulin arm (0.7-6.9%) than in the insulin icodec arm (0.7-4.4%) needed intensification of treatment. The need to intensify (increase dose or initiate) anti-diabetic treatment was similar or lower for insulin icodec compared to daily basal insulin in all studies except ONWARDS 3, where the proportion of subjects was higher in the insulin icodec arm. In ONWARDS 5, a larger proportion of subjects (about 20%) had changes in anti-diabetic medications during the trial, including intensification to treatment (about 12%). However, there was no indication of lack of efficacy of insulin icodec based on changes in background treatment.

Table 32. Subject disposition – summary, ONWARDS trials

	ONWARDS 1 N	ONWARDS 1 (%)	ONWARDS 3 N	ONWARDS 3 (%)	ONWARDS 5 N	ONWARDS 5 (%)	ONWARDS 2 N	ONWARDS 2 (%)	ONWARDS 4 N	ONWARDS 4 (%)	ONWARDS 6 N	ONWARDS 6 (%)
Randomised												
Insulin icodec	492	(100.0)	294	(100.0)	542	(100.0)	263	(100.0)	291	(100.0)	290	(100.0)
Daily basal insulin	492	(100.0)	294	(100.0)	543	(100.0)	263	(100.0)	291	(100.0)	292	(100.0)
Total	984	(100.0)	588	(100.0)	1085	(100.0)	526	(100.0)	582	(100.0)	582	(100.0)
Exposed												
Insulin icodec	492	(100.0)	293	(99.7)	542	(100.0)	262	(99.6)	291	(100.0)	290	(100.0)
Daily basal insulin	492	(100.0)	294	(100.0)	538	(99.1)	263	(100.0)	291	(100.0)	292	(100.0)
Total	984	(100.0)	587	(99.8)	1080	(99.5)	525	(99.8)	582	(100.0)	582	(100.0)
Full analysis set (FAS)												
Insulin icodec	492	(100.0)	294	(100.0)	542	(100.0)	263	(100.0)	291	(100.0)	290	(100.0)
Daily basal insulin	492	(100.0)	294	(100.0)	543	(100.0)	263	(100.0)	291	(100.0)	292	(100.0)
Total	984	(100.0)	588	(100.0)	1085	(100.0)	526	(100.0)	582	(100.0)	582	(100.0)
Safety analysis set (SAS)												
Insulin icodec	492	(100.0)	293	(99.7)	542	(100.0)	262	(99.6)	291	(100.0)	290	(100.0)
Daily basal insulin	492	(100.0)	294	(100.0)	538	(99.1)	263	(100.0)	291	(100.0)	292	(100.0)
Total	984	(100.0)	587	(99.8)	1080	(99.5)	525	(99.8)	582	(100.0)	582	(100.0)
Permanent discontinuation of trial product												
Insulin icodec	17	(3.5)	13	(4.4)	59	(10.9)	7	(2.7)	17	(5.8)	18	(6.2)
Daily basal insulin	12	(2.4)	11	(3.7)	50	(9.2)	10	(3.8)	22	(7.6)	9	(3.1)
Total	29	(2.9)	24	(4.1)	109	(10.0)	17	(3.2)	39	(6.7)	27	(4.6)
Withdrawn from trial												
Insulin icodec	10	(2.0)	6	(2.0)	45	(8.3)	3	(1.1)	16	(5.5)	11	(3.8)
Daily basal insulin	7	(1.4)	8	(2.7)	50	(9.2)	5	(1.9)	18	(6.2)	8	(2.7)
Total	17	(1.7)	14	(2.4)	95	(8.8)	8	(1.5)	34	(5.8)	19	(3.3)
Completed scheduled end-of-treatment visit												
Insulin icodec	482	(98.0)	288	(98.0)	496	(91.5)	260	(98.9)	278	(95.5)	277	(95.5)
Daily basal insulin	482	(98.0)	286	(97.3)	496	(91.3)	259	(98.5)	275	(94.5)	285	(97.6)
Total	964	(98.0)	574	(97.6)	992	(91.4)	519	(98.7)	553	(95.0)	562	(96.6)
Completed scheduled end-of-treatment visit without permanent discontinuation of trial product												
Insulin icodec	475	(96.5)	281	(95.6)	483	(89.1)	256	(97.3)	274	(94.2)	272	(93.8)
Daily basal insulin	479	(97.4)	283	(96.3)	493	(90.8)	253	(96.2)	269	(92.4)	283	(96.9)
Total	954	(97.0)	564	(95.9)	976	(90.0)	509	(96.8)	543	(93.3)	555	(95.4)
Completed scheduled end-of-treatment visit after permanent discontinuation of trial product												
Insulin icodec	7	(1.4)	7	(2.4)	13	(2.4)	4	(1.5)	4	(1.4)	5	(1.7)
Daily basal insulin	3	(0.6)	3	(1.0)	3	(0.6)	6	(2.3)	6	(2.1)	2	(0.7)
Total	10	(1.0)	10	(1.7)	16	(1.5)	10	(1.9)	10	(1.7)	7	(1.2)

Outcomes and estimation

Prespecified hierarchical testing in the confirmatory studies

The primary hypothesis was that insulin icodec was non-inferior to daily insulin comparator in terms of HbA$_{1c}$ change from baseline to week 26 (ONWARDS 2, 3, 4 and 6) or week 52 (ONWARDS 1 and 5). The non-inferiority margin was pre-specified at 0.3%-point.

In ONWARDS 1, 2, 3 and 5, additional hypotheses were adjusted for multiplicity via a hierarchical testing approach. Besides type I error control in ONWARDS 2, 3 and 5, to test for HbA1c superiority provided non-inferiority had been shown, multiplicity considerations had been made only for the key secondary endpoint TIR (time spent in glycaemic target range) in ONWARDS 1.

Primary endpoint

Change in HbA1c

The primary endpoint in all ONWARDS trials was change in HbA$_{1c}$ from baseline to end of treatment and was evaluated in the framework of the treatment policy estimand. The primary objective was met in all trials: insulin icodec treatment was non-inferior to marketed comparators (daily basal insulin) in reducing HbA$_{1c}$ from baseline. Furthermore, in ONWARDS 1, 3, and 5 with insulin-naïve T2DM subjects and in ONWARDS 2

with basal-switch T2DM subjects, insulin icodec was confirmed to be statistically superior to the daily basal insulins (insulins degludec and glargine) in reducing HbA$_{1c}$ from baseline to planned end of treatment (Table 33, Figure 22).

Table 33. HbA$_{1c}$ (%) Change from baseline at end of trial

	Insulin icodec	Daily insulin comparator	Estimated treatment difference [95% CI] Insulin icodec vs daily insulin comparator
Trial 4477 (ONWARDS 1)			
HbA$_{1c}$ (%) Estimated cfb (week 52)	-1.55	-1.35	ETD: -0.19 [-0.36; -0.03]♦
HbA$_{1c}$ (%) Estimated cfb (week 78)	-1.55	-1.44	ETD: -0.11 [-0.22; 0.00]
Trial 4478 (ONWARDS 2)			
HbA$_{1c}$ (%) Estimated cfb (week 26)	-0.93	-0.71	ETD: -0.22 [-0.37; -0.08]♦
Trial 4479 (ONWARDS 3)			
HbA$_{1c}$ (%) Estimated cfb (week 26)	-1.57	-1.36	ETD: -0.21 [-0.34; -0.08]♦
Trial 4480 (ONWARDS 4)			
HbA$_{1c}$ (%) Estimated cfb (week 26)	-1.16	-1.18	ETD: 0.02 [-0.11; 0.15]*
Trial 4481 (ONWARDS 5)			
HbA$_{1c}$ (%) Estimated cfb (week 52)	-1.68	-1.31	ETD: -0.38 [-0.66; -0.09]♦
Trial 4625 (ONWARDS 6)			
HbA$_{1c}$ (%) Estimated cfb (week 26)	-0.47	-0.51	ETD: 0.05 [-0.13; 0.23]*
HbA$_{1c}$ (%) Estimated cfb (week 52)	-0.37	-0.54	ETD: 0.17 [0.02; 0.31]

♦ Non-inferiority and statistically superiority confirmed for insulin icodec; * Non-inferiority confirmed for insulin icodec,

Figure 22. Estimated change in HbA$_{1c}$ in all ONWARDS trials

	ONWARDS 1	ONWARDS 3	ONWARDS 5	ONWARDS 2	ONWARD6 4	ONWARDS 6
Baseline HbA$_{1c}$ (%)	8.5	8.5	8.9	8.1	8.3	7.6
ETD [95%CI]	-0.19 [-0.36; -0.03]	-0.21 [-0.34; -0.08]	-0.38 [-0.66; -0.09]	-0.22 [-0.37; -0.08]	0.02 [-0.11; 0.15]	0.05 [-0.13; 0.23]
P-value non-inferiority	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0065
P-value superiority	0.0210	0.0016	0.0092	0.0028		
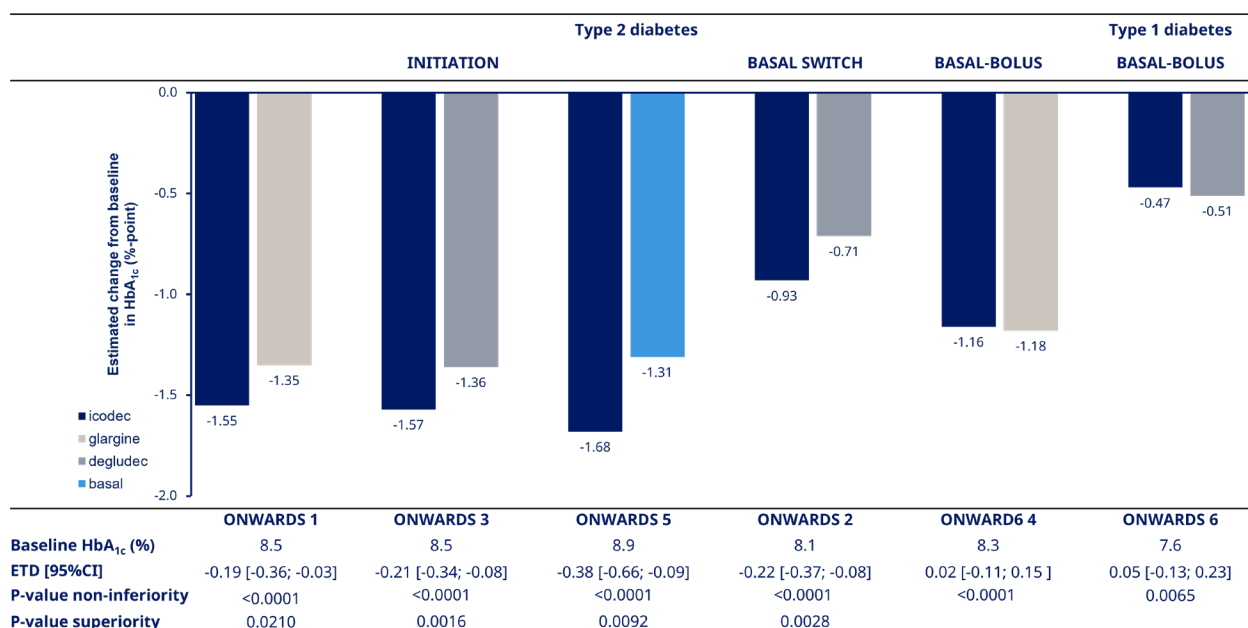
HbA1C over time

Mean baseline HbA1c was slightly higher in T2DM subjects (8.1%-8.9%) than in T1DM subjects (7.6%). Clinically relevant reductions in HbA1c were observed taking the baseline HbA1c into account. The change in HbA1c in the trials is presented over time in (Figure 23). In T1DM subjects, the HbA1c reduction was less pronounced for insulin icodec week 26 compared to week 18, while the HbA1c reduction was maintained for insulin degludec from week 18 to week 26At week 26, estimated reduction from baseline in mean HbA1c was -0.47% points for insulin icodec and -0.51% points for insulin degludec (ETD 0.05 [-0.13; 0.23]). At week 52, the efficacy had deteriorated for insulin icodec compared to insulin degludec. The change from baseline in mean HbA1c was -0.37% points with insulin icodec and -0.54% points with insulin degludec (ETD 0.17 [0.02; 0.31]) (Figure 24).

Figure 23. HbA₁c by treatment week, change from baseline, in-trial, mean plot, full analysis set
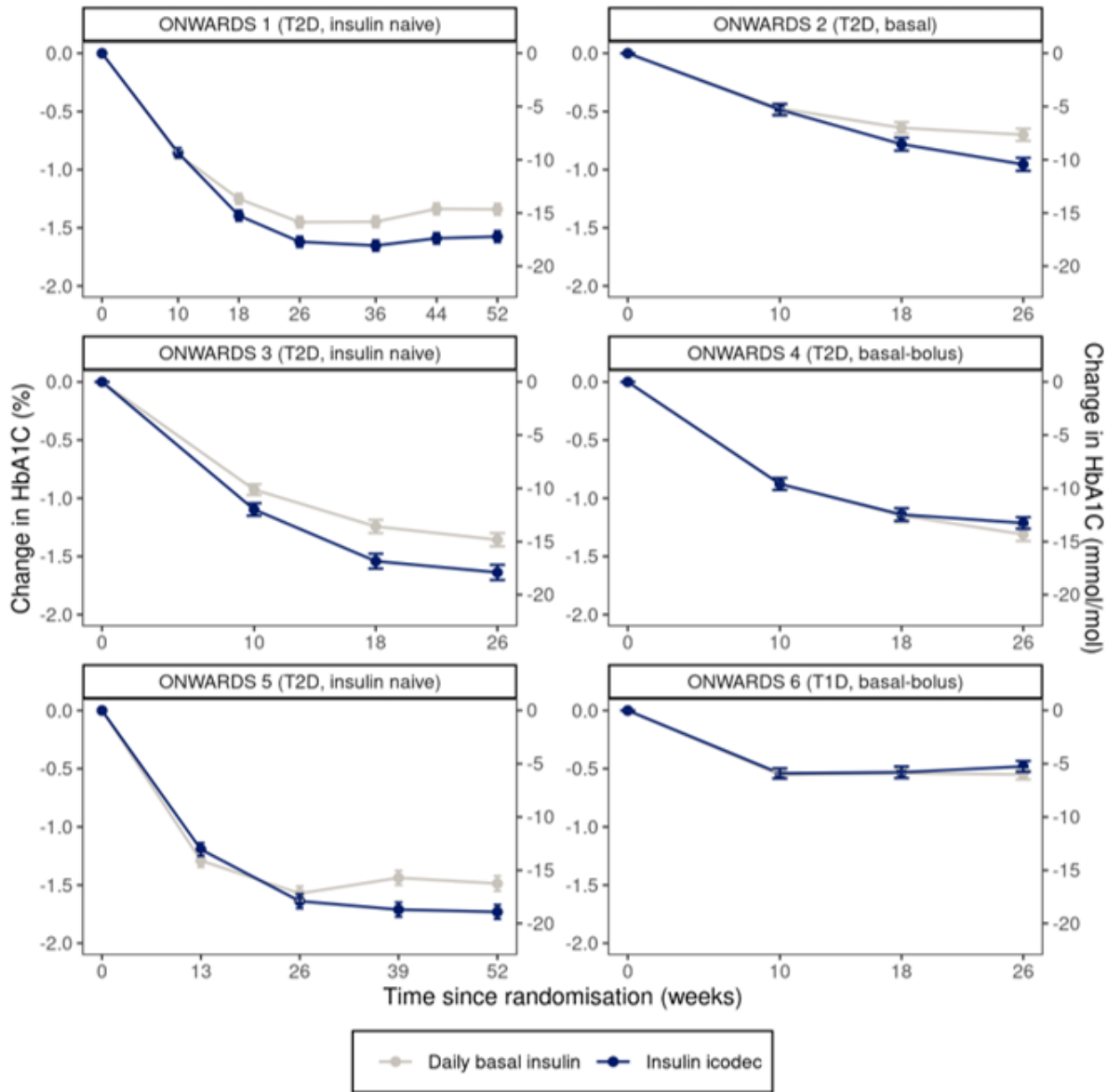
Figure 24. HbA1c by treatment week - change from baseline - in-trial -mean plot – full analysis set
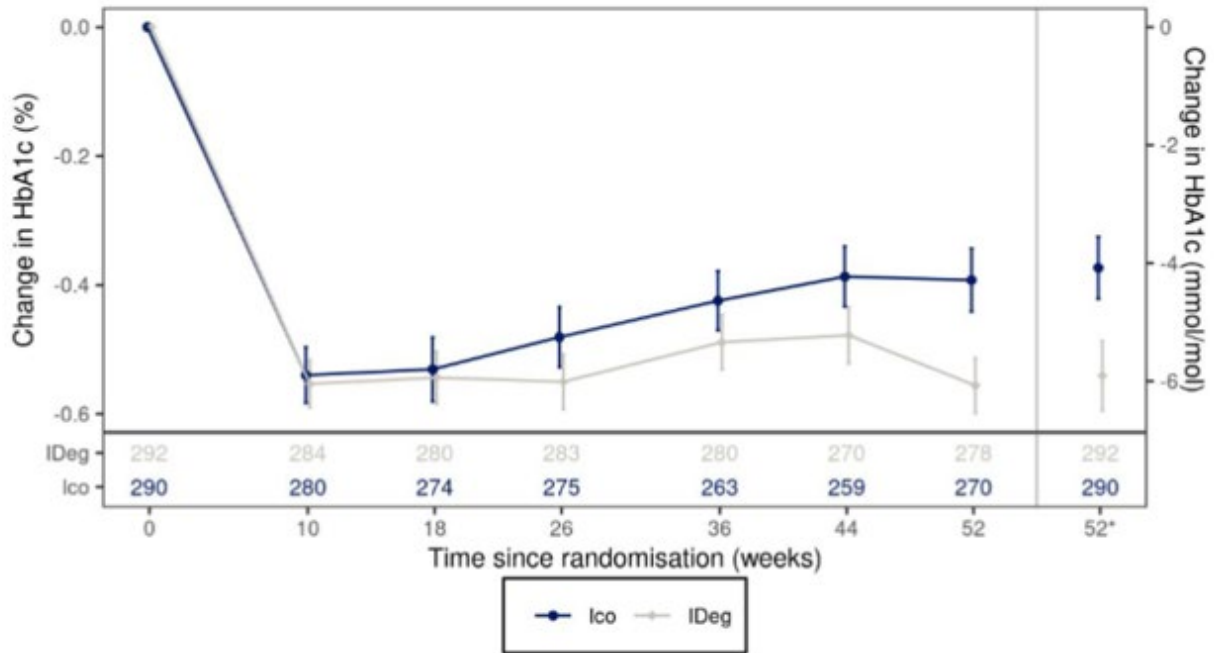
Secondary endpoints

Fasting plasma glucose

Change in fasting plasma glucose (FPG) from baseline to week 26 (week 52 in ONWARDS 1) was a supportive secondary endpoint in ONWARDS 1-4 and 6.

Mean FPG at baseline ranged between 8.36 mmol/L (150.70 mg/dL) and 10.37 mmol/L (186.78 mg/dL) across the trials. In T2DM subjects, no relevant difference in FPG reduction was observed between treatment arms. In T1DM subjects, the reduction in FPG from baseline to end of treatment was numerically larger for insulin degludec (-1.87 mmol/L) than for insulin icodec (-0.84 mmol/L); ETD: 1.03 [0.48; 1.58] (Table 34). This may be explained by FPG collected at the last day of the weekly dosing interval and that this difference potentially could reflect a higher variability of the FPG lowering effect throughout the insulin icodec dosing interval in T1DM subjects compared to T2DM subjects. The reduction in FPG for insulin degludec compared to insulin icodec was evident at the first post-baseline assessment (12 weeks) and the difference even increased from week 18 to week 26. At week 52, the reduction in FPG from baseline to end of treatment was -1.88 mmol/L for insulin degludec and -0.58 mmol/L for insulin icodec (ETD: 1.30 [0.73; 1.86] (Table 34).

Table 34. Change in fasting plasma glucose

	Insulin icodec	Daily insulin comparator	Estimated treatment difference/ratio [95% CI] Insulin icodec vs daily insulin comparator
Trial 4477 (ONWARDS 1)			
FPG			
Estimated cfb (week 52) mmol/L	-3.35	-3.33	ETD: -0.01 [-0.27; 0.24]
Estimated cfb (week 52) mg/dL	-60.32	-60.08	ETD: -0.24 [-4.89; 4.41]
FPG			
Estimated cfb (week 78) mmol/L	-3.32	-3.28	ETD: -0.04 [-0.31; 0.23]
Estimated cfb (week 78) mg/dL	-58.83	-59.09	ETD: -0.74 [-5.66; 4.17]
Trial 4478 (ONWARDS 2)			
FPG			
Estimated cfb (week 26) mmol/L	-1.58	-1.62	ETD: 0.04 [-0.28; 0.36]
Estimated cfb (week 26) mg/dL	-28.47	-29.18	ETD 0.71 [-5.12; 6.54]
Trial 4479 (ONWARDS 3)			
FPG			
Estimated cfb (week 26) mmol/L	-3.01	-2.99	ETD: -0.02 [-0.34; 0.29]
Estimated cfb (week 26) mg/dL	-54.28	-53.90	ETD: -0.38 [-6.05; 5.30]
Trial 4480 (ONWARDS 4)			
FPG			
Estimated cfb (week 26) mmol/L	-1.75	-1.61	ETD: -0.14 [-0.59; 0.31]
Estimated cfb (week 26) mg/dL	-31.54	-29.06	ETD: -2.48 [-10.59; 5.63]
Trial 4625 (ONWARDS 6)			
FPG			
Estimated cfb (week 26) mmol/L	-0.84	-1.87	ETD: 1.03 [0.48; 1.59]
Estimated cfb (week 26) mg/dL	-15.08	-33.66	ETD: 18.58 [8.58; 28.58]
FPG			
Estimated cfb (week 52) mmol/L	-0.58	-1.88	ETD: 1.30 [0.73; 1.86]
Estimated cfb (week 52) mg/dL	-10.46	-33.81	ETD: 23.35[13.11; 33.59]

Figure 25. Trial 4625 (ONWARDS 6): Fasting plasma glucose by treatment week - change from baseline - in-trial - mean plot – full analysis set
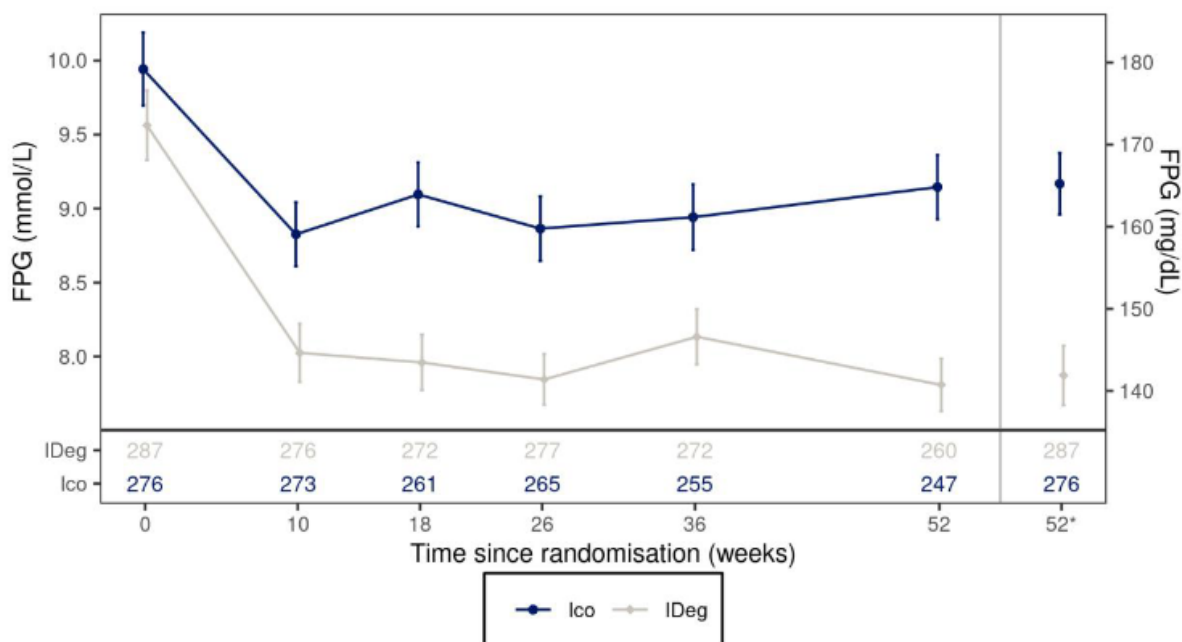
Time spent in glycaemic target range (CGM metrics)

In the insulin icodec phase 3a programme, ONWARDS 1, 2, 4 and 6 had CGM metrics endpoints for the last 4 weeks of planned treatment. The CGM data was blinded for both subjects and investigators in ONWARDS 1, 2 and 4 and unblinded in ONWARDS 6. Clinical guidance suggests that subjects should spend >70% of the time within the target range 3.9−10.0 mmol/L range to achieve optimal glycaemic control (ADA recommendation 2023).

Time spent in range (TIR) 3.9-10.0 mmol/L (70-180 mg/dL)

In ONWARDS 1, time spent in range (TIR) 3.9-10.0 mmol/L was a confirmatory secondary endpoint and in ONWARDS 2, 4 and 6, TIR was a supportive secondary endpoint. Insulin naïve subjects (ONWARDS 1), insulin icodec was statistically superior to daily basal insulin for TIR from week 48 to week 52. Generally, subjects spent most of the time within the range (Table 35).

Table 35. Time spent in range (TIR) 3.9-10.0 mmol/L (70-180 mg/dL)

	Insulin icodec	Daily insulin comparator	Estimated treatment difference [95% CI] Insulin icodec vs daily insulin comparator
Trial 4477 (ONWARDS 1)			
Time spent (%) week 48 to 52 Time in range 3.9-10.0 mmol/L	71.94	66.90	ETD: 4.27 [1.92: 6.62]•
Time spent (%) week 74 to 78 Time in range 3.9-10.0 mmol/L	70.18	64.83	ETD: 4.41 [1.92: 6.90]
Trial 4478 (ONWARDS 2)			
Time spent (%) week 22 to 26 Time in range 3.9-10.0 mmol/L	63.13	59.50	ETD: 2.41 [-0.84; 5.65]
Trial 4480 (ONWARDS 4)			
Time spent (%) week 22 to 26 Time in range 3.9-10.0 mmol/L	66.88	66.44	ETD: 0.29 [-2.52; 3.09]
Trial 4625 (ONWARDS 6)			
Time spent (%) week 22 to 26 Time in range 3.9-10.0 mmol/L	59.10	60.85	ETD: -2.00 [-4.38; 0.38]
Time spent (%) week 48 to 52 Time in range 3.9-10.0 mmol/L	57.26	59.60	ETD: -2.42 [-4.90; 0.07]

• Statistically superiority was confirmed for insulin icodec, p-value 0.0004, adjusted for multiplicity

Time spent below range (TBR) <3.0 mmol/L (54 mg/dL)

Time spent below range <3.0 mmol/L were secondary endpoints in ONWARDS 1, 2, 4 and 6. The amount of time spent below range <3.0 mmol/L was low in ONWARDS 1, 2 and 4 with no important differences. In T1DM subjects, subjects in the insulin icodec group vs. insulin degludec spent more time in TBR <3.0 mmol/L (1.02% vs. 0.68%) (Table 36) and TBR <3.9 mmol/L: 3.86% in the insulin icodec group and 2.90% in the insulin degludec group (Table 37).

Table 36. Time spent below range (TBR) < 3.0 mmol/L (54 mg/dL)

	Insulin icodec	Daily insulin comparator	Estimated treatment ratio [95% CI] Insulin icodec vs daily insulin comparator
Trial 4477 (ONWARDS 1)			
Time spent (%) week 48 to 52 Time spent < 3.0 mmol/L	0.27	0.21	ETR: 1.27 [0.94; 1.71]
Time spent (%) week 74 to 78 Time spent < 3.0 mmol/L	0.29	0.24	ETR: 1.20 [0.89; 1.61]
Trial 4478 (ONWARDS 2)			
Time spent (%) week 22 to 26 Time spent < 3.0 mmol/L	0.34	0.22	ETR: 1.37 [0.92; 2.04]
Trial 4480 (ONWARDS 4)			
Time spent (%) week 22 to 26 Time spent < 3.0 mmol/L	0.73	0.61	ETR: 1.20 [0.91; 1.58]
Trial 4625 (ONWARDS 6)			
Time spent (%) week 22 to 26 Time spent < 3.0 mmol/L	1.02	0.68	ETR: 1.46 [1.16; 1.85]
Time spent (%) week 48 to 52 Time spent < 3.0 mmol/L	0.84	0.80	ETR: 1.02 [0.80; 1.30]

Table 37. Time spent below range <3.9 mmol/L

	Insulin icodec	Daily insulin comparator	
Trial 4477 (ONWARDS 1)			
Time spent (%) week 48 to 52 Time spent < 3.9 mmol/L	1.20	0.83	
Trial 4478 (ONWARDS 2)			
Time spent (%) week 22 to 26 Time spent < 3.9 mmol/L	1.35	0.79	
Trial 4480 (ONWARDS 4)			
Time spent (%) week 22 to 26 Time spent < 3.9 mmol/L	2.65	2.26	
Trial 4625 (ONWARDS 6)			
Time spent (%) week 22 to 26 Time spent < 3.9 mmol/L	3.86	2.90	
Time spent (%) week 48 to 52 Time spent < 3.9 mmol/L	3.42	3.15	

Time spent above range (TAR) >10.0 mmol/L (180 mg/dL)

Time spent above range >10.0 mmol/L (TAR) were secondary endpoints in ONWARDS 1, 2, 4 and 6. In ONWARDS 1), subjects in the insulin icodec group vs. insulin glargine spent less time above range >10.0 mmol/L (26.9% vs. 32.3%). There were no important differences for TAR in ONWARDS 2, 4 and 6 (Table 38).

Table 38. Time spent above range (TAR) >10 mmol/L (180 mg/dL)

	Insulin icodec	Daily insulin comparator	Estimated treatment ratio [95% CI] Insulin icodec vs daily insulin comparator
Trial 4477 (ONWARDS 1)			
Time spent (%) week 48 to 52 Time spent >10 mmol/L	26.86	32.27	ETD: -4.58 [-6.99; -2.17]
Time spent (%) week 74 to 78 Time spent >10 mmol/L	28.71	34.34	ETD: -4.65[-7.20; -2.10]
Trial 4478 (ONWARDS 2)			
Time spent (%) week 22 to 26 Time spent >10 mmol/L	35.52	39.71	ETD: -2.93 [-6.25; 0.39]
Trial 4480 (ONWARDS 4)			
Time spent (%) week 22 to 26 Time spent >10 mmol/L	30.47	31.30	ETD: -0.60 [-3.47; 2.28]
Trial 4625 (ONWARDS 6)			
Time spent (%) week 22 to 26 Time spent >10 mmol/L	37.03	3625	ETD: 1.14 [-1.34; 3.61]
Time spent (%) week 48 to 52 Time spent >10 mmol/L	39.32	37.25	ETD: 2.27 [-0.39; 4.94]

Mean weekly insulin dose

To reflect medical practice for insulin therapy in diabetes treatment and to provide optimal individual treatment, there was no restriction on the maximum dose of insulin in the ONWARDS trials. The mean weekly basal insulin dose during the last two weeks of planned treatment is presented in Table 39 and Table 40.

In insulin naïve T2DM subjects (trial 4477 and 4479), the mean weekly insulin dose was numerically higher for insulin glargine vs. insulin icodec in trial 4477, while the opposite in trial 4479 where the average weekly basal insulin dose was numerically higher for insulin icodec vs. insulin degludec. In basal switch and basal-bolus T2DM subjects (trial 4478 and 4480) and in T1DM subjects (trial 4625), the mean weekly *basal insulin dose*, including the weight-correlated dose, was numerically higher for insulin icodec compared with daily basal insulin. However, the mean weekly *bolus insulin dose* and mean weekly *total insulin dose* (bolus + basal), respectively, was numerically lower for insulin icodec compared to daily basal insulin in trial 4478 and 4480. In ONWARDS 5, the mean weekly basal insulin dose was not an endpoint due to the different titration in the two arms. However, the estimated mean weekly basal insulin dose from week 50 to week 52 was numerically higher in the insulin icodec group (226.51 U) compared to the daily basal comparator group (185.23 U).

Table 39. Estimated mean weekly insulin dose during the last two weeks of planned treatment – ONWARDS 1 and 3

	Insulin icodec	Daily basal insulin	Estimated treatment ratio, ETR
ONWARDS 1 (w 48 to 52)			
Basal (U)	214.23	222.39	0.96 [0.89; 1.05]
Basal (U/kg)	2.52	2.64	0.95 [0.88; 1.03]
ONWARDS 1 (w 76 to 78)			
Basal (U)	223.81	234.35	0.96 [0.87; 1.04]
ONWARDS 3 (w 24 to 26)			
Basal (U)	204.28	186.52	1.10 [0.98; 1.22]
Basal (U/kg)	2.38	2.24	1.06 [0.97; 1.17]
ONWARDS 2 (w 24 to 26)			
Basal (U)	267.96	244.22	1.10 [1.01; 1.20]
Basal (U/kg)	3.26	3.05	1.07 [0.99; 1.16]

Table 40. Estimated mean weekly insulin dose during the last two weeks of planned treatment – ONWARDS 2, 4 and 6

	Insulin icodec	Daily basal insulin	Estimated treatment ratio, ETR
ONWARDS 2 (w 24 to 26)			
Basal (U)	267.96	244.22	1.10 [1.01; 1.20]
Basal (U/kg)	3.26	3.05	1.07 [0.99; 1.16]
ONWARDS 4 (w 24 to 26)			
Total	513.54	559.05	0.92 [0.85; 0.99]
Basal (U)	305.06	279.42	1.09 [1.01; 1.18]
Basal (U/kg)	3.59	3.34	1.08 [1.00; 1.16]
Bolus	197.45	255.26	0.77 [0.70; 0.86]
ONWARDS 6 (w 24 to 26)			
Total	310.52	322.68	0.96 [0.90; 1.03]
Basal (U)	169.96	151.24	1.12 [1.07; 1.18]
Basal (U/kg)	2.21	1.97	1.12 [1.07; 1.18]
Bolus	131.86	161.42	0.82 [0.74; 0.90]
ONWARDS 6 (w 50 to 52)			
Total	310.14	328.90	0.94 [0.88; 1.01]
Basal (U)	169.47	152.78	1.11 [1.04; 1.18]

	Insulin icodec	Daily basal insulin	Estimated treatment ratio, ETR
Bolus	135.72	161.25	0.84 [0.76; 0.93]

Number of hypoglycaemic events

See Clinical Safety section below.

Change in body weight

Weight gain is expected with intensified insulin treatment. The mean body weight increased numerically slightly more for insulin icodec compared to daily basal insulin in all studies. The estimated treatment difference, ETD, of weight gain was <1 kg in all studies except for ONWARDS 2 where the ETD of change from baseline in body weight after 26 weeks was 1.70 kg [0.76; 2.63] for insulin icodec vs insulin degludec.

ONWARDS 1: At baseline, the observed mean body weight was 85.17 kg in the insulin icodec treatment group and 84.31 kg in the insulin glargine treatment group. At week 52, the estimated mean body weight was 87.03 kg in the insulin icodec treatment group and 86.57 kg in the insulin glargine treatment group. Estimated change from baseline to week 52 in body weight (LS Means) was 2.29 kg with insulin icodec and 1.83 kg with insulin glargine. The estimated treatment difference of change in body weight for insulin icodec vs. insulin glargine: ETD = 0.46 [-0.12; 1.04].

ONWARDS 2: At baseline, the observed mean body weight was 83.72 kg in the insulin icodec treatment group and 81.54 kg in the insulin degludec treatment group. At week 26, the estimated mean body weight was 84.03 in the insulin icodec treatment group and 82.33 in the insulin degludec group. Estimated change from baseline to week 26 in body weight (LS Means) was 1.40 kg with insulin icodec and -0.30 kg with insulin degludec. The estimated treatment difference of change from baseline in body weight after 26 weeks for insulin icodec vs. insulin degludec was in favour of insulin degludec: ETD 1.70 [0.76; 2.63].

ONWARDS 3: At baseline, the observed mean body weight was 85.78 kg for subjects in the insulin icodec treatment group and 83.24 kg for subjects in the insulin degludec treatment group. At 26 weeks, the estimated mean body weight was 87.27 kg for subjects in the insulin icodec treatment group and 86.82 kg for subjects in the insulin degludec treatment group. Estimated change from baseline to week 26 in body weight (LS Means) was 2.77 kg with insulin icodec and 2.32 kg with insulin degludec. The estimated treatment difference of change in body weight from baseline to week 26 for insulin icodec vs. insulin degludec: ETD 0.46 [-0.19; 1.10].

ONWARDS 4: At baseline, the observed mean body weight was 85.51 kg in the insulin icodec treatment group and 83.08 kg in the insulin glargine treatment group. At week 26, the estimated mean body weight was 87.03 kg in the insulin icodec treatment group and 86.45 kg in the insulin glargine treatment group. Estimated change from baseline to week 26 in body weight (LS Means) was 2.73 kg with insulin icodec and 2.16 kg with insulin glargine. The estimated treatment difference of change from baseline (week 0) to week 26 in body weight for insulin icodec vs. insulin glargine: ETD 0.57 [-0.39; 1.54].

ONWARDS 6: At baseline, the observed mean body weight was 78.65 kg in the insulin icodec treatment group and 77.10 kg in the insulin degludec treatment group. At week 26, the estimated mean body weight was 79.16 kg in the insulin icodec treatment group and 78.88 kg in the insulin degludec group. Estimated change from baseline to week 26 in body weight was 1.29 kg with insulin icodec and 1.01 kg with insulin

degludec. The estimated treatment difference of change from baseline (week 0) to week 26 in body weight (LS Means) for insulin icodec vs. insulin degludec; ETD 0.28 [- 0.37; -0.92].

Patient reported outcomes

DTSQ

In ONWARDS 2, 5 and 6, the DTSQs (Diabetes Treatment Satisfaction Questionnaire) was used to assess the change in total treatment satisfaction from baseline to end of treatment. The total score can range from 0-36, as it is composed of 6 items scored on a scale of 0 to 6. The higher the score the greater the satisfaction with treatment.

The observed mean DTSQ total score at baseline was between 26 and 27 in both treatment arms in ONWARDS 2 and ONWARDS 5. At the end of treatment, the estimated mean DTSQ total score in the insulin icodec and daily basal insulin arm was 30.95 and 29.69, respectively, in ONWARDS 2 and 31.13 and 30.35, respectively, in ONWARDS 5. In ONWARDS 2, the estimated treatment difference in change from baseline in DTSQs score at the end of treatment was ETD 1.25 [0.41; 2.10] for insulin icodec vs insulin degludec and in ONWARDS 5, ETD 0.78 [0.10; 1.47] for insulin icodec vs daily basal insulin.

In T1DM subjects (ONWARDS 6), the observed mean DTSQ total score at baseline was 28.45 in the insulin icodec arm and 28.33 in the insulin degludec arm. At the end of treatment in the main phase at week 26, the estimated mean DTSQ total score was 30.36 and 31.46 in the insulin icodec and insulin degludec arm, respectively. In T2DM patients (ONWARDS 2 and 5), the change in DTSQ total score was numerically higher and in favour of insulin icodec; however, in T1DM patients, increase in the DTSQ total score was greater for insulin degludec (Figure 26). At week 52, the estimated mean DTSQ total score was 29.81 in the insulin icodec treatment group and 31.40 in the insulin degludec group. The estimated treatment difference in change from baseline in DTSQs score after 52 weeks was ETD -1.59 [-2.51;-0.67].

Figure 26. DTSQ total treatment satisfaction score by question at planned end of treatment - change from baseline - in-trial - mean plot - full analysis set
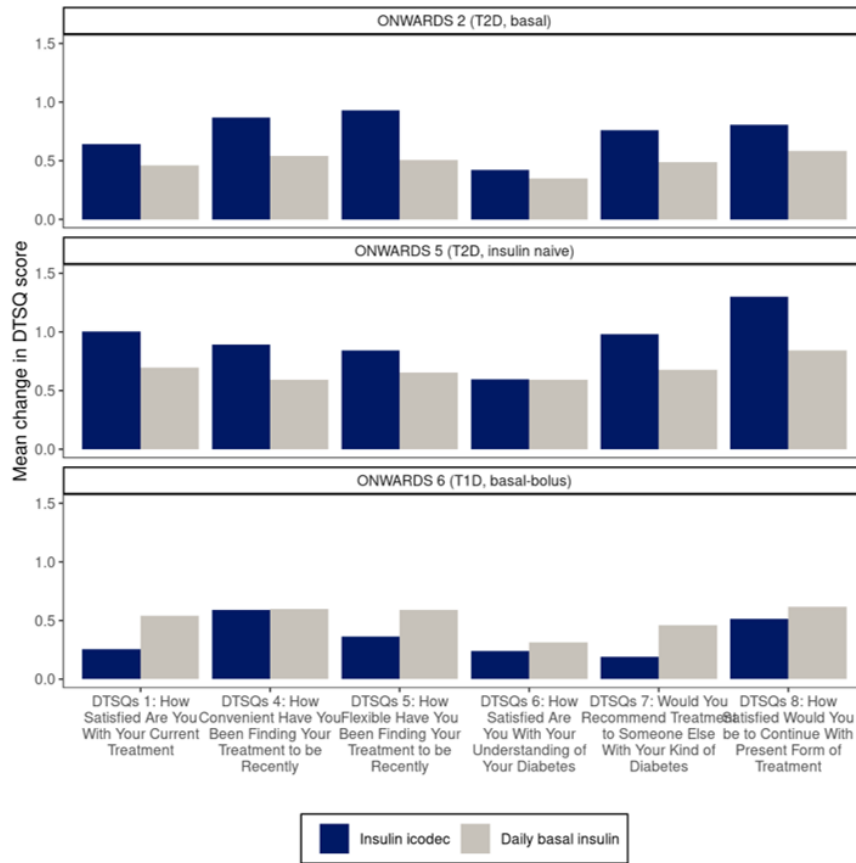
TRIM-D

In ONWARDS 5, the compliance domain of the TRIM-D (Treatment Related Impact Measures – Diabetes) questionnaire was used to measure the compliance within each treatment arm at end of treatment. The estimated TRIM-D compliance scores at week 52 were high in both arms with 90.42 and 87.37 out of 100. The score in the insulin icodec arm was higher compared to daily basal insulin (ETD 3.04 [1.28; 4.81].

Time from baseline to treatment discontinuation or intensification

Time from baseline to treatment discontinuation or intensification was a supportive endpoint in ONWARDS 5. Treatment intensification was defined as intensification to a basal bolus regimen or continuous use of bolus insulin. In both treatment groups, the main reason for permanent discontinuation of trial product was withdrawal of consent (3.3% of all subjects in insulin icodec with DoseGuide treatment group and 2.9% of all subjects in OD insulin analogue treatment group). Intensification to basal bolus regimen or continuous use of bolus insulin was reported for 1 (0.2%) subject in the insulin icodec with DoseGuide treatment group. There were no subjects in the OD insulin analogue treatment group reporting treatment intensification.

Ancillary analyses

Other efficacy analysis

Achievement of HbA$_{1c}$ <7.0% or ≤6.5% without level 2 or 3 hypoglycaemia episodes

A prespecified analysis of achievement of target HbA$_{1c}$ without hypoglycaemia was performed. In insulin naïve subjects and in T2DM subjects with basal switch (ONWARDS 1-3, 5), responder rates of achieving HbA$_{1c}$ <7% or ≤6.5 without severe or clinically significant hypoglycaemia were numerically higher for insulin icodec compared to daily basal insulin. In basal-bolus T2DM subjects (ONWARDS 4), the rates were comparable between the treatment groups. However, in T1DM subjects (ONWARDS 6), the responder rates of achieving HbA$_{1c}$ targets without level 2 or 3 hypoglycaemia was numerically lower for insulin icodec compared to insulin degludec. Responder rates of achieving HbA$_{1c}$ <7% without level 2 or 3 hypoglycaemia was 9.6% for insulin icodec and 16.7% for insulin degludec.

The odds of achieving HbA$_{1c}$ <7% or ≤6.5% without level 2 or 3 hypoglycaemia 12 weeks prior end of treatment is presented in Table 41 and Table 42.

Table 41. HbA$_{1c}$ <7.0% without level 2 or 3 hypoglycaemic episodes during the prior 12 weeks

Study	Estimated proportion of subjects (%)		Estimated odds ratio [95% CI] Insulin icodec vs insulin degludec
	Insulin icodec	Insulin degludec	
ONWARDS 1 (52 weeks)	52.56	42.58	1.49 [1.15; 1.94]
ONWARDS 1 (78 weeks)	54.45	46.36	1.38 [1.06; 1.80]
ONWARDS 2 (26 weeks)	36.73	26.79	1.59 [1.07; 2.36]
ONWARDS 3 (26 weeks)	52.13	39.86	1.64 [1.16; 2.33]
ONWARDS 4 (26 weeks)	26.48	25.24	1.07 [0.73; 1.55]
ONWARDS 5 (52 weeks)	40.53	31.61	1.47 [1.13; 1.92]
ONWARDS 6 (26 weeks)	9.55	16.74	0.52 [0.33; 0.85]
ONWARDS 6 (52 weeks)	7.21	11.63	0.59 [0.37 ; 0.95]

Table 42. HbA$_{1c}$ ≤6.5 % without level 2 or 3 hypoglycaemic episodes during the prior 12 weeks

Study	Estimated proportion of subjects (%)		Estimated odds ratio [95% CI] Insulin icodec vs insulin degludec
	Insulin icodec	Insulin degludec	
ONWARDS 1 (52 weeks)	29.68	22.74	1.43 [1.07; 1.92]
ONWARDS 1 (78 weeks)	33.47	27.35	1.34 [1.01; 1.76]
ONWARDS 2 (26 weeks)	12.54	7.77	1.70 [1.00; 2.91]
ONWARDS 3 (26 weeks)	28.33	18.69	1.72 [1.16; 2.54]
ONWARDS 4 (26 weeks)	11.24	12.64	0.88 [0.54; 1.41]
ONWARDS 5 (52 weeks)	20.43	14.73	1.49 [1.09; 2.03]
ONWARDS 6 (26 weeks)	5.48	7.59	0.71 [0.41; 1.23]
ONWARDS 6 (52 weeks)	3.56	7.50	0.45 [0.25 ; 0.83]

Evaluation of data supporting the dosing recommendation in the SmPC

In addition to the data on insulin doses as described above, the applicant has analysed the data supporting the dose recommendation.

Starting dose for T2DM subjects

The starting dose of insulin icodec was planned to be 70 U in insulin naïve subjects in ONWARDS 1, 3 and 5. The actual mean dose of insulin icodec for week 1 was 70.42 U in ONWARDS 1, 68.96 U in ONWARDS 3 and 70.03 U in ONWARDS 5.

In T2DM subjects previously on basal insulin (ONWARDS 2) or basal-bolus regime (ONWARDS 4), the mean starting dose of insulin icodec for week 1 was 244.05 U and 297.97 U, respectively. This actual starting dose of insulin icodec corresponded to the planned starting dose (the total daily basal insulin dose before randomisation multiplied by 7 and rounded off to the nearest 10 U with a one-time additional 50% dose) in most subjects.

Starting dose for T1DM subjects

The mean dose of insulin icodec for week 1 was 243.60 U in ONWARDS 6. This actual starting dose of insulin icodec corresponded to the planned starting dose (the total daily basal insulin dose before randomisation multiplied by 7 and rounded off to the nearest 10 U) with a one-time additional 50% or 100% dose in most subjects. The starting dose of 1040 U for one subject was due to a calculation error as described in a protocol deviation in the CTR.

CGM metrics during week 0-4

Across the studies, mean fasting SMPG decreased faster in the daily basal comparator group compared to insulin icodec during the initial 4 weeks of treatment. The 3-4 week time for reaching steady state with insulin icodec could possibly explain the initial higher mean fasting SMPG values. The occurrence of level 2 and 3 hypoglycaemic episodes during the initial 4 weeks were comparable for insulin icodec and daily basal insulin in insulin naïve subjects (ONWARDS 1, 3 and 5) and T2DM subjects on basal-bolus regimen

(ONWARDS 4). However, in T2DM subjects on basal switch (ONWARDS 2) and T1DM subjects (ONWARDS 6), the hypoglycaemic rate (level 2 and 3) for insulin icodec was increased compared to daily basal insulin at week 4. In all studies using CGM metrics (ONWARDS 1, 2, 4 and 6), data showed that slightly more subjects for insulin icodec than for daily basal insulin spent time below 3.9 mmol/L during the initial 4 weeks (Table 43).

Table 43. Time spent below range from week 0 to week 4 - in-trial - summary - full analysis set

	Insulin icodec			Daily basal insulin	
	N	Mean (SD)		N	Mean (SD)
Time spent < 3.9 mmol/L (70 mg/dL) (%)					
T2D, insulin naïve ONWARDS 1	470	0.33 (0.89)		463	0.28 (0.66)
T2D, basal ONWARDS 2	252	0.76 (1.77)		244	0.69 (1.91)
T2D, basal-bolus ONWARDS 4	268	1.87 (3.18)		262	1.68 (2.62)
T1D ONWARDS 6	284	3.56 (3.15)		284	3.19 (3.16)

Additional one-time dose in T1DM subjects

For evaluation of the two different one-time additional insulin icodec doses in ONWARDS 6, the subjects in the insulin degludec arm were split into 2 corresponding groups. Prior to randomisation, subjects with <8.0% or subjects who received insulin glargine U300 or twice daily basal insulin did receive a one-time additional 50% dose and subjects with HbA1c ≥8% did receive a one-time additional 100% dose. The one-time additional 100% insulin icodec dose led to a very steep decrease in mean fasting SMPG from week 0 to 1 (approximately 2 mmol/L), but no further decrease during the next 5 weeks. The one-time additional 50% insulin icodec dose led to a steadier decrease of mean SMPG during the initial 6 weeks. The size of the one-time additional insulin icodec dose did not seem to impact the HbA_{1c} reduction, as the one-time additional 50% insulin icodec dose group had a similar HbA_{1c} curve as the corresponding insulin degludec group (group 1), and subjects who had received the one-time additional 100% insulin icodec dose had a similar HbA_{1c} curve as the corresponding insulin degludec group (group 2).

For evaluation of the two different one-time additional doses, the occurrence of level 2 and 3 hypoglycaemic episodes in the 2 groups for the first 4 weeks was compared. Subjects who had received a one-time additional 50% insulin icodec dose and a one-time additional 100% insulin icodec dose had a similar rate of level 2 and 3 hypoglycaemic episodes during the first 4 weeks. Subjects on insulin icodec tended to have higher rates of level 2 and 3 hypoglycaemic episodes after week 2, when compared to the corresponding insulin degludec groups. When focusing on the daily TBR of 3.0 mmol/L during the first week, there were a few days where subjects given the one-time additional 100% dose (group 2) spent more TBR compared to the corresponding insulin degludec group and compared to subjects given the one-time additional 50% dose (group 1). In the second week, there was a peak for TBR at day 2 after the second insulin icodec injection in the one-time additional 100% dose group compared to the other groups, even though no additional dose was applied for week 2. At the same time, subjects given the one-time additional 100% dose spent less time above 10.0 mmol/L (180 mg/dL) compared to the corresponding insulin degludec group (group 2) on most days during the first week, which could indicate that the one-time additional 100% dose is higher than needed to prevent a glycaemic slip.

In T1DM patients, to avoid the increased risk of hypoglycaemic episodes during the initial weeks and to simplify the dosing recommendation, a single 50% one-time additional dose in alignment with the T2DM dosing recommendation is proposed. Data indicates that a one-time additional 100% dose increases the risk for hypoglycaemia; therefore, the approach to recommend an initial one-time additional 50% dose for T1DM subjects is accepted.

Titration and SMPG values

A 'treat-to-target' approach was applied for insulin icodec and the daily basal insulin in ONWARDS 1-4 and 6, while in ONWARDS 5 the insulin icodec arm was titrated with the same algorithm to the same glycaemic target (pre-breakfast SMPGs values of 4.4−7.2 mmol/L [80−130 mg/dL]) via Dosing guidance application, but with less extensive monitoring and follow-up. In all ONWARDS trials, the titration was based on fasting pre-breakfast SMPG values measured on the two days prior to titration and on the day of contact.

For insulin naïve subjects (ONWARDS 1, 3 and 5), the median time to reach SMPG target 4.4-7.2 mmol/L was 1 week longer in the insulin icodec arm compared to the daily basal insulin arm). In T2DM subjects previously on basal insulin and basal-bolus regimen (ONWARDS 2 and 4), the median time to reach SMPG target 4.4-7.2 mmol/L was 2 and 4 weeks longer in the insulin icodec arm compared to the daily basal insulin arm. In T1DM subjects (ONWARDS 6), the median time to reach SMPG target 4.4-7.2 mmol/L was 3 weeks longer in the insulin icodec arm compared to the insulin degludec arm.

When focusing on mean fasting SMPG values for the whole week, the SmPG values remained initially higher for insulin icodec compared to daily basal insulin across all trials except for trial ONWARDS 1. This was most pronounced for T1DM patients (ONWARDS 6).

Change of dosing day and missed dose

In the phase 3a programme, a missed dose guidance was provided in all ONWARDS trials except ONWARDS 6 (T1DM patients). If an insulin icodec dose was missed for ≤3 days after the planned dosing day, subjects should inject the planned dose as soon as possible. Doses taken 1-3 days after the planned dosing day are referred to as missed doses. If the dose was not taken within 3 days after the planned dosing day, the subject should await the next planned day-of-injection.

In ONWARDS 1-4 and 6, nearly half or more of the subjects on insulin icodec changed the weekly dosing day at some point (49%-67%) or missed a dose (40-62%) during the trial. In ONWARDS 5, the frequency of dose changes (87%) and missed doses (85%) was higher (Table 44, Table 45).

The planned dosing day was on average changed by 1.23-1.45 days across all ONWARDS trials. In all trials, changes of -1 and +1 days were the most frequent. This could reflect that when subjects due to practical circumstances preponed or postponed the dosing by 1 day, they subsequently changed back to dosing at the originally planned weekday. When focusing on the missed doses (i.e., where the dosing occurred up to 3 days later than planned) , the proportion of subjects and the number of cases per subject were lower, but the general pattern across trials was similar as for change of dosing day (Table 46).

To evaluate the potential impact of shortening the dosing interval, the incidence of level 2 and 3 hypoglycaemic episodes after preponing a dose was evaluated at steady state (maintenance phase >12 weeks). The proportion of subjects with severe or clinically significant hypoglycaemic episodes, (including the hypoglycaemic rate) in week 1, 2, 3 and 4, respectively, after preponing a dose in the maintenance phase is presented in Table 47 and Figure 27. Preponing the dose up to 3 days increased the risk of severe or clinically significant hypoglycaemia for all patients in the ONWARDS trials, with the highest incidence and rate in T1DM patients. Shortening the dosing interval and the increased risk of hypoglycaemia over several days was

discussed in the CHMP scientific advice given. A new study with icodec addressing the safety of shifting the dose interval was recommended necessary to be performed. This study has not been performed. Extending the dosing interval was recommended by CHMP to be reserved for the exceptional situations where an injection is forgotten.

Due to the increased risk of severe or clinically significant hypoglycaemic events, patients should not be recommended to prepone dosing. A missed dose should be injected as soon as possible.

Table 44. Change of weekly insulin dosing day - icodec - on-treatment - summary - safety analysis set

	ONWARDS 1	ONWARDS 3	ONWARDS 5	ONWARDS 2	ONWARDS 4	ONWARDS 6
Number of subjects	492	293	542	262	291	290
Subjects changing dosing day at any time						
Yes	332	147	469	159	142	172
No	160	146	73	103	149	118
Number of times dosing day changed during trial						
N	332	147	469	159	142	172
Mean (SD)	6.98 (6.48)	3.54 (2.76)	8.07 (5.62)	4.57 (3.66)	4.12 (3.25)	4.25 (3.34)
Median	4.00	2.00	7.00	3.00	3.00	3.00
Min ; Max	1 ; 33	1 ; 15	1 ; 27	1 ; 16	1 ; 17	1 ; 16
Average number of days by which the dosing day changed						
N	332	147	469	159	142	172
Mean (SD)	1.35 (0.48)	1.37 (0.51)	1.30 (0.39)	1.31 (0.47)	1.45 (0.53)	1.23 (0.39)
Median	1.15	1.00	1.20	1.00	1.25	1.00
Min ; Max	1.00 ; 3.00	1.00 ; 3.00	1.00 ; 3.00	1.00 ; 3.00	1.00 ; 3.00	1.00 ; 3.00

N: Number of subjects changing the dosing day at any time, SD: Standard deviation. The average number of days is calculated based on the absolute number of days by which the dosing day changed. Data from ONWARDS 1-6, only main part of ONWARDS 1 and 6. Change of the dosing day of weekly insulin icodec up to +/-3 days is allowed in ONWARDS 1-5.

Table 45. Missed dose of weekly insulin dosing - insulin icodec - on-treatment - summary - safety analysis set

	ONWARDS 1	ONWARDS 3	ONWARDS 5	ONWARDS 2	ONWARDS 4	ONWARDS 6
Number of subjects	492	293	542	262	291	290
Subjects delaying dose at any time						
Yes	305	125	463	140	115	164
No	187	168	79	122	176	126
Number of delayed doses during trial						
N	305	125	463	140	115	164
Mean (SD)	3.74 (3.29)	1.97 (1.29)	4.27 (3.00)	2.49 (1.95)	2.21 (1.61)	2.43 (1.72)
Median	2.00	1.00	4.00	2.00	2.00	2.00
Min ; Max	1 ; 16	1 ; 6	1 ; 15	1 ; 9	1 ; 7	1 ; 9
Average number of days delay from OW schedule						
N	305	125	463	140	115	164
Mean (SD)	1.34 (0.49)	1.31 (0.51)	1.31 (0.40)	1.29 (0.48)	1.34 (0.48)	1.24 (0.40)
Median	1.00	1.00	1.20	1.00	1.00	1.00
Min ; Max	1.00 ; 3.00	1.00 ; 3.00	1.00 ; 3.00	1.00 ; 3.00	1.00 ; 3.00	1.00 ; 3.00

N: Number of subjects delaying the dose at any time, SD: Standard deviation, Data from ONWARDS 1-6, only main part of ONWARDS 1 and 6. OW: Once weekly. A missed dose is defined as a dose that was taken with up to +3 days delay according to the weekly schedule.

Table 46. Frequency deviation days from weekly schedule - insulin icodec - on treatment - summary - safety analysis set

	ONWARDS 1 N	(%)	ONWARDS 3 N	(%)	ONWARDS 5 N	(%)	ONWARDS 2 N	(%)	ONWARDS 4 N	(%)	ONWARDS 6 N	(%)
Total number of doses taken	25733		7562		24068		7099		7388		7373	
Deviation type												
-3	78	(0.30)	21	(0.28)	122	(0.51)	29	(0.41)	46	(0.62)	18	(0.24)
-2	234	(0.91)	63	(0.83)	283	(1.18)	77	(1.08)	85	(1.15)	48	(0.65)
-1	862	(3.35)	190	(2.51)	1404	(5.83)	272	(3.83)	200	(2.71)	267	(3.62)
1	853	(3.31)	182	(2.41)	1500	(6.23)	260	(3.66)	176	(2.38)	309	(4.19)
2	196	(0.76)	45	(0.60)	295	(1.23)	68	(0.96)	55	(0.74)	70	(0.95)
3	93	(0.36)	19	(0.25)	181	(0.75)	21	(0.30)	23	(0.31)	19	(0.26)

Data from ONWARDS 1-6, only main part of ONWARDS 1 and 6. N: Number of doses taken where the deviation type was used. %: Percentage of doses. Change of the dosing day of weekly insulin icodec up to +/-3 days is allowed in ONWARDS 1-5.

Table 47. Incidence and rate of severe or clinically significant hypoglycaemic episodes by trial – week 1 to 4 since preponed dose for insulin icodec – maintenance phase (>12 weeks)

Study	Week 1 Incidence (%) of severe or clinically significant hypoglycaemia (Rate: number of hypoglycaemic events per 100 PYE)	Week 2 Incidence (%) of severe or clinically significant hypoglycaemia (Rate: number of hypoglycaemic events per 100 PYE)	Week 3 Incidence (%) of severe or clinically significant hypoglycaemia (Rate: number of hypoglycaemic events per 100 PYE)	Week 4 Incidence (%) of severe or clinically significant hypoglycaemia (Rate: number of hypoglycaemic events per 100 PYE)
ONWARDS 1 (insulin naïve)	1.9% (R: 48.00)	2.3 % (R: 46.08)	1.1% (R: 38.50)	0.8% (R: 18.01)
ONWARDS 3 (insulin naïve)	0	0	1.0% (R: 38.49)	0
ONWARDS 2 (basal switch)	3.6% (R: 126.65)	1.8 % (R: 53.44)	0.9% (R:31.41)	0.9% (R 34.69)
ONWARDS 4 (basal bolus T2DM)	7.0% (R: 245.84)	8.1 % (R: 387.33)	5.8% (R:216.38)	7.0% (R: 324.05)
ONWARDS 6 (basal bolus T1DM)	28.6% (R: 2068.03)	30.6 % (R: 2196.71)	22.4% (R: 2392.07)	16.3% (R: 1249.23)

Figure 27. Percentage of subjects with severe (level 3) or clinically significant (level 2) hypoglycaemic episodes by week after preponed dose - week 1-4 since preponed dose - maintenance phase - on- treatment/main-on-treatment - bar plot - safety analysis set
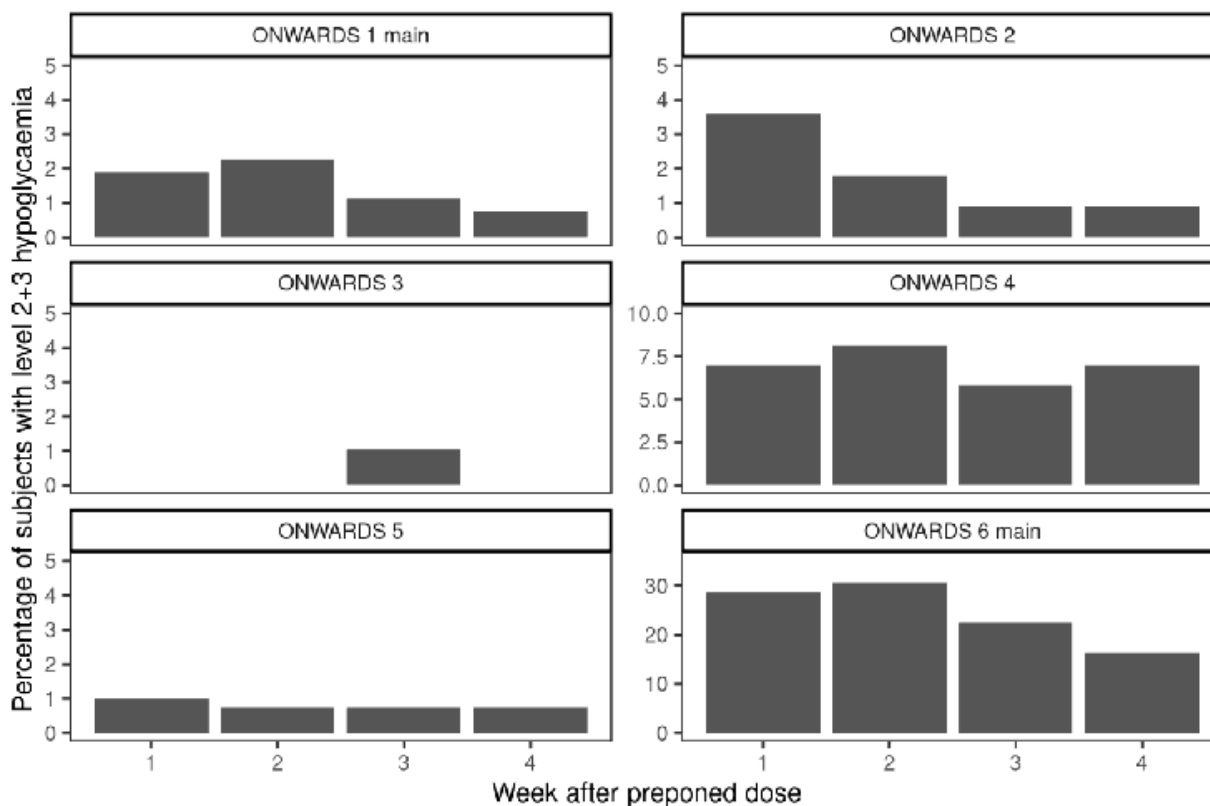
Subgroup analysis

Treatment effect by demographic factors

There were no apparent differences in subgroups based on demographic factors (age, sex, BMI, race, ethnicity, and region). The exceptions observed were mainly in subgroups with few subjects and wide confidence intervals. An investigation of the impact of differences between the Japanese population and the overall population in relation to the outcome was performed in a separate subgroup analysis (Table 48).

Japanese subjects were included in ONWARDS 1 (n=164; 17%), ONWARDS 2 (n=100; 19%), ONWARDS 4 (n=85; 15%) and ONWARDS 6 (n=80; 14%). Slightly lower BMI and eGFR was noted in the Japanese population compared to the entire population. Overall, the glucose-lowering effect appears to be somewhat lower with insulin icodec compared to daily basal insulin in Japanese subjects. In the Japanese subgroup of T1DM subjects (ONWARDS 6), the mean HbA1c decreased from baseline to week 10 in both treatment arms, after which mean HbA1c increased toward baseline with insulin icodec while it remained stable with insulin degludec. At week 26, the estimated change from baseline in HbA1C was –0.07% points with insulin icodec and -0.33% points with insulin degludec (ETD 0.26 (0.01; 0.51)). At week 52, the estimated change from baseline in HbA1C was 0.02% points with insulin icodec and -0.42% points with insulin degludec (ETD 0.44 (0.13; 0.75)) (Figure 28). In T1DM population, the incidence of severe or clinically significant hypoglycaemic episodes was higher for insulin icodec (96.9%) than for insulin degludec (75.0%) at week 52. The rate of severe or clinically significant hypoglycaemic episodes was 1913.99 events per 100 PY for insulin icodec and 789.54 events per 100 PY for insulin degludec. The rate of nocturnal severe or clinically significant

hypoglycaemic episodes was 498.04 events per 110 PY for insulin icodec and 162.10 events per 100 PY for insulin degludec. Overall, there was a higher rate of severe or clinically significant hypoglycaemic episodes, including nocturnal, for insulin icodec compared to insulin degludec in the Japanese population than in the entire T1DM population.

In conclusion, the mean HbA1c gradually increased toward baseline from week 10 onwards in the Japanese subgroup of T1DM patients. At week 26 to week 52, there was no glycaemic effect with regard to reduced mean HbA1c in the Japanese subgroup, while the incidence and rate of severe or clinically significant hypoglycaemic episodes (including nocturnal) was higher for insulin icodec compared to insulin degludec.

Figure 28. HbA1c up to week 52 by treatment week - in-trial – mean plot - estimated – full analysis set - Japanese population (left) and entire trial population (right) – Trial 4625
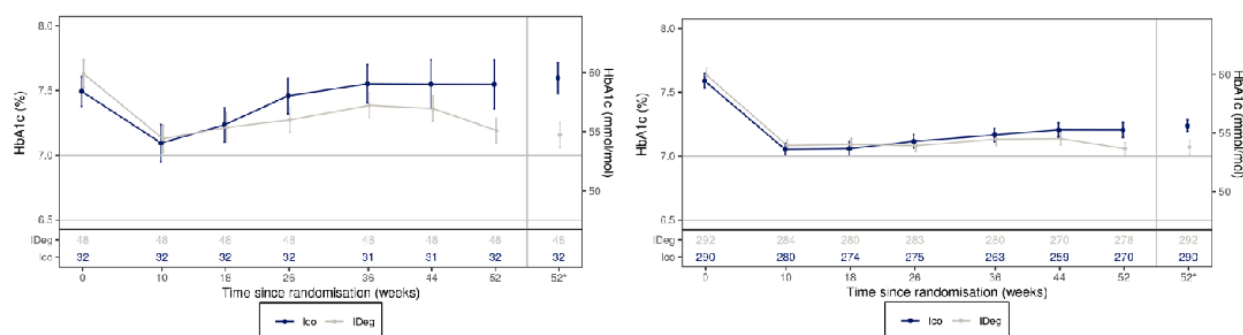
Table 48. HbA$_{1c}$ (%) - in-trial - summary - full analysis set - Japanese population and entire trial population - ONWARDS 1, 2, 4 and 6 (trial 4477, 4478, 4480 and 4625)

	ONWARDS 1 (trial 4477)		ONWARDS 2 (trial 4478)		ONWARDS 4 (trial 4480)		ONWARDS 6 (trial 4625)	
Japanese population								
	Ico (N=78)	IGlar (N=86)	Ico (N=51)	IDeg (N=49)	Ico (N=44)	IGlar (N=41)	Ico (N=32)	IDeg (N=48)
Baseline[a]	8.06±0.83 (78)	8.01±0.84 (86)	8.10±0.70 (51)	7.98±0.74 (49)	7.90±0.70 (44)	8.15±0.83 (41)	7.49±0.65 (32)	7.63±0.74 (48)
Week 52 / Week 26[a, b]	6.86±0.61 (78)	6.91±0.62 (85)	7.24±0.78 (51)	7.10±0.68 (48)	6.90±0.62 (44)	6.79±0.59 (41)	7.46±0.78 (32)	7.27±0.67 (48)
Change from baseline[a]	-1.20±0.87 (78)	-1.10±0.74 (85)	-0.87±0.83 (51)	-0.86±0.68 (48)	-1.00±0.63(44)	-1.36±0.79 (41)	-0.03±0.66 (32)	-0.36±0.57 (48)
Estimated mean change from baseline[c]	-1.18 (78)	-1.09 (86)	-0.83 (51)	-0.89 (49)	-1.08 (44)	-1.27 (41)	-0.07 (32)	-0.33 (48)
Estimated treatment difference (ico – comparator) [95%CI]	-0.09 [-0.30; 0.12]		0.05 [-0.22; 0.33]		0.19 [-0.04; 0.43]		0.26 [0.01; 0.51]	
Entire trial population								
	Ico (N=492)	IGlar (N=492)	Ico (N=263)	IDeg (N=263)	Ico (N=291)	IGlar (N=291)	Ico (N=290)	IDeg (N=292)
Baseline[a]	8.50±0.99 (492)	8.44±1.02 (492)	8.17±0.77 (263)	8.10±0.77 (263)	8.29±0.86 (291)	8.31±0.90 (291)	7.59±0.96 (290)	7.63±0.93 (292)
Week 52 / Week 26[a, b]	6.93±0.78 (479)	7.09±0.82 (479)	7.21±0.74 (256)	7.39±0.78 (253)	7.06±0.73 (275)	6.99±0.71 (264)	7.11±0.88 (274)	7.08±0.79 (283)
Change from baseline[a]	-1.58±1.05 (479)	-1.34±1.06 (479)	-0.95±0.89 (256)	-0.70±0.83 (253)	-1.21±0.83 (275)	-1.31±0.93 (264)	-0.48±0.77 (274)	-0.55±0.71 (283)
Estimated mean change from baseline[c]	-1.55 (492)	-1.35 (492)	-0.93 (263)	-0.71 (263)	-1.16 (291)	-1.18 (291)	-0.47 (290)	-0.51 (292)
Estimated treatment difference (ico – comparator) [95%CI]	-0.19 [-0.36; -0.03]		-0.22 [-0.37; -0.08]		0.02 [-0.11; 0.15]		0.05 [-0.13; 0.23]	

Treatment effect by disease factor

There was a tendency of greater reduction of HbA1c for the subgroup of HbA$_{1c}$ ≥8%.

Subjects were divided into two subgroups according to their diabetes duration: <10 years and ≥10 years. The estimated treatment contrast for change in HbA$_{1c}$ for insulin icodec vs daily basal insulin were similar for both subgroups across all trials and no important treatment by diabetes duration interaction was identified.

The proportion of subjects with normal function and mild renal impairment ranged from 37-67% and 31-46%, respectively. Moderate renal impairment was seen for 8-16% of T2DM subjects and 2% of T1DM subjects. Overall, T2DM subjects with moderate renal impairment tended to have a smaller insulin icodec treatment effect compared with subjects with normal and mild renal impairment, except for ONWARDS 2 where treatment was in favour for subjects with moderate renal impairment. In T1DM subjects, too few subjects with moderate renal impairment (n=14) were included in the trials to make any conclusions.

Impaired hepatic function was an exclusion criterion in ONWARDS 1-4 and 6. There were too few subjects with hepatic impairment to draw any conclusions.

Treatment effect by anti-diabetic treatment

There were no apparent differences in subgroups based on treatment factors regarding pre-trial SU use or GLP-1 use at baseline. For ONWARDS 2, 4 and 6, subjects were divided into four pre-trial basal insulin subgroups: pre-trial insulin degludec, pre-trial insulin glargine U100, pre-trial insulin glargine U300 and other. In ONWARDS 2, there was a similar treatment effect for insulin icodec and daily basal insulin in the pre-trial insulin degludec subgroup, while the treatment contrast was in favour of insulin icodec for the other subgroups. In ONWARDS 4, the estimated treatment contrast for change in HbA$_{1c}$ tended to be in favour of daily basal insulin (insulin glargine) for the pre-trial insulin degludec subgroups. Overall, no important treatment by pre-trial basal insulin interaction was identified.

Table 49. Summary of main efficacy results

Endpoint	Population		Trial	Insulin icodec	Daily insulin comparator	Insulin icodec vs. Daily insulin comparator			
				Estimated mean change from baseline		ETD/ETR[a]	95% CI	P Value	
								Non-inferiority	Superiority[b]/no difference
ΔHbA$_{1c}$ (%)	T2D	Insulin naïve	4477 (OW1)	-1.55	-1.35	-0.19	-0.36 ; -0.03	<0.0001	0.0210
			4479 (OW3)	-1.57	-1.36	-0.21	-0.34 ; -0.08	<0.0001	0.0016
			4481 (OW5)	-1.68	-1.31	-0.38	-0.66 ; -0.09	<0.0001	0.0092
		Basal switch	4478 (OW2)	-0.93	-0.71	-0.22	-0.37 ; -0.08	<0.0001	0.0028
		Basal/bolus	4480 (OW4)	-1.16	-1.18	0.02	-0.11 ; 0.15	<0.0001	
	T1D	Basal/bolus	4625 (OW6)	-0.47	-0.51	0.05	-0.13 ; 0.23	0.0065	
ΔFPG (mmol/L)[c]	T2D	Insulin naïve	4477 (OW1)	-3.35	-3.33	-0.01	-0.27 ; 0.24		0.9200
			4479 (OW3)	-3.01	-2.99	-0.02	-0.34 ; 0.29		0.8965
		Basal switch	4478 (OW2)	-1.58	-1.62	0.04	-0.28 ; 0.36		0.8121
		Basal/bolus	4480 (OW4)	-1.75	-1.61	-0.14	-0.59 ; 0.31		0.5489
	T1D	Basal/bolus	4625 (OW6)	-0.84	-1.87	1.03	0.48 ; 1.59		0.0003
				Estimated frequency					
HbA$_{1c}$ <7.0% w/o level 2 or level 3 hypoglycaemic episodes (%)	T2D	Insulin naïve	4477 (OW1)	52.56	42.58	1.49*	1.15 ; 1.94		0.0028
			4479 (OW3)	52.13	39.86	1.64*	1.16 ; 2.33		0.0054
			4481 (OW5)	40.53	31.61	1.47*	1.13 ; 1.92		0.0040
		Basal switch	4478 (OW2)	36.73	26.79	1.59*	1.07 ; 2.36		0.0223
		Basal/bolus	4480 (OW4)	26.48	25.24	1.07*	0.73 ; 1.55		0.7352
	T1D	Basal/bolus	4625 (OW6)	9.55	16.74	0.52*	0.33 ; 0.85		0.0080

Endpoint	Population		Trial	Insulin icodec	Daily insulin comparator	Insulin icodec vs. Daily insulin comparator		
HbA$_{1c}$ ≤6.5% w/o level 2 or level 3 hypoglycaemic episodes (%)	T2D	Insulin naïve	4477 (OW1)	29.68	22.74	1.43*	1.07 ; 1.92	0.0149
			4479 (OW3)	28.33	18.69	1.72*	1.16 ; 2.54	0.0065
			4481 (OW5)	20.43	14.73	1.49*	1.09 ; 2.03	0.0123
		Basal switch	4478 (OW2)	12.54	7.77	1.70*	1.00 ; 2.91	0.0517
		Basal/bolus	4480 (OW4)	11.24	12.64	0.88*	0.54 ; 1.41	0.5837
	T1D	Basal/bolus	4625 (OW6)	5.48	7.59	0.71*	0.41 ; 1.23	0.2197
				Observed mean for last 4 weeks of treatment				
TIR (%)^g	T2D	Insulin naïve	4477 (OW1)^{d,e}	71.94	66.90	4.27	1.92 ; 6.62	0.0004
		Basal switch	4478 (OW2)^f	63.13	59.50	2.41	-0.84 ; 5.65	0.1461
		Basal/bolus	4480 (OW4)^f	66.88	66.44	0.29	-2.52 ; 3.09	0.8406
	T1D	Basal/bolus	4625 (OW6)^f	59.10	60.85	-2.00	-4.38 ; 0.38	0.0991
TBR (%)^g	T2D	Insulin naïve	4477 (OW1)^d	0.27	0.21	1.27*	0.94 ; 1.71	0.1134
		Basal switch	4478 (OW2)^f	0.34	0.22	1.37*	0.92 ; 2.04	0.1180
		Basal/bolus	4480 (OW4)^f	0.73	0.61	1.20*	0.91 ; 1.58	0.2050
	T1D	Basal/bolus	4625 (OW6)^f	1.02	0.68	1.46*	1.16 ; 1.85	0.0014
TAR (%)^g	T2D	Insulin naïve	4477 (OW1)^d	26.86	32.27	-4.58	-6.99 ; 2.17	0.0002
		Basal switch	4478 (OW2)^f	35.52	39.71	-2.93	-6-25 ; 0.39	0.0833
		Basal/bolus	4480 (OW4)^f	30.47	31.30	-0.60	-3.47 ; 2.28	0.6826
	T1D	Basal/bolus	4625 (OW6)^f	37.03	36.25	1.14	-1.34 ; 3.61	0.3689

Endpoint	Population		Trial	Insulin icodec	Daily insulin comparator	Insulin icodec vs. Daily insulin comparator		
				Estimated mean during last 2 weeks of treatment^h				
Average Weekly Total Insulin Dose (U)	T2D	Insulin naïve	4477 (OW1)	214.23	222.39	0.96*	0.89 ; 1.05	0.3701
			4479 (OW3)	204.28	186.52	1.10*	0.98 ; 1.22	0.0932
			4481 (OW5)^i	226.51	185.23	1.22*	1.12 ; 1.33	
		Basal switch	4478 (OW2)	267.96	244.22	1.10*	1.01 ; 1.20	0.0348
		Basal/bolus	4480 (OW4)	513.54	559.05	0.92*	0.85 ; 0.99	0.0342
	T1D	Basal/bolus	4625 (OW6)	310.52	322.68	0.96*	0.90 ; 1.03	0.2748
Average Weekly Basal Insulin dose (U)	T2D	Basal/bolus	4480 (OW4)	305.06	279.42	1.09*	1.01 ; 1.18	0.0286
	T1D	Basal/bolus	4625 (OW6)	169.96	151.24	1.12*	1.07 ; 1.18	<0.0001
Average Weekly Bolus Insulin Dose (U)	T2D	Basal/bolus	4480 (OW4)	197.45	255.26	0.77*	0.70 ; 0.86	<0.0001
	T1D	Basal/bolus	4625 (OW6)	131.86	161.42	0.82*	0.74 ; 0.90	<0.0001
ΔDTSQs total satisfaction score	T2D	Insulin naïve	4481 (OW5)	4.68	3.90	0.78	0.10 ; 1.47	0.0247
		Basal switch	4478 (OW2)	4.22	2.96	1.25	0.41 ; 2.10	0.0036
	T1D	Basal/bolus	4625 (OW6)	1.97	3.06	-1.09	-1.85 ; -0.34	0.0044
				Estimated mean score at end of treatment				
TRIM-D (score)	T2D	Insulin naïve	4481 (OW5)	90.42	87.37	3.04	1.28 ; 4.81	0.0007

2.6.5.3. Clinical studies in special populations

All trials in the phase 3a ONWARDS programme were randomised controlled trials. A total of 180 patients above the age of 75 years were included in the controlled insulin icodec trials, thereby fulfilling the requirements set out in ICH E7 (Table 50).

Table 50. Age groups at baseline - summary - full analysis set

	Insulin icodec		Daily basal insulin		Total	
	N	(%)	N	(%)	N	(%)
ONWARDS 1						
Full analysis set	492	(100.0)	492	(100.0)	984	(100.0)
65<= to <75 years	134	(27.2)	144	(29.3)	278	(28.3)
75<= to <85 years	25	(5.1)	16	(3.3)	41	(4.2)
85<= years	0		0		0	
ONWARDS 2						
Full analysis set	263	(100.0)	263	(100.0)	526	(100.0)
65<= to <75 years	99	(37.6)	99	(37.6)	198	(37.6)
75<= to <85 years	17	(6.5)	15	(5.7)	32	(6.1)
85<= years	2	(0.8)	0		2	(0.4)
ONWARDS 3						
Full analysis set	294	(100.0)	294	(100.0)	588	(100.0)
65<= to <75 years	74	(25.2)	84	(28.6)	158	(26.9)
75<= to <85 years	10	(3.4)	9	(3.1)	19	(3.2)
85<= years	0		0		0	
ONWARDS 4						
Full analysis set	291	(100.0)	291	(100.0)	582	(100.0)
65<= to <75 years	92	(31.6)	96	(33.0)	188	(32.3)
75<= to <85 years	9	(3.1)	11	(3.8)	20	(3.4)
85<= years	1	(0.3)	0		1	(0.2)
ONWARDS 5						
Full analysis set	542	(100.0)	543	(100.0)	1085	(100.0)
65<= to <75 years	150	(27.7)	154	(28.4)	304	(28.0)
75<= to <85 years	32	(5.9)	26	(4.8)	58	(5.3)
85<= years	1	(0.2)	0		1	(0.1)
ONWARDS 6						
Full analysis set	290	(100.0)	292	(100.0)	582	(100.0)
65<= to <75 years	20	(6.9)	18	(6.2)	38	(6.5)
75<= to <85 years	3	(1.0)	3	(1.0)	6	(1.0)
85<= years	0		0		0	
Phase 3a pool						
Full analysis set	2172	(100.0)	2175	(100.0)	4347	(100.0)
65<= to <75 years	569	(26.2)	595	(27.4)	1164	(26.8)
75<= to <85 years	96	(4.4)	80	(3.7)	176	(4.0)
85<= years	4	(0.2)	0		4	(0.1)

N: Number of subjects, %: Percentage of subjects.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of once weekly insulin icodec has been investigated in six confirmatory phase 3 studies, of which five trials in T2DM patients (ONWARDS 1-5) and one trial in T1DM patients (ONWARDS 6). All studies were open-label, except for one T2DM study which was double-blinded with a double dummy design (trial ONWARDS 3). The efficacy was evaluated in insulin naïve T2DM patients (ONWARDS 1, 3 and 5), in T2DM patients previously treated with basal insulin (ONWARDS 2) and in T2DM and T1DM patients previously treated with basal-bolus insulin (ONWARDS 4 and 6).

All trials applied a treat-to-target design, except for ONWARDS 5, which was undertaken to evaluate effectiveness of insulin icodec and was designed to mimic a clinical practice setting with fewer dedicated visits and routine assessment left to the treating physician. ONWARDS 5 was a study in insulin naïve T2DM patients where insulin icodec was used together with a dosing guide application under investigation. The dosing guide application provided automated dose guidance to subjects randomised to insulin icodec. The applicant was

advised by CHMP to avoid the provision of an app in one treatment arm as this could have an impact on the estimated treatment effect and compliance aspects. Based on the information provided in the dossier, the DoseGuide App is considered a medical device as defined in article 2 of the (EU) regulation 2017/745 (MDR).

The primary hypothesis in all ONWARDS studies was that insulin icodec is non-inferior to daily basal insulin comparator in change from baseline to week 26/52 in HbA1c using a non-inferiority margin of 0.3%. For study ONWARDS 1 and, specifically study ONWARDS 5, additional considerations were made, and these were also the two studies that had been planned with the largest sample sizes: 970 subjects (ONWARDS 1) and 1,096 subjects (ONWARDS 5). The planned total sample size in ONWARDS 2 was 520 subjects, and in ONWARDS 3-4 and 6, 580 subjects. Overall, sample size estimations appear appropriate; discussions provided on expected importance of the estimand definition and expected frequency of intercurrent events and their potential impact on the expected difference is appreciated. In all studies randomisation (via IWRS) was 1:1. Only two studies used a stratified randomisation: ONWARDS 3 (region, treatment with sulphonylureas (SU) or glinides) and ONWARDS 6 (pre-trial basal insulin treatment, HbA1c (<8% or ⩾8%). In ONWARDS 5, the once daily basal insulin analogue that a subject was to receive if randomised to the control arm was to have been selected by the investigator prior to randomisation as per standard of care. This was expected and hence, is endorsed.

The T2DM trials included 3,729 subjects, of which 1,085 subjects in ONWARDS 5. The T1DM trial enrolled rather few subjects (n=582). The applicant was recommended in the CHMP scientific advice provided to consider increasing the number of participants. The T2DM trials were 26-52 weeks of duration and the T1DM trial was 26 weeks (main phase), including a 26-week extension period. The 52-week T2DM trial (ONWARDS 1 in insulin naïve subjects) also included a 26-week extension part.

All trials were performed with an active comparator. The once daily basal insulin analogues IDeg was used in ONWARDS 2, 3 and 6 and IGlar was used in ONWARDS 1 and 4. In ONWARDS 5, the comparator was once daily IDeg or IGlar (once or twice daily). The trials were designed as non-inferiority trials with a margin for HbA1c of 0.3%, which is considered appropriate and in line with the current CHMP diabetes guideline and given scientific advice. Insulin doses were titrated according to predefined titration algorithms. Prefilled pens were used throughout the trials for insulin icodec and the comparators. Insulin icodec was formulated as a 4200 nmol/mL solution equivalent to 700 U/mL and filled in 3 mL cartridges.

All the phase 3 studies were open label except for ONWARDS 3 that was performed under double-blind conditions using double-dummy technique. The remaining trials were open label for different reasons, including increased treatment burden due to the high number of injections required for a double-blind, double dummy trial (ONWARDS 1 and 2) and risk of pen-mix-up in a double-blind, double-dummy trial using three different pens (two basal and one bolus pen) in ONWARDS 4 and 6. Further, design elements in ONWARDS 5, made the blinding of this study unfeasible. These reasons are considered acceptable. While the CHMP scientific advice expressed the fact that masking of treatments was preferred, the issue of assay sensitivity have by now been alleviated in the studies that were successful in showing superiority. The main reason for the ONWARDS 3 double-blind design appears to have been to ensure collection of blinded safety data. According to instructions, insulin icodec was to be administered in the left thigh and insulin degludec was to be administered in the right thigh. Thus, this approach may have led to unintentional unblinding of treatments in case of apparent differences in local reactions between placebo and active treatment.

Based on the data from the clinical pharmacology trial 4314, the starting dose of 70 U (7 times the starting dose of daily insulin) in insulin naïve T2DM subjects was evaluated in trials 4383 and 4465. Three phase 2 exploratory trials (4383, 4465 and 4466) investigated the effect on glycaemic control and safety of insulin icodec compared to daily basal insulin. In trial 4383, the starting dose of 70 U for insulin icodec was

evaluated. Different titration algorithms and different basal switch approaches were tested in the trials 4465 and 4466, respectively. Preponing the dose up to 3 days increased the risk of severe or clinically significant hypoglycaemia for all patients in the ONWARDS trials, with the highest incidence and rate in T1DM patients. Due to the increased risk of severe or clinically significant hypoglycaemic events, patients should not be recommended to prepone dosing. A missed dose should be injected as soon as possible, which is appropriately reflected in SmPC section 4.2).

The inclusion and exclusion criteria were considered adequate and ensured enrolling a representative population of T1DM and T2DM subjects. Patients with severe renal impairment (eGFR <30 ml/min/1.73m^2) were excluded from ONWARDS 1-4 and 6. The T2DM trials allowed to maintain current non-insulin anti-diabetic treatment at the same dose level, except for glinides or sulphonylureas. To minimise the risk of hypoglycaemia, treatment with glinides or sulphonylureas was to be discontinued (ONWARDs 1, 2 and 4) or reduced by approximately 50% at randomisation (ONWARDS 3 and 5). In ONWARDS 5, the inclusion and exclusion criteria were broader and subjects with comorbidities were not excluded as far as there was no safety concern as judged by the investigator.

The chosen primary and secondary outcomes are acceptable. The treatment policy approach is in line with the given scientific advice. The change in HbA1c at the end of the trial is the appropriate choice of primary outcome. In ONWARDS 1-4, less than 11% made any changes in their anti-diabetic treatment, of which slightly more subjects in the daily basal insulin arm (0.7-6.9%) than in the insulin icodec arm (0.7-4.4%) needed intensification of treatment. There was no indication of lack of efficacy of insulin icodec based on changes in background treatment.

The occurrence of clinically significant episodes of hypoglycaemia (level 2 and 3) was included as an endpoint. In the study programme, hypoglycaemia was defined and classified by 3 levels: level 1 (<3.9 mmol/L), level 2 (<3.0 mmol/L) and level 3 (severe hypoglycaemia), in line with the ADA classification and the given scientific advice. In the same advice, hypoglycaemia was highlighted as the main concern for insulin icodec. The prolonged effect of insulin icodec hampers the possibility to adjust insulin doses and may delay recovery from hypoglycaemia. Thus, a secondary combined endpoint reflecting achieved target HbA1c without hypoglycaemia was recommended by the CHMP. The applicant has presented analyses of the proportion of subjects reaching HbA1c target without suffering hypoglycaemia episodes. This analyses are discussed as ancillary analyses.

The occurrence of insulin antibodies is discussed in the Clinical Safety section below.

Study-specific separate statistical analysis plans have been provided. Based on study similarities common statistical principles were applied and with a similarly defined primary endpoint as well as primary hypothesis, the ONWARDS studies shared a number of analysis features. Overall, the primary analysis can be agreed although it might have benefited from more comprehensive multiple testing procedures and the planning of a supplemental estimand analysis to challenge a conclusion of non-inferiority. The implementation of amendment(s) to the SAP, in all studies except for ONWARDS 6, raise no concern. However, the adding in ONWARDS 5 of analyses of hypoglycaemic episodes identified using an alternative definition based on SMPG measurements is noticed. The rational for additional analyses to supplement protocol defined ditto was a difference between randomised arms in how data on hypoglycaemic episodes were collected. This is per se a deficiency affecting the comparison between treatments of the occurrence of hypoglycaemia.

The planned primary analysis seems to have been well aligned with the primary estimand. The primary analysis set (FAS) included all randomised subjects. This is agreed. The use in the primary analysis of an ANCOVA model is accepted. Given the lack of a stratified randomisation in all studies but two in the light of

how the primary analysis model was defined, it was expected that the inclusion of a term for region (ONWARDS 1, 2, 4-6) as well as a term for personal CGM device use (ONWARDS 2 and 4) had been justified. This is however considered minor; of importance is the fact that the primary model had been predefined.

Intercurrent events handled by the treatment policy strategy were defined in the Clinical Study Reports as follows: discontinuation of randomised insulin treatment, withdrawal from the trial (in all OW studies) and initiation of bolus insulin treatment for more than 2 weeks (in OW1, OW2, and OW3, per protocol, there was no bolus insulin used in these studies unless it needed for reaching or maintaining the glycaemic control – i.e., as rescue medication). With the treatment policy strategy followed that subjects were to remain in follow-up irrespective of adherence to randomised treatment or changes to anti-diabetic background medication and any data collected were to be used in the analysis of HbA1c. However, in ignoring e.g., changes to anti-diabetic background medication, the primary estimand may have been biased towards non-inferiority. The occurrence of intercurrent events is thus informative on its own and of interest in this respect, was the ICE pattern in study ONWARDS 4 and ONWARDS 6 where the primary and only formal hypothesis aimed at showing non-inferiority. In the ONWARDS 1-3 studies, the proportion of subjects with an intercurrent event was low (<5%) and similar across the treatment arms. In ONWARDS 1 there were 4/492 subjects (0.8%) who initiated bolus insulin for more than 14 days, in ONWARDS 2 and ONWARDS 3 no subjects were reported to have initiated bolus insulin for more than 14 days. In study ONWARDS 4, the proportion of subjects with an intercurrent event was slightly higher compared with ONWARDS 1-3, also reporting a small difference between the treatments: 5.8% (17/291): insulin icodec and 7.6% (22/291): insulin glargine U100. In study ONWARDS 6 there was also a difference between the treatment arms but in the opposite direction. In this study the proportion of subjects with an intercurrent event was higher in the insulin icodec arm than in the comparator arm: 6.2% (18/290) versus 3.1% (9/292), respectively.

The study with most intercurrent events observed was ONWARDS 5 (approximately 10%).

With regard to study ONWARDS 1, 2, 3 and 5, they were all successful in the predefined multiplicity corrected secondary analysis aiming at showing HbA1c superiority (further discussed below).

In ONWARDS 1-3, missing HbA1c at the week 26/52 visit (regardless of treatment completion status) was handled using multiple imputation from subjects who had discontinued their randomised treatment or initiated bolus insulin treatment for more than 2 weeks prior to the week 26/52 visit and had a measurement at the week 26/52 visit. In ONWARDS 4-6, the approach was in principle identical although used data only from those who had discontinued their randomised treatment and had a measurement at the week 26/52 visit. The underlying assumption was that subjects with missing data behave similarly as subjects that discontinue randomised treatment *or* initiated treatment with bolus insulin for more than 2 weeks (ONWARDS 1-3). Missing data handling appears reasonable (including the distinction made between ONWARDS 1-3 and ONWARDS 4-6 based on intercurrent events).

In case there were limitations in the amount of available data to preclude meaningful imputation, a few options had been pre-defined and also ranked. This is endorsed. As was clarified by the applicant during the procedure, another option than the primary had to be used in the analysis of the primary endpoint in three of the studies. For study ONWARDS 2 and 3, this implied that the imputation model was simplified. In ONWARDS 4 the imputation model was replaced by a return-to-baseline imputation approach. Imputing no change could be reasonable in implying a lack of glycaemic control, however, based on an assumption of lack of a treatment efficacy, another option eventually being a HbA1c value implying HbA1c worsening (loss of glycaemic control).

For the multiplicity adjusted secondary endpoint in ONWARDS 1 (TIR: Time in range), limitations in the amount of available data implied that missing data was replaced by imputation based on the subjects in the comparator arm who had completed the treatment. This is accepted based on the fact that this analysis tested a superiority hypothesis.

For the primary endpoint, there was one predefined sensitivity analysis, and the performance of Tipping point analyses is appreciated. However, for challenging robustness of the non-inferiority conclusions in ONWARDS 4 and 6, it is considered less useful in the way that it investigates the robustness of the assumptions about the missing data and not intercurrent events per se. The statistical strength of the NI conclusion, especially in ONWARDS 4, was acknowledged. However, for ONWARDS 4 and ONWARDS 6, the applicant was invited to propose a supplemental (estimand) and/or sensitivity analysis of the primary endpoint. In response, a supplemental analysis was performed using a hypothetical estimand. Data collected after treatment discontinuation was ignored and in case of missing week 26 HbA1c measurements, data was imputed using multiple imputation based on subjects from the same arm who completed randomised treatment. The approach is accepted. The provided analyses supported the primary non-inferiority conclusion in both study ONWARDS 4 and study ONWARDS 6.

In order to control the overall Type I error at a 5% level (2-sided), a hierarchical testing procedure had been defined: a few hypotheses were to be adjusted for multiplicity and were only to tested if the primary hypothesis had been confirmed. This is an agreed approach to control the overall type I error. However, the predefined confirmatory testing strategy cannot be considered anything but non-existing in study ONWARDS 4 and ONWARDS 6 (included no secondary hypotheses), and in ONWARDS 2, ONWARDS 3 and ONWARDS 5, sparse: in case non-inferiority could be shown, HbA1c superiority was to be tested. In the ONWARDS 1 study, the multiple testing procedure included one key secondary endpoint (i.e., time in range (TIR)) besides the HbA1c non-inferiority test and if shown, a test for HbA1c superiority.

The above implies limitations in the ability to support a successful primary outcome with formally valid secondary efficacy outcome conclusions. For ONWARDS 4 and ONWARDS 6, statistical conclusions will only be accepted based on the primary HbA1c non-inferiority analysis.

In ONWARDS 5, the primary objective was to demonstrate the effectiveness of once weekly insulin icodec used with a DoseGuide App compared with once daily basal insulin analogues without the use of the DoseGuide App, contrary CHMP advice (see also discussion above). The scope of this application is the efficacy and safety of once weekly insulin icodec and since the B/R of the use of once weekly insulin icodec cannot be isolated when the DoseGuide was not available in the control arm, ONWARDS 5 has been given less weight in the assessment of data to support the currently sought indication. Given the ONWARDS 5 study design implying that the DoseGuide was not available in the control arm, the efficacy of once weekly insulin icodec cannot be isolated. Obviously, neither can the performance of the DoseGuide application. Therefore, it is not accepted to present ONWARDS 5 study data in section 5.1 of the SmPC.

No subgroup analyses had been pre-planned, which is somewhat striking since this usually expected in pivotal studies for at least a numerically confirmation of consistency across different levels of (important) baseline characteristics.

None of the phase 3a studies included a formal interim analysis. For the studies with an extension reporting was to be split into a main phase and an extension phase, where the results of the main phase could be reported before last subject last visit. To preserve trial integrity during the extension phase, dissemination of results from the main phase was initially to be limited to communication internally and with regulatory authorities.

The ONWARDS studies were more or less run in parallel. They were initiated during 2020 or 2021 and completed during 2022 and thus performed during the COVID-19 pandemic. According to an applicant statement, the ONWARDS studies were only "minimally impacted by COVID-19".

The studies were generally well conducted. The clinical study programme is considered adequate both with regards to design, study size and duration, except for the T1DM study regarding the number of enrolled subjects and study duration.

Efficacy data and additional analyses

Overall, the populations recruited are considered representative for the target population. Across the study programme, the treatment groups were generally well balanced with regards to demographic and diabetes characteristics. A total of 180 patients >75 years were included in the trials. The proportion of subjects with normal function and mild renal impairment ranged from 37-67% and 31-46%, respectively. Moderate renal impairment was seen for 8-16% of T2DM subjects and 2% of T1DM subjects. About 47% of T1DM subjects and 24-48% of T2DM subjects were recruited from Europe of which ONWARDS 3 included the least proportion of European subjects (24%). Asian subjects contributed to 21-37% of the study population in ONWARDS 1-4 and 6. In ONWARDS 1, 3, 4 and 6, 14-19% Japanese subjects were included. The consistency in efficacy between the Japanese subgroup and the entire trial population has been analysed. In the Japanese subgroup of T1DM patients, the mean HbA1c gradually increased toward baseline from week 10 onwards. At week 26 to week 52, there was no glycaemic effect with regard to reduced mean HbA1c in the Japanese subgroup, while the incidence and rate of severe or clinically significant hypoglycaemic episodes (including nocturnal) was higher for insulin icodec compared to insulin degludec.

The pretrial treatments with regards to insulin reflects the current treatment practice and was well balanced between groups. The T2DM groups were well balanced with regards to non-insulin anti-diabetic treatment, except for a slight imbalance regarding treatment of SGLT-2 inhibitors (40% vs 32% for insulin Ico vs IDeg) and GLP-1 agonists (22% vs 16% for Ico vs IDeg) in trial 4479. Metformin was used by 84-92% of insulin naïve and basal switch patients and by 66% of basal-bolus patients. In general, drop-out rates were low and balanced between the groups.

A large proportion of patients completed the trials without permanent discontinuation of trial product 93-97% in ONWARDS 1-4 and 6 and 90% in ONWARDS 5.

In T2DM subjects, non-inferiority was demonstrated for the primary endpoint mean change in HbA1c from baseline (ONWARDS 1: -0.19% [-0.36; -0.03], ONWARDS 2: -0.22% [-0.37; -0.08], ONWARDS 3: -0.21% [-0.34; -0.08], ONWARDS 4: 0.02% [-0.11; 0.15] and ONWARDS 5: -0.38% [-0.66; -0.09]) and the 95% CI was within the non-inferiority margin. Furthermore, statistical superiority was confirmed in insulin naïve (ONWARDS 1, 3 and 5) and T2DM subjects previously treated on basal insulin (ONWARDS 2). In ONWARDS 1, changes in HbA1c were maintained at week 78 (ETD -0.11% [-0.22; 0.00]). In T1DM subjects, clinically relevant reductions in HbA1c were observed and the primary endpoint was met (ONWARDS 6: 0.05% [-0.13; 0.23]. However, the HbA1c reduction in T1DM subjects was less pronounced for insulin icodec week 26 compared to week 18, while the HbA1c reduction was maintained for insulin degludec between week 18 and week 26.

Multiple testing procedure was in place for the key secondary endpoint in trial ONWARDS 1. Other secondary endpoints were not corrected for multiplicity.

In insulin naïve subjects (ONWARDS 1), there was a statistically significant difference in favour of insulin

icodec for the key secondary endpoint time spent in glycaemic range (TIR) 3.9-10.0 mmol/L; ETD: 4.27 [1.92: 6.62]. In ONWARDS 1, subjects in the insulin icodec group vs. insulin glargine spent less time above range (TAR) >10.0 mmol/L (26.9% vs. 32.3%) and there were no important differences between the treatment groups in time spent below range (TBR) <3.0 mmol/L. In basal switch and basal-bolus T2DM subjects, there were no important differences for TIR, TAR or TBR between treatment groups. In T1DM subjects, subjects in the insulin icodec group vs. insulin degludec spent more time in TBR <3.0 mmol/L (1.02% vs. 0.68%) and TBR <3.9 mmol/L (3.86% vs 2.90%); however, no important differences for TIR and TAR between treatment groups.

In T2DM subjects, no relevant difference in fasting plasma glucose (FPG) reduction was observed between treatment arms. In T1DM subjects, the reduction in FPG from baseline to end of treatment was numerically larger for insulin degludec (-1.87 mmol/L) than for insulin icodec (-0.84 mmol/L); ETD: 1.03 [0.48; 1.58]. The difference in FPG reduction between insulin degludec and insulin icodec was evident at the first post-baseline assessment (12 weeks) and the difference even increased from week 18 to week 26. The applicant argues that the difference in FPG is mostly due to a less even weekly effect in T1DM subjects compared to T2DM subjects.

In insulin naïve T2DM subjects (ONWARDS 1 and 3), the mean weekly insulin dose was numerically higher for insulin glargine vs. insulin icodec in ONWARDS 1, while the opposite was seen in ONWARDS 3 ,where the average weekly basal insulin dose was numerically higher for insulin icodec vs. insulin degludec. In basal switch and basal-bolus T2DM subjects (ONWARDS 2 and 4) and in T1DM subjects (ONWARDS 6), the mean weekly *basal insulin dose*, including the weight-correlated dose, was numerically higher for insulin icodec compared with daily basal insulin. However, the mean weekly *bolus insulin dose* and mean weekly *total insulin dos*e (bolus + basal), respectively, was numerically lower for insulin icodec compared to daily basal insulin in ONWARDS 2 and 4.

Across the studies, the incidence rate of level 2 or level 3 hypoglycaemic episodes was higher for insulin icodec compared to daily basal insulin, except for in basal-bolus T2DM subjects (ONWARDS 4) where the rates were similar between the treatment groups. In T1DM subjects, the rate of level 2 or 3 hypoglycaemia for insulin icodec vs. insulin degludec was 1.89 [1.54; 2.33] and the rate of nocturnal hypoglycaemic episodes (level 2 or 3) was 2.13 [1.56; 2.91].

Weight gain is expected with intensified insulin treatment. The mean body weight increased numerically slightly more for insulin icodec compared to daily basal insulin in all studies. The ETR of weight gain was <1 kg in all studies except for bolus switch subjects (ONWARDS 2) where the ETD of change from baseline in body weight after 26 weeks was 1.70 kg [0.76; 2.63] for insulin icodec vs. insulin degludec.

Patient-reported outcome measures (PROM) were included in ONWARDS 2, 5 and 6. In T2DM patients (ONWARDS 2 and 5), the change in DTSQ total score was numerically higher and in favour of insulin icodec; however, in T1DM patients, increase in the DTSQ total score was greater for insulin degludec compared to insulin icodec. Assessment of PRO measures in open-label trials is challenging. Therefore, PROM data is not included in section 5.1 of the SmPC.

A prespecified analysis of achievement of target HbA$_{1c}$ without hypoglycaemia was performed. In insulin naïve subjects and in T2DM subjects with basal switch, responder rates of achieving HbA$_{1c}$ <7% or ≤6.5 without severe or clinically significant hypoglycaemia were numerically higher for insulin icodec compared to daily basal insulin. In basal-bolus T2DM subjects, the rates were comparable between the treatment groups. However, in T1DM subjects, the responder rates of achieving HbA$_{1c}$ targets without level 2 or 3 hypoglycaemia was numerically lower for insulin icodec compared to insulin degludec. Responder rates of

achieving HbA$_{1c}$ <7% without level 2 or 3 hypoglycaemia was 9.6% for insulin icodec and 16.7% for insulin degludec.

2.6.7. Conclusions on the clinical efficacy

The glucose-lowering effect of insulin icodec has been adequately shown in T2DM patients. The data further support the proposed dosing recommendations; however, due to the increased risk of severe or clinically significant hypoglycaemic events, patients should not be recommended to prepone dosing. A missed dose should be injected as soon as possible, which is adequately reflected in the SmPC.

The proposed indication in T1DM subjects was supported for the primary endpoint; however, the HbA1c reduction for insulin icodec was less pronounced at week 26 compared to week 18, while the HbA1c reduction was maintained for insulin degludec between week 18 and week 26. Data up to 52 weeks of treatment with insulin icodec indicate a somewhat lower glucose reducing effect compared to insulin degludec (EDT 0.17% [0.02; 0.31]). Considering that patients with type 1 diabetes still have to take daily bolus insulin injections, the benefit of weekly dosing may be limited. Further, long-acting insulin may not be optimal in T1DM without endogenous insulin production. It is acknowledged that there may be some patients with T1DM that benefit from a weekly posology and for which this benefit outweighs the risk. However, it should be emphasised that patients with T1DM should only be treated with insulin icodec if a clear benefit from a once weekly posology is expected, and this will rather be a decision for the prescriber.

2.6.8. Clinical safety

The application for once-weekly insulin icodec is based on safety data from 18 clinical trials in the insulin icodec clinical development programme including six (6) phase 3a confirmatory efficacy and safety trials (ONWARDS 1-6), three (3) phase 2 exploratory trials and nine (9) clinical pharmacology trials (Figure 4). Focus for the safety evaluation of the once-weekly insulin icodec and the target population, has primarily been on pooled data (the "Phase 3a pool") from the six (6) phase 3a confirmatory efficacy and safety trials (ONWARDS 1-5 performed in subjects with T2DM and ONWARDS 6 performed in subjects with T1DM) supplemented with the T2DM pool and individual trials, as applicable for an overall safety evaluation. Of importance to consider during the safety evaluation is the fact that all trials in the Phase 3a pool, except ONWARDS 3 (performed in insulin naïve subjects with T2DM), had open-label designs. Results from the extension-phases of ONWARDS 1 (week 52-78) and ONWRDS 6 (week 26-52) have also been submitted and ire reflected in the safety section below.

2.6.8.1. Patient exposure

The total exposure to insulin icodec in the on-treatment/main-on-treatment observation period was 1681.23 PYE (n=2170) in the phase 3a pool, 1538.92 PYE (n=1880) in the T2DM pool and 300.16 PYE (n=290) in subjects with T1DM previously treated with a basal-bolus insulin regime (data from the complete 52-week ONWARDS 6 trial).

In the T2DM population (ONWARDS 1-5) 1811 subjects were exposed to insulin icodec for ≥6 months and 614 subjects for ≥12 months (Table 51). Additional data from the extension phase of ONWARDS 1 (insulin naïve patients with T2DM), demonstrates that 465 subjects also were exposed to insulin icodec for ≥82 weeks.

For the T1DM population (ONWARD 6), 249 subjects previously treated with a basal-bolus insulin regime, were treated with insulin icodec for at least 54 weeks (Table 52).

Use of insulin icodec in newly diagnosed (not previously treated with basal insulin) subjects with T1DM has not been evaluated. This fact is appropriately reflected in the SmPC.

Table 51. Exposure by month - summary - safety analysis set – T2DM pool (ONWARDS 1-5)

	Insulin icodec		Daily basal insulin		Total	
	N	(%)	N	(%)	N	(%)
Number of subjects	1880		1878		3758	
Duration of exposure						
>= 1 month	1868	(99.4)	1866	(99.4)	3734	(99.4)
>= 2 months	1859	(98.9)	1845	(98.2)	3704	(98.6)
>= 3 months	1851	(98.5)	1835	(97.7)	3686	(98.1)
>= 4 months	1837	(97.7)	1828	(97.3)	3665	(97.5)
>= 5 months	1828	(97.2)	1818	(96.8)	3646	(97.0)
>= 6 months	1811	(96.3)	1809	(96.3)	3620	(96.3)
>= 7 months	1779	(94.6)	1777	(94.6)	3556	(94.6)
>= 8 months	985	(52.4)	993	(52.9)	1978	(52.6)
>= 9 months	981	(52.2)	987	(52.6)	1968	(52.4)
>= 10 months	974	(51.8)	986	(52.5)	1960	(52.2)
>= 11 months	972	(51.7)	982	(52.3)	1954	(52.0)
>= 12 months	614	(32.7)	643	(34.2)	1257	(33.5)

Table 52. Exposure by treatment week - summary - safety analysis set in T1DM (ONWARD 6)

	Ico		IDeg	
	N	(%)	N	(%)
Number of subjects	290		292	
Exposure				
N	290	(100.0)	292	(100.0)
0 < to <= 2 weeks	2	(0.7)	0	
2 < to <= 6 weeks	0		4	(1.4)
6 < to <= 10 weeks	2	(0.7)	1	(0.3)
10 < to <= 14 weeks	2	(0.7)	1	(0.3)
14 < to <= 18 weeks	3	(1.0)	1	(0.3)
18 < to <= 22 weeks	4	(1.4)	1	(0.3)
22 < to <= 26 weeks	2	(0.7)	1	(0.3)
26 < to <= 30 weeks	3	(1.0)	0	
30 < to <= 34 weeks	3	(1.0)	2	(0.7)
34 < to <= 38 weeks	4	(1.4)	0	
38 < to <= 42 weeks	1	(0.3)	1	(0.3)
42 < to <= 46 weeks	1	(0.3)	1	(0.3)
46 < to <= 50 weeks	1	(0.3)	1	(0.3)
50 < to <= 54 weeks	0		0	
54 < to <= 58 weeks	249	(85.9)	272	(93.2)
> 55 weeks	262	(90.3)	278	(95.2)
> 56 weeks	260	(89.7)	276	(94.5)
> 57 weeks	220	(75.9)	89	(30.5)
> 58 weeks	13	(4.5)	6	(2.0)
> 59 weeks	4	(1.4)	2	(0.7)
Unknown	0		0	

N: Number of subjects, %: Percentage of subjects.

2.6.8.2. Adverse events

Overall, in the Phase 3a pool, there was no pronounced difference in the proportion of subjects reporting the most common AEs when comparing insulin icodec with the daily basal insulin group or the T2DM populations with the T1DM population. Serious adverse events (SAEs) were in the T2DM pool balanced between the

insulin icodec and comparator groups (~8%). In the T1DM population a slightly higher proportion of subjects and rate of SAEs were reported in the insulin icodec group (3.8%) compared to the insulin IDeg group (2.4%). The difference was driven by a higher reporting of hypoglycaemic SAE events in the insulin icodec group. Fatal events were balanced between groups (0.3%) in the phase 3a pool. No death was reported in connection to hypo- or hyperglycaemia (Table 53 and Table 54).

Table 53. Adverse events - on-treatment/main-on-treatment - summary - phase 3a pool

	Insulin icodec				Daily basal insulin			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Number of subjects	2170				2170			
PYE (years)	1681.23				1680.58			
Events	1328	(61.2)	3985	254.67	1263	(58.2)	3878	250.90
Serious								
Yes	166	(7.6)	245	14.82	169	(7.8)	238	13.68
No	1287	(59.3)	3740	239.85	1223	(56.3)	3640	237.22
Missing	0				0			
Severity								
Severe	92	(4.2)	121	7.70	89	(4.1)	133	7.32
Moderate	512	(23.6)	931	57.09	478	(22.0)	856	52.52
Mild	1113	(51.3)	2933	189.88	1073	(49.4)	2889	191.06
Missing	0				0			
Related to basal insulin								
Probable	82	(3.8)	120	8.27	76	(3.5)	133	8.04
Possible	125	(5.8)	179	12.41	105	(4.8)	178	12.49
Unlikely	1276	(58.8)	3674	233.12	1226	(56.5)	3561	229.99
Missing	8	(0.4)	12	0.87	6	(0.3)	6	0.37
Related to technical complaint for basal insulin								
Yes	11	(0.5)	11	0.87	7	(0.3)	8	0.64
No	1325	(61.1)	3961	252.84	1258	(58.0)	3862	249.73
NA	1	(0.0)	1	0.08	1	(0.0)	1	0.08
Missing	8	(0.4)	12	0.87	7	(0.3)	7	0.45
Outcome								
Fatal	14	(0.6)	18	1.17	13	(0.6)	15	0.81
Not recovered/not resolved	589	(27.1)	1087	67.66	570	(26.3)	1042	65.31
Recovered/resolved with sequelae	10	(0.5)	10	0.53	16	(0.7)	18	1.10
Recovering/resolving	96	(4.4)	136	9.08	92	(4.2)	111	7.34
Recovered/resolved	1122	(51.7)	2733	176.18	1039	(47.9)	2690	176.24
Unknown	1	(0.0)	1	0.04	2	(0.1)	2	0.09
Missing	0				0			

%: Percentage of subjects with one or more events, E: Number of adverse events, N: Number of subjects with one or more events, PYE: Patient years of exposure (1 PYE = 365.25 days), R: Rate (number of adverse events per 100 PYE). Adj.: Adjusted percentages and rates were calculated using the Cochran-Mantel Haenszel method to account for differences between trials. On- treatment: Onset date on or after the first dose of trial product and no later than the first date of either the follow-up visit (FU2), the last date on trial product + 5 weeks for once daily insulin and + 6 weeks for once weekly insulin or the end-date for the in-trial period. Main-on treatment: Onset date on or after the first dose of trial product and no later than the first date of either the end date of the on-treatment period or the last planned visit in the main part of the trial. Daily basal insulin: IDeg, IGlar U100, and IGlar U300. Phase 3a pool: ONWARDS 1-6, only main part of ONWARDS 1 and 6.

Table 54. Summary of AEs reported in phase 3a trials – on-treatment/main-on-treatment

Trial / duration (weeks)		Total AEs		Serious AEs		Severe AEs	
		Insulin icodec	Daily basal insulin	Insulin icodec	Daily basal insulin	Insulin icodec	Daily basal insulin
ONWARDS 1 (4477) / 52[a]	%	71.3	68.1	10.4	10.0	3.7	4.1
	R	252.53	239.57	15.23	15.05	5.35	7.01
ONWARDS 2 (4478) / 26	%	61.5	51.0	8.4	6.1	4.2	4.2
	R	300.17	214.70	19.32	13.09	10.95	8.51
ONWARDS 3 (4479) / 26	%	60.4	56.8	5.1	5.1	4.4	1.4
	R	299.01	247.76	12.87	10.52	8.19	2.34
ONWARDS 4 (4480) / 26	%	58.8	57.4	7.6	8.6	4.5	4.1
	R	271.87	329.74	20.91	19.78	11.95	8.39
ONWARDS 5 (4481) / 52	%	51.5	50.2	8.3	10.6	5.2	7.1
	R	146.37	141.78	12.33	15.16	6.08	11.24
ONWARDS 6 (4625) / 26[a]	%	65.2	65.1	3.8	2.4	3.1	1.4
	R	356.27	429.50	10.54	6.24	7.03	3.47

[a] main part of trial. % = percentage of subjects with one or more events; R = rate (number of adverse events per 100 PYE); PYE = patient years of exposure (1 PYE = 365.25 days)

Common adverse events

In the Phase 3a pool, AEs were reported most frequently within the SOCs "Infections and infestations" (insulin icodec 29.9% and daily basal insulin), "Gastrointestinal disorders" (insulin icodec 12.8% and daily basal insulin 11.3%) and "Musculoskeletal and connective tissue disorders" (insulin icodec 12.6% and daily basal insulin 13.3%) both for the insulin icodec and the daily basal insulin group (Figure 29). Overall, the frequencies of reported AEs on a SOC-level in the Phase 3a pool were similar between the insulin icodec and the comparator group both for subjects with T2DM and subjects with T1DM. The minor differences noted could be attributed the open-label designs in most of the studies (Figure 29).

The most frequently reported AEs in the insulin icodec group in the Phase 3a pool were "Covid-19", "nasopharyngitis", "diarrhoea", "headache" and "upper-respiratory infection" (Table 55). Overall, there was no pronounced difference in proportion of subjects reporting the most common AEs (PT) when comparing insulin icodec with the daily basal insulin group or the T2DM populations with the T1DM population.

In the Phase 3a pool, the PTs "Diarrhea", "Upper respiratory tract infection", "Gastroenteritis", "Bronchitis", "Fatigue" and "Muscle spasms" were reported with a higher proportion (≥0.5%) of the subjects in the insulin icodec group vs daily basal insulin group. However, the differences were still small and not considered clinically significant. Furthermore, the difference noticed for some of the PTs might be explained by the open label trial design and by random variation. For the PTs "Diarrhea", "Bronchitis" and "Muscle spasm" no differences ≥0.5% were noted in the double-blinded, double dummy trial ONWARDS 3.

Safety results from the extension phase (week 52-83) of ONWARDS 1 (insulin naïve T2DM population) are overall in line with the results from the main treatment period (0-52 weeks).
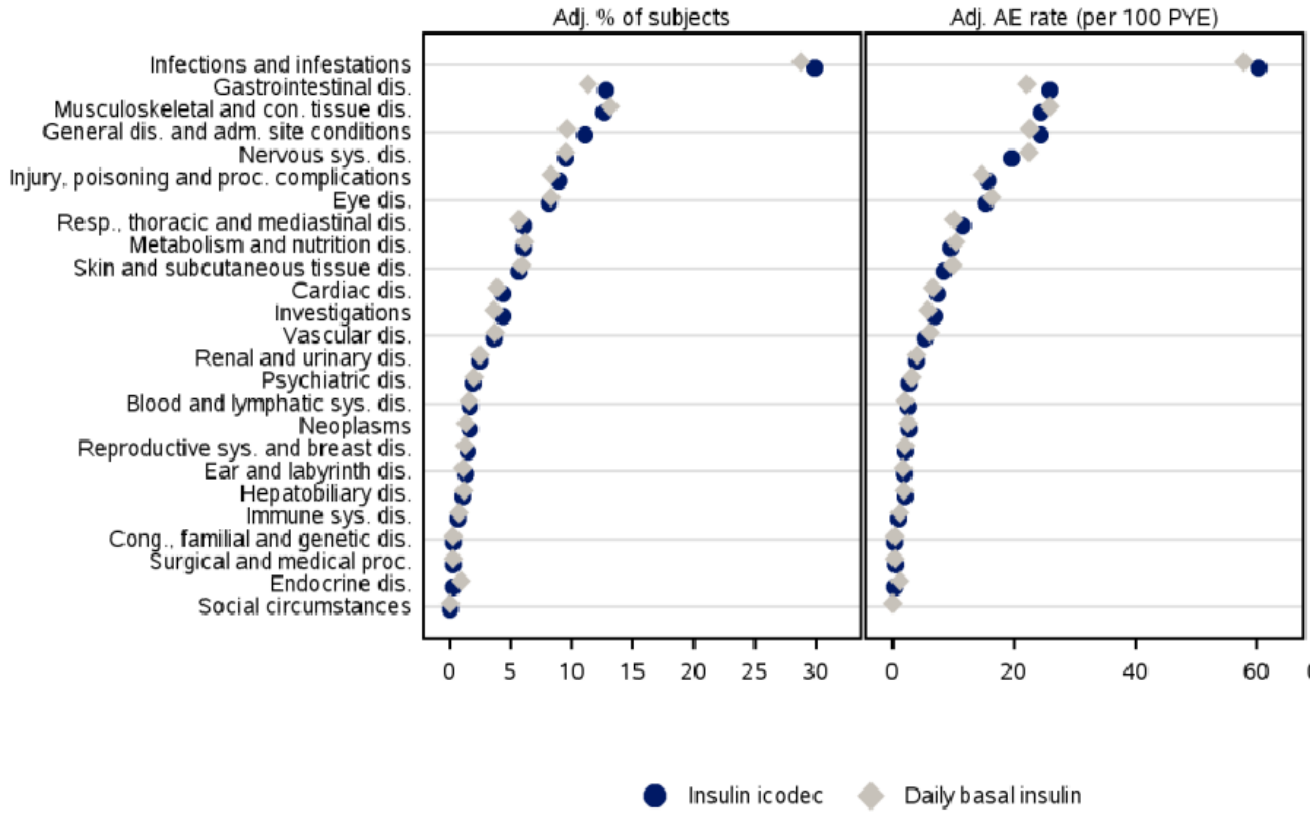
Figure 29. Phase 3a pool - Adverse events by SOC – on-treatment/main-on-treatment

Table 55. Adverse events by system organ class and preferred term - most frequent [>=1%] - on-treatment/main- on-treatment – summary in Phase 3a pool.

	Insulin icodec				Daily basal insulin			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Number of subjects	2170				2170			
PYE (years)	1681.23				1680.58			
Events	792	(36.5)	1425	93.75	764	(35.2)	1337	88.10
Infections and infestations								
COVID-19	181	(8.3)	185	11.92	192	(8.9)	199	12.26
Nasopharyngitis	117	(5.4)	141	10.08	115	(5.3)	135	9.65
Upper respiratory tract infection	68	(3.1)	81	4.86	52	(2.4)	56	3.54
Urinary tract infection	43	(2.0)	46	3.05	50	(2.3)	56	3.41
Gastroenteritis	32	(1.5)	33	2.45	18	(0.8)	19	1.34
Bronchitis	30	(1.4)	31	2.05	19	(0.9)	19	1.20
Influenza	29	(1.3)	32	2.34	33	(1.5)	36	2.69
Gastrointestinal disorders								
Diarrhoea	89	(4.1)	108	6.65	55	(2.5)	57	3.70
Nausea	41	(1.9)	42	2.58	35	(1.6)	37	2.47
Vomiting	31	(1.4)	39	2.79	21	(1.0)	24	1.55
Nervous system disorders								
Headache	70	(3.2)	92	6.52	64	(2.9)	80	5.30
Dizziness	40	(1.8)	51	3.18	39	(1.8)	47	3.07
Musculoskeletal and connective tissue disorders								
Back pain	65	(3.0)	69	4.18	72	(3.3)	89	6.32
Arthralgia	51	(2.4)	59	3.67	57	(2.6)	63	4.16
Pain in extremity	37	(1.7)	39	2.31	37	(1.7)	43	2.90
Muscle spasms	25	(1.2)	27	1.79	9	(0.4)	9	0.52
Osteoarthritis	24	(1.1)	26	1.58	26	(1.2)	29	1.77
Eye disorders								
Diabetic retinopathy	64	(3.0)	70	5.14	72	(3.3)	76	5.44
Cataract	28	(1.3)	33	1.97	27	(1.2)	30	1.83
General disorders and administration site conditions								
Pyrexia	41	(1.9)	43	2.86	43	(2.0)	45	2.87
Fatigue	32	(1.5)	36	2.31	16	(0.7)	16	0.91
Vascular disorders								
Hypertension	37	(1.7)	37	2.37	38	(1.8)	43	2.71

%: Percentage of subjects with one or more events, E: Number of adverse events, N: Number of subjects with one or more events, PYE: Patient years of exposure (1 PYE = 365.25 days), R: Rate (number of adverse events per 100 PYE). Adj.: Adjusted percentages and rates were calculated using the Cochran-Mantel-Haenszel method to account for differences between trials. MedDRA version 24.1. On-treatment: Onset date on or after the first dose of trial product and no later than the first date of either the follow-up visit (FU2), the last date on trial product + 5 weeks for once daily insulin and + 6 weeks for once weekly insulin or the end-date for the in-trial period. Main-on- treatment: Onset date on or after the first dose of trial product and no later than the first date of either the end-date of the on-treatment period or the last planned visit in the main part of the trial. Daily basal insulin: IDeg, IGlar U100, and IGlar U300. Phase 3a pool: ONWARDS 1-6, only main part of ONWARDS 1 and 6.

Adverse events of special interest

Hypoglycaemic episodes

The used classification of hypoglycaemia is presented in Table 56. Nocturnal hypoglycaemic episodes were defined as episodes occurring between 00:01 and 05:59.

Hypoglycaemic data are presented for the on-treatment period for ONWARDS 2-5 and if nothing else is mentioned main-on-treatment periods for ONWARDS 1 and 6 are used. In the phase 3a trials in insulin-experienced subjects, subjects were to be excluded in case of known hypoglycaemic unawareness or recurrent severe hypoglycaemic episodes within the last year before screening as judged by the investigator.

In ONWARDS 1-4: Subjects were to report PG values <3.9 mmol/L (70 mg/dL) as hypoglycaemic events. PG should always be measured by the trial BG meter and hypoglycaemic episodes should be recorded in the eDiary. Severe hypoglycaemic episodes were to be reported without confirmed PG values.

In ONWARDS 5: In this trial titration of insulin icodec was guided by the DoseGuide System and not by investigators adjustments as in ONWARDS 1-4 and 6 (see section on Clinical Efficacy above). In the daily basal insulin group, low SMPG values (<3.9 mmol/L) automatically triggered a hypoglycaemic episode form for the subjects. In the insulin icodec group, subjects had to manually start the hypoglycaemic episode form in the eDiary and add the lowest SMPG value, date, start time and stop time. To ensure that this difference in data collection did not lead to an underreporting of hypoglycaemic episodes in the insulin icodec with DoseGuide treatment group, SMPG-based hypoglycaemic episode analyses were added as sensitivity analyses (see discussion below).

In ONWARDS 6, the subjects used CGM throughout the entire study and the results were open. In case a hypoglycaemic value was detected on the CGM, this should be verified by BG measure and register in the Diary.

Upon onset of a hypoglycaemic episode the subject was recommended to measure PG every 15 minutes until the PG value is ≥ 3.9 mmol/L (70 mg/dL) and/or symptoms were resolved.

Table 56. Classification of hypoglycaemia

Classification of hypoglycaemia		
Level	**Glycaemic criteria**	**Description**
Hypoglycaemia alert value (level 1)	< 3.9 mmol/L (70 mg/dL) and ≥ 3.0 mmol/L (54 mg/dL)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycaemia (level 2)	<3.0 mmol/L (54 mg/dL)	Sufficiently low to indicate serious, clinically important hypoglycaemia
Severe hypoglycaemia (level 3)	No specific glucose threshold	Hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery

Hypoglycaemic episodes in the T2DM population (ONWARDS 1-5)

Severe (level 3) hypoglycaemia

In the T2DM population, severe (level 3) hypoglycaemic episodes were reported in similar low proportions in the insulin icodec groups (0-1.4%) and the daily insulin groups (0.4-0.7%) (Table 57). No severe nocturnal hypoglycaemic episode was reported in any of T2DM icodec treated groups.

Table 57. Severe (level 3) hypoglycaemic episodes in the T2DM population – on treatment/main-on-treatment - summary - safety analysis set

	Insulin icodec				Daily basal insulin			
	N	(%)	E	R	N	(%)	E	R
T2D, insulin-naïve								
ONWARDS 1								
Number of subjects	492				492			
Severe hypoglycaemia (level 3)	1	(0.2)	1	0.21	3	(0.6)	3	0.62
ONWARDS 3								
Number of subjects	293				294			
Severe hypoglycaemia (level 3)	0				2	(0.7)	2	1.17
ONWARDS 5								
Number of subjects	542				538			
Severe hypoglycaemia (level 3)	0				4	(0.7)	5	0.89
T2D, basal insulin								
ONWARDS 2								
Number of subjects	262				263			
Severe hypoglycaemia (level 3)	0				1	(0.4)	1	0.65
T2D, basal-bolus insulin								
ONWARDS 4								
Number of subjects	291				291			
Severe hypoglycaemia (level 3)	4	(1.4)	7	4.18	2	(0.7)	3	1.80

%: Percentage of subjects with one or more events, E: Number of events, N: Number of subjects with one or more events, PYE: Patient years of exposure (1 PYE = 365.25 days), R: Rate (number of adverse events per 100 PYE). Severe hypoglycaemia (level 3): Hypoglycaemia with severe cognitive impairment requiring external assistance for recovery. Daily basal insulin: IDeg (ONWARDS 2, ONWARDS 3), IGlar U100 (ONWARDS 1, ONWARDS 4), and once-daily analogues (IDeg, IGlar U100, IGlar U300) (ONWARDS 5). Data from ONWARDS 1-5, only main part of ONWARDS 1.

Clinically significant (level 2) hypoglycaemic episodes

Insulin naïve type 2 diabetes populations (ONWARDS 1, 3 and 5): The overall proportions of subjects reporting clinically significant hypoglycaemic episodes in this population during the main study periods, were slightly higher in the insulin icodec groups (8.9%-11.8%) compared to the comparators (5.8%-10.0%). However, the <u>rates</u> were apparently higher in all insulin icodec groups compared to the comparators across these three trials (ONWARDS 1: 29.43 vs 14.46 events per 100 PYE rate ratio 1.67 [0.99; 2.84], ONWARDS 3; 31.01 vs 14.44 events per 100 PYE, rate ratio 2.09 [0.99; 4.41] and ONWARDS 5: 18.59 vs 13.55 events per 100 PYE, rate ratio 1.23 [0.77; 1.98]) (Table 59).

For updated results including data from the complete study period (0-78 weeks) for ONWARDS 1 see section "*Severe (level 3) or clinically significant (level 2) hypoglycaemic episodes*" below.

The results of the sensitivity analysis performed in ONWARDS 5 (insulin naïve subjects with T2DM**)** showed that the rate of clinically significant (level 2) hypoglycaemic episodes for insulin icodec was more similar to that seen for insulin icodec in the other insulin naïve T2DM trials (25.56 episodes per 100 PYE compared to 18.56 episodes per 100 PYE in the per protocol analysis). These episodes were reported by 11.1% of the subjects. For the daily basal insulin analogue group, the rate was 15.87 episodes per 100 PYE (compared to 13.55 episodes per 100 PYE in the per protocol analysis) reported by 8.6% of the subjects.

T2DM population previously treated with basal insulin (ONWARDS 2): Both the proportion of subjects reporting, and the rate of clinically significant hypoglycaemic episodes were markedly higher in the insulin icodec groups as compared to the daily basal insulin groups (14.1% vs 7.2% and rate 72.79 vs 26.84 event per 100 PYE, rate ratio 1.98 [0.95; 4.12]) (Table 59).

T2DM population previously treated with basal-bolus insulin (ONWARDS 4): In this population there was no difference of clinical relevance in the proportion of subjects reporting and the rate of clinically significant hypoglycaemic episode between the two treatment groups (50.9% vs 55.0% and rate 555.86 vs 560.56 episodes per 100 PYE, rate ratio 0.99 [0.73;1.34]) (Table 59).

Severe (level 3) or clinically significant (level 2) hypoglycaemic episodes

A summary of Severe (level 3) or clinically significant (level 2) hypoglycaemic episodes in the T2DM population - on-treatment/main-on-treatment by trials is presented in Table 58.

Estimated rate ratio by trial including severe (level 3) and clinically significant (level 2) hypoglycaemic episodes is presented in Table 59.

In the T2DM population the highest proportion of subjects and rates of "severe (level 3) or clinically significant (level 2) hypoglycaemic episodes" were reported by the subjects previously treated with basal-bolus insulin (ONWARDs 4; 52%) followed by the T2DM population previously treated with basal insulin (ONWARD 2; 14%). The lowest proportions of subjects reporting any "severe (level 3) or clinically significant (level 2) hypoglycaemic episodes" were noted in the insulin naïve T2DM populations (ONWARDS 1 main treatment period [10%], ONWARDS 3 [9%] and ONWARDS 5 [12%]) (Table 58).

Insulin naïve T2DM populations (ONWARDS 1, 3 and 5): The overall proportion of subjects reporting any "severe (level 3) or clinically significant (level 2) hypoglycaemic episodes" were slightly higher in the insulin icodec groups (9% -12%) as compared to the comparators (6-11%). However, the rates were apparently higher in all insulin icodec groups as compared to the comparators across these three trials (ONWARDS 1: 29.64 vs 16.08 events per 100 PYE; ONWARDS 3: 31.01 vs 14.61 per 100 PYE and ONWARDS 5: 18.59 vs 14.45 events per 100 PYE). The estimated rate ratios varied between 1.17 and 1.83 (Table 59).

Updated results including data from the complete study period (0-78 weeks) for ONWARDS 1, did not change the safety profile regarding hypoglycaemic episodes in treatment naïve subjects with T2DM. At the end of the completed trial, the proportion of subjects with at least one severe (level 3) or clinically significant (level 2) hypoglycaemic episodes was similar in the two treatment groups (12% in the icodec group and 14% in the daily insulin group). However, the rate after 78 weeks was also twice as high in the insulin icodec group (29.65 episodes per 100 PYE) compared to the insulin glargine group (15.78 episodes per 100 PYE). The difference is mainly explained by three subjects in the insulin icodec group that accounted for 105 of the 226 SMPG registered clinically significant hypoglycaemic episodes. The estimated rate ratio was 1.63 (1.02; 2.61) (Table 59).

T2DM population previously treated with basal insulin (ONWARDS 2): In this population both the proportion of subjects reporting and the rates of "severe or clinically significant hypoglycaemic episodes"

were markedly higher in the insulin icodec groups compared to the comparator groups (14% vs 7% and rate 72 vs 27 per 100 PYE, estimated rate ratio 1.98 [0.95; 4.12]) (Table 58 and Table 59).

T2DM population on a previous basal-bolus insulin regimen (ONWARDS 4): In this population the reported proportions and rates of "severe or clinically significant hypoglycaemic episodes" were similar in the two treatment groups (Table 58 and Table 59).

Table 58 - Severe (level 3) or clinically significant (level 2) hypoglycaemic episodes in the T2DM population - on-treatment/main-on-treatment - summary - safety analysis set

	Insulin icodec				Daily basal insulin			
	N	(%)	E	R	N	(%)	E	R
T2D, insulin-naïve								
ONWARDS 1								
Number of subjects	492				492			
Severe (level 3) or clinically significant (level 2) hypoglycaemia	48	(9.8)	144	29.64	52	(10.6)	78	16.08
ONWARDS 3								
Number of subjects	293				294			
Severe (level 3) or clinically significant (level 2) hypoglycaemia	26	(8.9)	53	31.01	18	(6.1)	25	14.61
ONWARDS 5								
Number of subjects	542				538			
Severe (level 3) or clinically significant (level 2) hypoglycaemia	64	(11.8)	104	18.59	45	(8.4)	81	14.45
T2D, basal insulin								
ONWARDS 2								
Number of subjects	262				263			
Severe (level 3) or clinically significant (level 2) hypoglycaemia	37	(14.1)	113	72.79	19	(7.2)	42	27.49
T2D, basal-bolus insulin								
ONWARDS 4								
Number of subjects	291				291			
Severe (level 3) or clinically significant (level 2) hypoglycaemia	150	(51.5)	944	564.05	162	(55.7)	938	562.36

%: Percentage of subjects with one or more events, BG: Blood glucose, E: Number of events, N: Number of subjects with one or more events, PYE: Patient years of exposure (1 PYE = 365.25 days), R: Rate (number of adverse events per 100 PYE). Clinically significant hypoglycaemia (level 2): Plasma glucose value of < 3.0 mmol/L (54 mg/dL) confirmed by BG meter. Severe hypoglycaemia (level 3): Hypoglycaemia with severe cognitive impairment requiring external assistance for recovery. Daily basal insulin: IDeg (ONWARDS 2, ONWARDS 3), IGlar U100 (ONWARDS 1, ONWARDS 4), and once-daily analogues (IDeg, IGlar U100, IGlar U300) (ONWARDS 5). Data from ONWARDS 1-5, only main part of ONWARDS 1

Table 59. Hypoglycaemic episodes by trial - on-treatment/main-on-treatment - estimate rate ratios

Treatment rate ratios	Clinically significant (level 2) hypoglycaemic episodes Estimate [CI]	Severe (level 3) or clinically significant (level 2) hypoglycaemic episodes Estimate [CI]
Insulin naïve T2DM population		
ONWARDS 1 (main trial period [0-52 weeks])	1.67 [0.99; 2.84]	1.64 [0.98; 2.75]
ONWARDS 1 (complete trial period [0-78 weeks])		1.63 [1.02; 2.61]
ONWARDS 3	2.09 [0.99; 4.41]	1.82 [0.87;3.80]
ONWARDS 5	1.23 [0.77; 1.98]	1.17 [0.73; 1.86]
T2DM population on a previous basal insulin regimen		
ONWARDS 2	1.98 [0.95; 4.12]	1.93 [0.93;4.02]
T2DM population on a previous basal-bolus insulin regimen		
ONWARDS 4	0.99 [0.73;1.34]	0.99 [0.73;1.33]
T1DM population previous basal-bolus insulin regimen		
ONWARDS 6 (complete 52-week trial period)	1.79 [1.48; 2.18]	1.80 [1.48;2.18]

Nocturnal severe (level 2) or clinically relevant (level 2) hypoglycaemia

Nocturnal hypoglycaemia episodes are regarded as particularly hazardous because the patient has limited options to react when asleep. Overall, in the T2DM population, apart from the population on a previous basal insulin regimen (ONWARDS 2), no pronounced difference regarding reporting of nocturnal severe or clinically significant hypoglycaemic episodes was noted between subjects treated with insulin icodec and the comparators, respectively.

Treatment naïve T2DM population (ONWARDS 1,3 and 5): Any nocturnal severe (level 3) or clinically significant (level 2) hypoglycaemic episodes were reported in similarly low rates in the icodec groups as in the daily basal insulin group (~2%). No severe nocturnal hypoglycaemic episodes were reported in the insulin icodec group.

T2DM population on a previous basal insulin regimen (ONWARDS 2): Any nocturnal clinically significant (level 2) hypoglycaemia episodes were reported by 6.1% (rate 20.61 events per 100 PYE) in the insulin icodec group and 3.4% (rate 8.51 events per 100 PYE) in the daily basal insulin group. No severe nocturnal hypoglycaemic episodes were reported in any of the two treatment groups.

T2DM subjects on a previous basal-bolus insulin regimen (ONWARDS 4): Any nocturnal severe (level 3) or clinically significant (level 2) hypoglycaemic episodes were reported by 18.6% (rate 78.27 events per 100 PYE) in the insulin icodec group compared to 24.7% (rate 103.72 events per 100 PYE) in the daily basal insulin group. No severe nocturnal hypoglycaemic episodes were reported in the insulin icodec group.

Table 60. Nocturnal severe (level 3) or clinically significant (level 2) hypoglycaemic episodes in the T2DM population - on-treatment/main-on-treatment

	Insulin icodec				Daily basal insulin			
	N	(%)	E	R	N	(%)	E	R
T2D, insulin-naïve								
ONWARDS 1								
Number of subjects	492				492			
Severe (level 3) or clinically	9	(1.8)	20	4.12	11	(2.2)	15	3.09
significant (level 2) hypoglycaemia								
ONWARDS 3								
Number of subjects	293				294			
Severe hypoglycaemia (level 3)	0				0			
significant (level 2) hypoglycaemia								
ONWARDS 5								
Number of subjects	542				538			
Severe (level 3) or clinically	11	(2.0)	13	2.32	12	(2.2)	19	3.39
significant (level 2) hypoglycaemia								
T2D, basal insulin								
ONWARDS 2								
Number of subjects	262				263			
Severe (level 3) or clinically	16	(6.1)	32	20.61	9	(3.4)	13	8.51
significant (level 2) hypoglycaemia								
T2D, basal-bolus insulin								
ONWARDS 4								
Number of subjects	291				291			
Severe (level 3) or clinically	54	(18.6)	131	78.27	72	(24.7)	173	103.72
significant (level 2) hypoglycaemia								

%: Percentage of subjects with one or more events, E: Number of events, N: Number of subjects with one or more events, PYE: Patient years of exposure (1 PYE = 365.25 days), R: Rate (number of adverse events per 100 PYE). Severe hypoglycaemia (level 3): Hypoglycaemia with severe cognitive impairment requiring external assistance for recovery. Daily basal insulin: IDeg (ONWARDS 2, ONWARDS 3), IGlar U100 (ONWARDS 1, ONWARDS 4), and once-daily analogues (IDeg, IGlar U100, IGlar U300) (ONWARDS 5). Data from ONWARDS 1-5, only main part of ONWARDS 1. Nocturnal: The period between 00:01 and 05:59 (both included)

CGM-verified nocturnal clinically significant hypoglycaemia (level 2)

In ONWARDS 1, 2 and 4 CGM was used in four-week periods throughout the trials (see section on Clinical Efficacy above). Data from these periods demonstrates that the percentages of subjects with and rates of (events /PYE) CGM-verified nocturnal clinically significant hypoglycaemia (level 2) are higher in both treatment groups compared to SMPG -based episodes (see above). Nocturnal hypoglycaemic episodes are more frequent when verified by CGM as compared to SMPG. However, the increased frequency is noted in both treatment groups and there the difference noted is not considered clinically relevant.

Insulin naïve T2DM population (ONWARDS 1): Across the five four-week CGM periods, the percentages of subjects with one or more CGM-verified nocturnal clinically significant (level 2) hypoglycaemia episodes were 12-30% (rate 285-916 events per PYE) for insulin icodec and 10-27% (rate 230-804 event per PYE) for the daily basal insulin group.

Previously basal insulin treated T2DM population (ONWARDS 2): Across the three four-week CGM periods the percentages of subjects with one or more CGM-verified nocturnal clinically significant (level 2) hypoglycaemia episodes were 19-31% (rate 541-758 events per PYE) for insulin icodec vs 16-29% (rate 430-851 event per PYE) for the daily basal insulin group.

Previously basal bolus insulin treated T2DM population (ONWARDS 4): Across the three four-week CGM periods the percentages of subjects with one or more CGM-verified nocturnal clinically significant (level

2) hypoglycaemia episodes were 28-41% (rate 1004-1372 events per PYE) for insulin icodec vs 34-43% (rate 1185-1588 event per PYE) for the daily basal insulin group.

Hypoglycaemic events reported as serious adverse events

In the T2DM population (ONWARDS 1-5), the number of hypoglycaemic episodes reported as SAEs was low. In total, four SAEs occurred in the insulin icodec group (all in ONWARDS 4) and four in the daily basal insulin groups (distributed across ONWARDS 1, 3 and 5).

Recurrence of hypoglycaemic episodes

In the T2DM population, most of the subjects reporting any "severe or clinically significant hypoglycaemia" episodes reported 1-9 episodes each.

In the insulin naïve subjects with T2DM (ONWARDS 1, 3 and 5) and previously daily basal insulin treated subjects with T2DM (ONWARDS 2) the proportion of subjects that reported >10 episodes was (0-0.8%). The T2DM population previously treated with basal-bolus insulin (ONWARD 4) has a remarkably different pattern in the distribution of event number compared to all other T2DM ONWARDS studies. In this trial, the proportion of subjects that reported >10 episodes in the icodec group was 10.3% in both the insulin icodec and the daily basal insulin groups. In ONWARDS 4, the maximum number of hypoglycaemic events experienced by a certain patient in this trial is as high as 67 episodes. However, patients in the glargine arm seem to be similarly prone to undergo a higher or even very high number of hypoglycaemic episodes as in the icodec arm. The risk of recurrent hypoglycaemia episodes is appropriately reflected in the SmPC.

Occurrence of hypoglycaemic episodes during the week

In ONWARDS 1, 3 and 5 with insulin naïve T2DM subjects, the highest proportion of subjects in the insulin icodec groups with severe (level 3) or clinically significant (level 2) episodes by treatment day was observed on day 2-4 and the proportion of subjects with episodes on those days was 2.4-3.7%. In ONWARDS 2, with T2DM previously on basal insulin, and in ONWARDS 4, with T2DM previously on a basal-bolus insulin regimen, the highest proportion of subjects with severe (level 3) or clinically significant (level 2) hypoglycaemic episodes by treatment day was observed on day 3 or 4 with 6.1% and with 25.8% subjects reporting episodes, respectively (Figure 30).
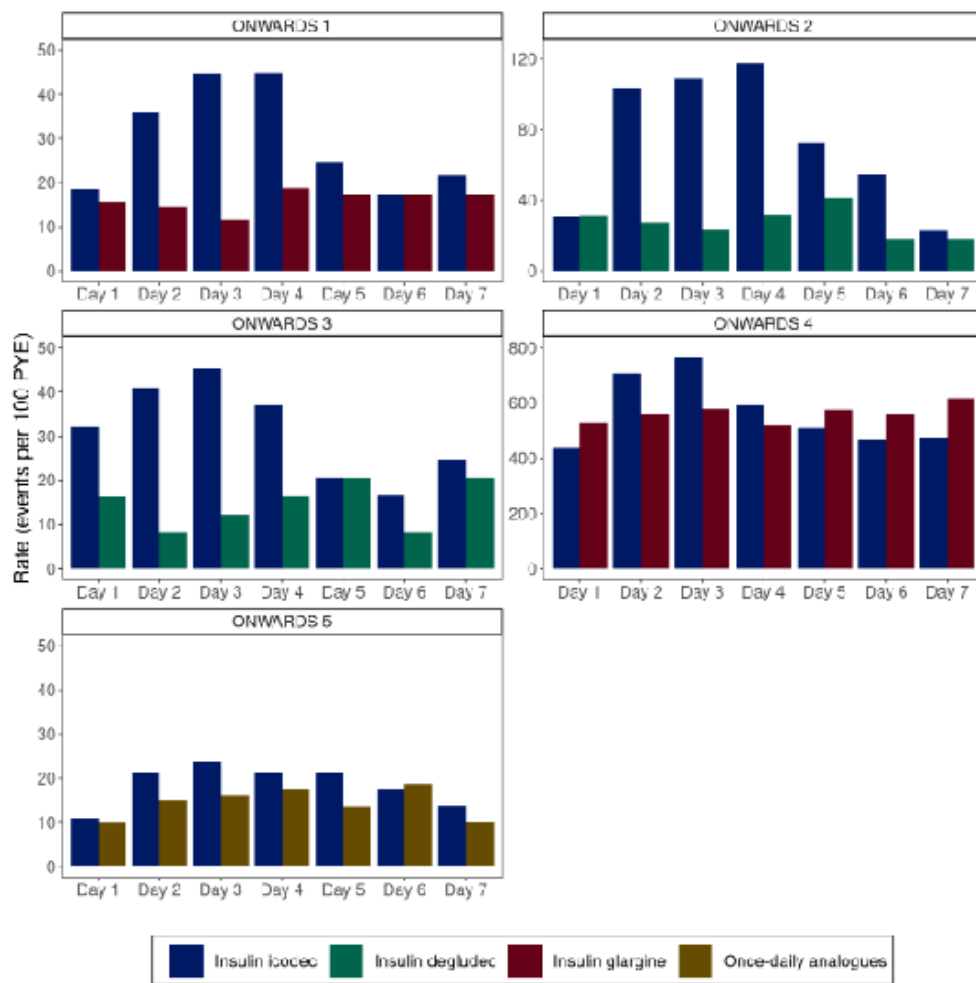
BG: Blood glucose, PYE: Patient years of exposure (1 PYE = 365.25 days). Safety analysis set. Observed data. Clinically significant hypoglycaemia (level 2): Plasma glucose value of < 3.0 mmo/L (54 mg/dL) confirmed by BG meter. Severe hypoglycaemia (level 3): Hypoglycaemia with severe cognitive impairment requiring external assistance for recovery. OD analogues: Once-daily basal insulin analogues (IDeg, IGlar U100, IGlar U300). Data from ONWARDS 1-5, only main part of ONWARDS 1.

Figure 30. Severe (level 3) or clinically significant hypoglycaemia (level 2) by trial and treatment day - ONWARDS 1-5 - on-treatment/main-on-treatment - bar plot - safety analysis set

Temporal occurrence of hypoglycaemic episodes over the course of the trials

Across the five Phase 3a trials performed in T2DM (ONWARDS 1-5), the mean number of severe (level 3) or clinically significant (level 2) hypoglycaemic episodes per subject was similar between the insulin icodec groups and the comparator groups during the initial part of the titration phases (Figure 31 and Figure 32). Thereafter, the curves diverge and the number of "severe (level 3) or clinically significant (level 2) hypoglycaemic episodes" per subject is larger for the icodec group as compared to the comparators throughout the studies. This applies for all trials except ONWARDS 4 (T2DM population previously treated with daily basal-bolus insulin) and ONWARDS 5 (insulin naïve subjects with T2DM). In these trials no difference or only a minor difference is noted between the two treatment groups over time. In ONWARDS 3 (insulin naïve T2DM population) the mean number of severe (level 3) or clinically significant (level 2) hypoglycaemic episodes per subject appears to decrease over time for both treatment groups. However, in ONWARDS 1 and ONWARDS 2 no apparent decrease is noted over time for the insulin icodec groups whereas this is noted for the comparator (Figure 32). In ONWARDS 1 and ONWARDS 2 a few subjects (n=3 and n=2,

respectively) accounted for many hypoglycaemic episodes in the icodec groups (and none in the respective comparator groups). This fact might to some extent explain the divergent curves in these trials.

Reassuringly, data from the extension of ONWARDS 1, demonstrates that neither the rate (episodes/100 PYE) or the proportion (%) of subjects with at least one severe (level 3) or clinically significant (level 2) hypoglycaemic episodes increase, in any of the two treatment groups, during 12-18 months' time-period compared to the first 12 months. The overall proportions are low in both groups each month during 12-18 months' time-period varying between 0.6%-1.5% in the insulin icodec group and 0.8-1.9% in the IGlar group. The rate is, however, constantly higher in the insulin icodec group throughout the complete 18 months' study period time.

The submitted data demonstrate, as expected, that the proportion of subjects with any severe (level 3) or clinically significantly (level 2) hypoglycaemia episodes had increased slightly in both treatment groups after 78 weeks compared to after 52 weeks (from 9.8% to 12.4% in the insulin icodec arm and from 10.6% to 14.2% in the daily basal insulin group). No new severe hypoglycaemic episode were reported in the insulin icodec group during the extension periods. The rate of severe (level 3) or clinically significant (level 2) hypoglycaemia, had not increased but were still, as during the main 52-week study phase, at the end of the complete study (week 78) twice as high in the insulin icodec group (29.65 event/100 PYE) as compared to the daily basal insulin group (15.78 event /100 PYE). The difference is mainly explained by three subjects in the insulin icodec group that accounted for 105 of the 226 SMPG reported clinically significant hypoglycaemic episodes.
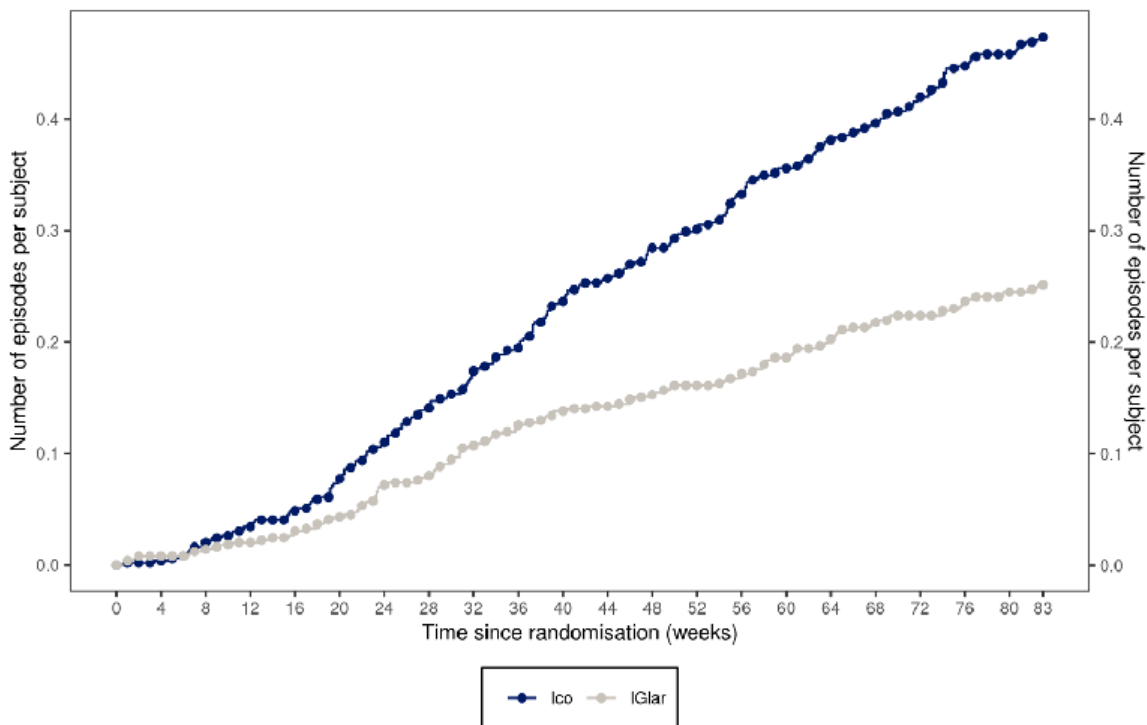
Safety analysis set. Observed data. BG: Blood glucose. Clinically significant hypoglycaemia (level 2): Plasma glucose value of < 3.0 mmol/L (54 mg/dL) confirmed by BG meter. Severe hypoglycaemia (level 3): Hypoglycaemia with severe cognitive impairment requiring external assistance for recovery.

Figure 31. Severe (level 3) or clinically significant hypoglycaemia (level 2) - on-treatment - mean cumulative function - safety analysis set ONWARDS 1.
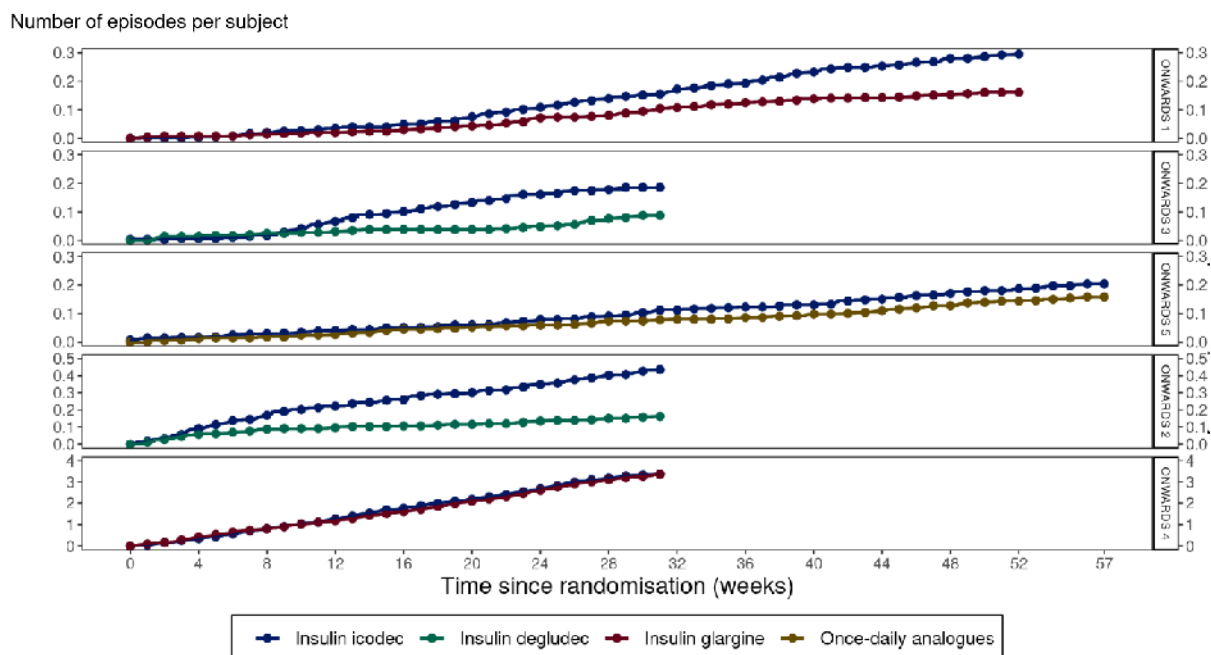
Figure 32. Severe (level 3) or clinically significant hypoglycaemia (level 2) by trial - ONWARDS 2-5 - on- treatment/main-on-treatment - mean cumulative function - safety analysis.

Concomitant antidiabetogenic treatment

Results from the five trials in T2DM (ONWARDS 1-5) do not indicate any increased risk of hypoglycaemia when insulin icodec is used with metformin, GLP-1RA, SGLT-2i or DPP-4 i.

Due to the exclusion criteria, experience of use with SU/glinides concomitantly with insulin icodec is limited. However, a higher risk for hypoglycaemic episodes should always be considered during use of SU/glinides. This is appropriately reflected in SmPC sections 4.2 and 4.5.

Hypoglycaemic episodes in the T1DM population (ONWARDS 6)

Severe (level 3) hypoglycaemia

At the end of the completed trial (i.e., end of trial visit, week 57), the proportion of subjects reporting severe hypoglycaemic episodes was the same in the two treatment groups; ~4% (Table 61). However, the rate of severe hypoglycaemia was higher in the insulin icodec group compared to the IDeg group (18.66 vs 8.08 events per 100 PYE at week 52). This difference is partly explained by one subject in the insulin icodec arm who accounted for 34 episodes of the level 56 severe hypoglycaemic episodes.

Clinically significant (level 2) hypoglycaemic episodes

At the end of the completed trial (i.e., end of trial visit, week 57), both the proportion of subjects and the rate of clinically significant (level 2) hypoglycaemic episodes were higher in the insulin icodec group compared to the IDeg group (90.3% vs 85.6% and rate 1681.44 vs 908.00 events per 100 PYE). The estimated rate ratio was 1.79 (1.48; 2.18) (Table 59 and Table 61).

Clinically severe and significant hypoglycaemic episodes

At the end of the completed trial (i.e., end of trial visit, week 57), both the reported proportions of subjects and the rate of severe or clinically significant hypoglycaemic episodes were higher in the insulin icodec group (90.7% and 1700.10 episodes per 100 PYE) compared to the IDeg treated group (85.6% and 916.07 episodes per 100 PYE). The estimated rate ratio was 1.80 [1.48; 2.18) (Table 59 and Table 61).

Table 61. Hypoglycaemic episodes ONWARDS 6 by classification - on-treatment - summary - safety analysis set

	Ico				IDeg			
	N	(%)	E	R	N	(%)	E	R
Number of subjects	290				292			
PYE (years)	300.16				309.58			
Hypoglycaemia alert value (level 1)	288	(99.3)	20406	6798.40	289	(99.0)	14819	4786.77
Clinically significant hypoglycaemia (level 2)	262	(90.3)	5047	1681.44	250	(85.6)	2811	908.00
Severe hypoglycaemia (level 3)	13	(4.5)	56	18.66	12	(4.1)	25	8.08
Severe (level 3) or clinically significant (level 2) hypoglycaemia	263	(90.7)	5103	1700.10	250	(85.6)	2836	916.07

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of events, R: Rate (number of events per 100 PYE), PYE: Patient years of exposure (1 PYE = 365.25 days), On-treatment: Onset date on or after the first dose of trial product and no later than the first date of either the follow-up visit (FU2), the last date on trial product + 5 weeks for once daily insulin and + 6 weeks for once weekly insulin or the end-date for the in-trial period. Hypoglycaemia alert value (level 1): Plasma glucose value of < 3.9 mmol/L (70 mg/dL) and >= 3.0 mmol/L (54 mg/dL) confirmed by BG meter. Clinically significant hypoglycaemia (level 2): Plasma glucose value of < 3.0 mmol/L (54 mg/dL) confirmed by BG meter. Severe hypoglycaemia (level 3): Hypoglycaemia with severe cognitive impairment requiring external assistance for recovery. BG: Blood glucose

Nocturnal hypoglycaemic episodes

Nocturnal severe (level 3) or clinically significant (level 2) hypoglycaemic episodes were reported by a higher proportion and with a higher rate among the insulin icodec treated subjects compared to the IDeg group (59.0% vs 47.9%; rate 289.85 vs 149.23 per 100 PYE; estimated rate ratio 1.89 [1.44; 2.48). Severe nocturnal hypoglycaemic episodes were reported similarly low in the two treatment groups (1.4%). However, the rates of severe nocturnal hypoglycaemia differed slightly in favour for IDeg (Table 62).

CGM data including the extension period (i.e., week 0-52) demonstrate that almost all subjects in both treatment groups (94% in the insulin icodec group and 92% in the IDeg group) had at least one nocturnal clinically significant hypoglycaemic event. The rate (number of events per 100 PYE) was higher in the insulin icodec group (2147 per 100 PYE) as compared to the IDeg group (1746 events per 100 PYE).

Table 62. Nocturnal hypoglycaemic episodes ONWARDS 6 by classification - on-treatment - summary – safety analysis set

	Ico N	Ico (%)	Ico E	Ico R	IDeg N	IDeg (%)	IDeg E	IDeg R
Number of subjects	290				292			
PYE (years)	300.16				309.58			
Hypoglycaemia alert value (level 1)	237	(81.7)	1953	650.66	211	(72.3)	1523	491.95
Clinically significant hypoglycaemia (level 2)	171	(59.0)	861	286.85	140	(47.9)	458	147.94
Severe hypoglycaemia (level 3)	4	(1.4)	9	3.00	4	(1.4)	4	1.29
Severe (level 3) or clinically significant (level 2) hypoglycaemia	171	(59.0)	870	289.85	140	(47.9)	462	149.23

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of events, R: Rate (number of events per 100 PYE), PYE: Patient years of exposure (1 PYE = 365.25 days), On-treatment: Onset date on or after the first dose of trial product and no later than the first date of either the follow-up visit (FU2), the last date on trial product + 5 weeks for once daily insulin and + 6 weeks for once weekly insulin or the end-date for the in-trial period. Nocturnal: The period between 00:01 and 05:59 (both included). Hypoglycaemia alert value (level 1): Plasma glucose value of < 3.9 mmol/L (70 mg/dL) and >= 3.0 mmol/L (54 mg/dL) confirmed by BG meter. Clinically significant hypoglycaemia (level 2): Plasma glucose value of < 3.0 mmol/L (54 mg/dL) confirmed by BG meter. Severe hypoglycaemia (level 3): Hypoglycaemia with severe cognitive impairment requiring external assistance for recovery. BG: Blood glucose.

Recurrence of hypoglycaemic episodes

During the main treatment period (week 0-26), the proportion of subjects that reported ≥20 episodes in the icodec group were higher (14.8%) both compared to the T2DM populations and compared to the IDeg group (5.8%) (Table 63).

No unique risk factors for recurrent hypoglycaemia were identified with insulin icodec distinctly from those recognised for use of currently available insulins in the literature, e.g., longer duration of diabetes, lower body weight, higher HbA1c at baseline, higher glycaemic variability.

The risk for recurrence of hypoglycaemic episodes in T1DM is appropriately reflected in the SmPC.

Table 63. Severe (level 3) or clinically significant hypoglycaemia (level 2) in the T1DM population - main-on- treatment - summary of categories of total number of episodes - safety analysis set.

	Insulin icodec			Daily basal insulin	
	N	(%)		N	(%)
ONWARDS 6					
Number of subjects	290			292	
Severe (level 3) or clinically significant (level 2) hypoglycaemia					
No episodes	43	(14.8)		69	(23.6)
1-9 episodes	139	(47.9)		171	(58.6)
10-19 episodes	65	(22.4)		35	(12.0)
>=20 episodes	43	(14.8)		17	(5.8)

%: Percentage of subjects, BG: Blood glucose, N: Number of subjects. Clinically significant hypoglycaemia (level 2): Plasma glucose value of < 3.0 mmol/L (54 mg/dL) confirmed by BG meter. Severe hypoglycaemia (level 3): Hypoglycaemia with severe cognitive impairment requiring external assistance for recovery. Daily basal insulin: IDeg (ONWARDS 6). Data from only main part of ONWARDS 6.

Temporal occurrence of hypoglycaemic episodes over the course of the trials

The mean number of severe (level 3) or clinically significant (level 2) hypoglycaemic episodes per subject was similar between the insulin icodec groups and the comparators groups during the initial part of the titration phase (4 weeks).

Thereafter, the number of reported hypoglycaemic episodes per subject and rates diverge for the two groups (Figure 33). The rates are approximately twice as high for the icodec group compared to the IDeg group throughout the complete study period. For the IDeg group the number of reported hypoglycaemic episodes per subject seems stable throughout the study. Reassuringly, the rate over time decreased, from 1992.86 events per 100 PYE, at week 26 weeks to 1700.1 events per 100 PYE at week 52. In the IDeg group, a corresponding pattern was noted with a decrease in rate from 1036.33 after 26 weeks to 916.07 events per 100 PYE after 52 weeks.
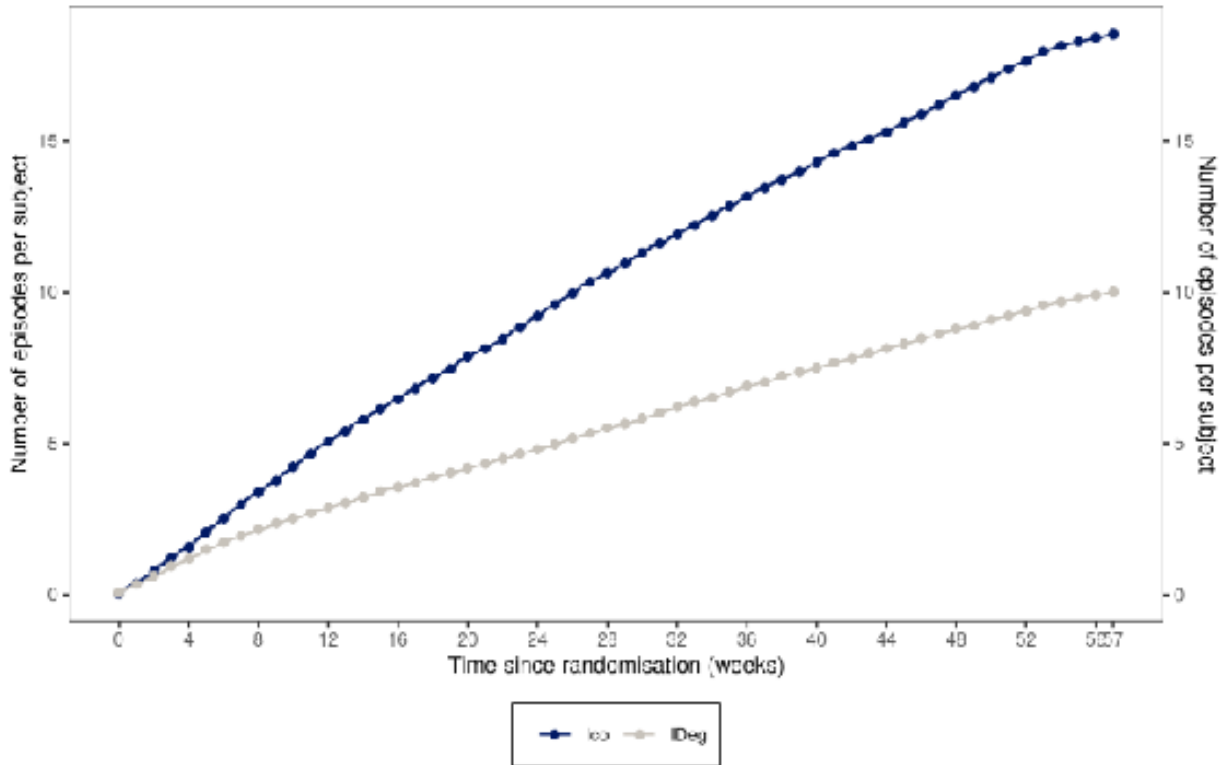
Figure 33. Severe (level 3) or clinically significant (level 2) hypoglycaemia in ONWARDS 6 -on treatment - mean cumulative function - safety analysis set

Occurrence during the week

In the T1DM population (ONWARSD 6), the highest rates of severe (level 3) hypoglycaemic episodes and clinically significant (level 2) hypoglycaemic episodes were observed on day 2-4. These day-rates were markedly higher in the insulin icodec group compared to the IDeg group (Figure 34).

Information regarding the occurrence of hypoglycaemic episodes during the week is reflected in the SmPC section 4.8.
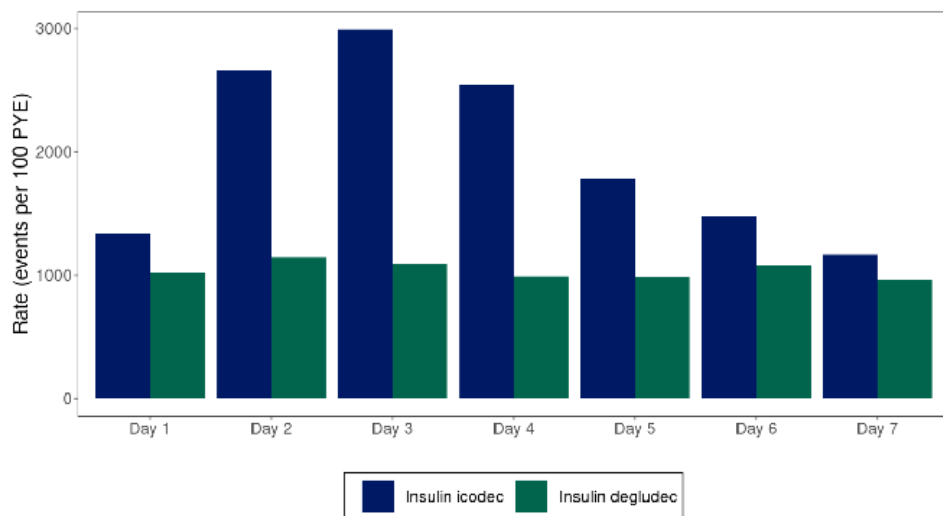
Figure 34. Severe (level 3) or clinically significant hypoglycaemia (level 2) by treatment day - ONWARDS 6 - main-on-treatment - bar plot - safety analysis set

Hypoglycaemic events reported as SAEs

In ONWARDS 6, a total of 14 hypoglycaemic SAEs were reported by nine (9) subjects (rate 4.66 events per 100 PYE) during the complete study period (52 weeks) compared to three (3) hypoglycaemic SAEs reported by three (3) subjects (rate 0.97 per 100 PYE) in the IDeg group.

Other hypoglycaemic aspects - both T2DM and T2DM

Duration of hypoglycaemic episodes

In the phase 2 PD-trial (4462) performed in subjects with T2DM previously treated with insulin, time to recover from hypoglycaemia was evaluated (see section on Clinical Efficacy above).

In the phase 3a trials the recovery from hypoglycaemic episodes was measured by SMPG. Upon onset of a hypoglycaemic episode the subject was recommended to measure PG every 15 minutes until the PG value is ≥ 3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved. Available data indicate that the median time to recovery from clinically significant hypoglycaemic episodes in the insulin icodec group was higher (ONWARDS 1 [31.5 vs 14.0 min] and ONWARDS 2 [30.0 vs 20.0 min]) or similar (ONWARDS 3-6) as compared to the daily basal insulin groups. Further, overall, across all trials a larger proportion of the insulin icodec SMPG-verified clinically significant (level 2) hypoglycaemic episodes had a duration of >360 min compared to daily basal insulin episodes (ONWARDS 1, 8.5% vs 2.4% in ONWARDS 1; 6.2% vs 0% in ONWARDS 2; 8.7% vs 0% in ONWARDS 3: 3.4% vs 1.9% in ONWARDS 4; 6.6% vs 2.9% ONWARDS 5 and 4.1% vs 2.5% in ONWARDS 6).

A warning for prolonged hypoglycaemia with insulin icodec is included in SmPC section 4.4.

Hypoglycaemia leading to discontinuation of trial product

Across all main treatment periods of the trials in the phase 3a pool, there was a low number (n=4; three in ONWARDS 5 and one in ONWARDS 6) of subjects treated with insulin icodec that discontinued treatment with insulin icodec due to hypoglycaemia. One subject in the daily basal insulin group discontinued treatment with insulin icodec due to hypoglycaemia. None of the five episodes were reported as SAEs or as severe (level 3) hypoglycaemic episodes.

Subgroup analysis – hypoglycaemic pattern

Subgroup analysis in the T1DM and the T2DM population did not demonstrate any difference regarding in the hypoglycaemic pattern when stratifying for baseline renal function, baseline BMI or age group.

Injection site reactions

In the Phase 3a pool (including main-on-treatment phases), injection site reaction(s) was reported by 1.9% (rate 6.04 events per 100 PYE) in the insulin icodec group and 1.7% (rate 3.97 events per 100 PYE) in the comparator group. However, the open-label design of trial ONWARDS 1, 2 and 4-6, could lead to unintentional bias in adverse effect reporting (including ISRs). Of interest is therefore results from the double-blinded trial **ONWARDS 3** performed in insulin naïve subjects with T2DM. In this trial, subjects in the investigational arm were to receive one insulin icodec and seven placebo injections (on the left thigh) each week while subjects in the comparator arm were to receive one placebo and seven insulin degludec injections (on the right thigh) each week. Rotation of injection site on the respective thigh was recommended. A higher frequency and rate of ISR were reported for insulin icodec group (8.5%; rate 36.28 PYE [62 events]) compared to the comparator group (4.4%; rate 12.86 PYE [22 events]). The higher rate in the icodec group was driven by two subjects together reporting 24 of the 62 ISR events. However, still twice as many subjects reported any ISR in the insulin icodec group compared to the daily insulin group. On a PT-level the main difference between the two groups is the unspecific event "Injection site reaction" (3.1% in the insulin icodec group and 0.7% in the IDeg group). The remaining PTs were reported by 1-3 subjects. Reassuringly, most of the events in both treatment groups were mild (95%) and no event in either group was serious or severe (Table 65).

The risk of injection site reactions is adequately reflected in the SmPC section 4.8.

Table 64. Injection site reactions – on-treatment/main-on- treatment – summary – safety analysis set – phase 3a pool

	Insulin icodec				Daily basal insulin			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Number of subjects	2170				2170			
PYE (years)	1681.23				1680.58			
Events	42	(1.9)	81	6.04	37	(1.7)	67	3.97
Serious								
Yes	0				0			
No	42	(1.9)	81	6.04	37	(1.7)	67	3.97
Missing	0				0			
Severity								
Severe	0				0			
Moderate	4	(0.2)	4	0.25	3	(0.1)	3	0.14
Mild	40	(1.8)	77	5.78	34	(1.6)	64	3.83
Missing	0				0			
Related to basal insulin								
Probable	18	(0.8)	32	2.38	24	(1.1)	52	3.01
Possible	8	(0.4)	15	1.15	9	(0.4)	9	0.58
Unlikely	21	(1.0)	34	2.50	6	(0.3)	6	0.37
Missing	0				0			
Related to technical complaint for basal insulin								
Yes	1	(0.0)	1	0.08	0			
No	41	(1.9)	80	5.96	37	(1.7)	67	3.97
NA	0				0			
Missing	0				0			
Outcome								
Fatal	0				0			
Not recovered/not resolved	1	(0.0)	2	0.09	2	(0.1)	2	0.09
Recovered/resolved with sequelae	0				0			
Recovering/resolving	3	(0.1)	4	0.32	2	(0.1)	2	0.13
Recovered/resolved	40	(1.8)	75	5.63	34	(1.6)	63	3.75
Unknown	0				0			
Missing	0				0			

%: Percentage of subjects with one or more events, E: Number of adverse events, N: Number of subjects with one or more events, NA: Not applicable, PYE: Patient years of exposure (1 PYE = 365.25 days), R: Rate (number of adverse events per 100 PYE). Adj.: Adjusted percentages and rates were calculated using the Cochran-Mantel-Haenszel method to account for differences between trials. On- treatment: Onset date on or after the first dose of trial product and no later than the first date of either the follow-up visit (FU2), the last date on trial product + 5 weeks for once daily insulin and + 6 weeks for once weekly insulin or the end-date for the in-trial period. Main-on-treatment: Onset date on or after the first dose of trial product and no later than the first date of either he end-date of the on-treatment period or the last planned visit in the main part of the trial. Daily basal insulin: IDeg, IGlar U100, and IGlar U300. Phase 3a pool: ONWARDS 1-6, only main part of ONWARDS 1 and 6. MedDRA version 24.1. Events found via MedDRA queries.

Table 65. Injection site reactions by SOC and PT in ONWARDS 3 - on-treatment - summary

	Ico				IDeg			
	N	(%)	E	R	N	(%)	E	R
Number of subjects	293				294			
PYE (years)	170.90				171.13			
Events	25	(8.5)	62	36.28	13	(4.4)	22	12.86
General disorders and administration site conditions	24	(8.2)	61	35.69	13	(4.4)	22	12.86
Injection site reaction	9	(3.1)	23	13.46	2	(0.7)	2	1.17
Injection site pain	3	(1.0)	3	1.76	6	(2.0)	6	3.51
Injection site bruising	2	(0.7)	2	1.17	1	(0.3)	1	0.58
Injection site erythema	2	(0.7)	4	2.34	0			
Injection site haematoma	2	(0.7)	6	3.51	3	(1.0)	8	4.67
Injection site haemorrhage	2	(0.7)	2	1.17	1	(0.3)	1	0.58
Injection site pruritus	2	(0.7)	17	9.95	1	(0.3)	1	0.58
Application site bruise	1	(0.3)	1	0.59	0			
Application site pruritus	1	(0.3)	1	0.59	0			
Injection site rash	1	(0.3)	1	0.59	0			
Injection site swelling	1	(0.3)	1	0.59	1	(0.3)	1	0.58
Injection site induration	0				1	(0.3)	1	0.58
Injection site oedema	0				1	(0.3)	1	0.58
Infections and infestations	1	(0.3)	1	0.59	0			
Injection site abscess	1	(0.3)	1	0.59	0			

N: Number of subjects with one or more events, %: Percentage of subjects with one or more events, E: Number of adverse events, R: Rate (number of adverse events per 100 PYE), PYE: Patient years of exposure (1 PYE = 365.25 days). On-treatment: Onset date on or after the first dose of trial product and no later than the first date of either the follow-up visit (FU2), the last date on trial product + 5 weeks for once daily insulin and + 6 weeks for once weekly insulin or the end-date for the in-trial period.

<u>Lipodystrophy and localised cutaneous amyloidosis</u>

In the phase 3a pool, there were three (3) events of lipodystrophy. One (1) event in the insulin icodec group (0.05 events per 100 PYE) and two (2) events in 2 subjects in the daily basal insulin group (0.13 events per 100 PYE). All events were reported as non-serious and mild. There were no event of localised/cutaneous amyloidosis reported across the phase 3a trials.

The risk for lipodystrophy and cutaneous amyloidosis is adequately reflected in the SmPC.

<u>Hypersensitivity reactions</u>

In the Phase 3a pool (treatment/main-on-treatment phases), a similar proportion (~ 4%) of subjects reported hypersensitivity reactions in the insulin icodec and the comparator groups. The most reported PTs were rash, reported in 0.6% and eczema reported in 0.5% of the subjects in the insulin icodec group (Table 66). In both treatment groups few serious hypersensitivity events were reported (0.1%; n=2 in the insulin icodec group). One SAE in the insulin icodec group concerned urticaria and one subject reported an anaphylactic reaction. However, the latter case was confounded by administration of another drug.

In the double blinded, double dummy ONWRDS 3 trial performed in insulin naïve subjects with T2DM a slightly higher reporting rate of these events was noted for the comparator (insulin degludec) group (4.4%) compared to the insulin icodec group (2.4%).

in the T1DM population (ONWARDS 6), an overall higher frequency of hypersensitivity events was reported for both treatment groups (~8%) compared to the T2DM population (~3%). The most reported PTs in the T1DM population was in both treatment groups "Medical device site rash" (~2%). No serious hypersensitivity reactions were reported in the T1DM population. The risk of hypersensitivity reactions is considered sufficiently reflected in the SmPC section 4.8.

Table 66. Hypersensitivity reactions (predefined MedDRA search) - adverse events by SOC and PT – on treatment/main-on-treatment - summary - phase 3a pool

	Insulin icodec				Daily basal insulin			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Number of subjects	2170				2170			
PYE (years)	1681.23				1680.58			
Events	83	(3.8)	93	6.20	96	(4.4)	115	7.47
Skin and subcutaneous tissue disorders	51	(2.4)	52	3.33	58	(2.7)	63	4.09
Rash	14	(0.6)	14	0.95	11	(0.5)	12	0.62
Eczema	10	(0.5)	10	0.56	7	(0.3)	7	0.50
Dermatitis	7	(0.3)	7	0.55	7	(0.3)	8	0.51
Dermatitis contact	7	(0.3)	8	0.47	14	(0.6)	14	1.00
Urticaria	7	(0.3)	7	0.45	12	(0.6)	12	0.72
Rash erythematous	2	(0.1)	2	0.17	0			
Dermatitis allergic	2	(0.1)	2	0.09	1	(0.0)	1	0.06
Angioedema	1	(0.0)	1	0.05	3	(0.1)	3	0.18
Urticaria contact	1	(0.0)	1	0.05	0			
Dermatitis atopic	0				2	(0.1)	2	0.19
Skin reaction	0				1	(0.0)	1	0.06
Drug eruption	0				1	(0.0)	1	0.05
Pruritus allergic	0				1	(0.0)	1	0.06
Rash maculo-papular	0				1	(0.0)	1	0.06
General disorders and administration site conditions	22	(1.0)	26	1.88	25	(1.2)	32	2.10
Medical device site dermatitis	7	(0.3)	10	0.67	11	(0.5)	18	1.03
Medical device site rash	6	(0.3)	6	0.57	8	(0.4)	8	0.73
Injection site hypersensitivity	2	(0.1)	2	0.09	0			
Swelling face	2	(0.1)	2	0.14	2	(0.1)	2	0.12
Injection site urticaria	1	(0.0)	2	0.19	1	(0.0)	1	0.05
Injection site rash	1	(0.0)	1	0.06	1	(0.0)	1	0.06
Injection site dermatitis	1	(0.0)	1	0.05	0			
Medical device site eczema	1	(0.0)	1	0.05	2	(0.1)	2	0.09
Medical device site hypersensitivity	1	(0.0)	1	0.05	0			
Immune system disorders	5	(0.2)	5	0.43	2	(0.1)	2	0.16
Hypersensitivity	3	(0.1)	3	0.27	1	(0.0)	1	0.08
Anaphylactic reaction	1	(0.0)	1	0.08	1	(0.0)	1	0.08
Drug hypersensitivity	1	(0.0)	1	0.08	0			
Respiratory, thoracic and mediastinal disorders	3	(0.1)	3	0.22	10	(0.5)	14	0.94
Rhinitis allergic	2	(0.1)	2	0.14	6	(0.3)	10	0.64
Bronchospasm	1	(0.0)	1	0.08	1	(0.0)	1	0.08
Allergic cough	0				2	(0.1)	2	0.17
Allergic bronchitis	0				1	(0.0)	1	0.05
Investigations	3	(0.1)	3	0.13	3	(0.1)	3	0.13
Blood immunoglobulin E increased	3	(0.1)	3	0.13	3	(0.1)	3	0.13
Eye disorders	2	(0.1)	3	0.17	1	(0.0)	1	0.04
Conjunctivitis allergic	2	(0.1)	3	0.17	0			
Eyelid oedema	0				1	(0.0)	1	0.04

%: Percentage of subjects with one or more events, E: Number of adverse events, N: Number of subjects with one or more events, PYE: Patient years of exposure (1 PYE = 365.25 days), R: Rate (number of adverse events per 100 PYE). Adj.: Adjusted percentages and rates were calculated using the Cochran-Mantel-Haenszel method to account for differences between trials. On-treatment: Onset date on or after the first dose of trial product and no later than the first date of either the follow-up visit (FU2), the last date on trial product + 5 weeks for once daily insulin and + 6 weeks for once weekly insulin or the end-date for the in-trial period. Main-on-treatment: Onset date on or after the first dose of trial product and no later than the first date of either the end-date of the on-treatment period or the last planned visit in the main part of the trial. Daily basal insulin: IDeg, IGlar U100, and IGlar U300. Phase 3a pool: ONWARDS 1-6, only main part of ONWARDS 1 and 6. MedDRA version 24.1. Events found via MedDRA queries

Hyperglycaemia including diabetic ketoacidosis

In the Phase 3a safety pool (treatment/main-on-treatment phases), the proportion of subjects reporting, and rates of AEs of hyperglycaemia or diabetic ketoacidosis were low and even lower for the insulin icodec group (0.5%) than the daily basal insulin group (1.0%). No SAE or any event of diabetes ketoacidosis were reported (Table 67).

No AEs of hyperglycaemia or diabetic ketoacidosis were reported in the T1DM population with insulin icodec.

The risk of hyperglycaemia is adequately reflected in SmPC section 4.4.

Table 67. Hyperglycaemia incl. diabetic ketoacidosis by SOC and PT – on-treatment/main-on-treatment – summary – safety analysis set – phase 3a pool

	Insulin icodec			Daily basal insulin		
	N	(Adj.%)	E Adj.R	N	(Adj.%)	E Adj.R
Number of subjects	2170			2170		
PYE (years)	1681.23			1680.58		
Events	10	(0.5)	11 0.66	21	(1.0)	22 1.38
Metabolism and nutrition disorders	9	(0.4)	10 0.62	17	(0.8)	17 1.10
Hyperglycaemia	6	(0.3)	7 0.48	14	(0.6)	14 0.92
Diabetes mellitus	2	(0.1)	2 0.09	1	(0.0)	1 0.05
Diabetes mellitus inadequate control	1	(0.0)	1 0.04	0		
Insulin resistance	0			2	(0.1)	2 0.14
Investigations	1	(0.0)	1 0.05	4	(0.2)	5 0.27
Glycosylated haemoglobin increased	1	(0.0)	1 0.05	2	(0.1)	3 0.13
Blood glucose increased	0			2	(0.1)	2 0.14

%: Percentage of subjects with one or more events, E: Number of adverse events, N: Number of subjects with one or more events, PYE: Patient years of exposure (1 PYE = 365.25 days), R: Rate (number of adverse events per 100 PYE). Adj.: Adjusted percentages and rates were calculated using the Cochran-Mantel-Haenszel method to account for differences between trials. On-treatment: Onset date on or after the first dose of trial product and no later than the first date of either the follow-up visit (FU2), the last date on trial product + 5 weeks for once daily insulin and + 6 weeks for once weekly insulin or the end-date for the in-trial period. Main-on-treatment: Onset date on or after the first dose of trial product and no later than the first date of either the end-date of the on-treatment period or the last planned visit in the main part of the trial. Daily basal insulin: IDeg, IGlar U100, and IGlar U300. Phase 3a pool: ONWARDS 1-6, only main part of ONWARDS 1 and 6. Events found via MedDRA queries

Cardiovascular events

The overall proportion of subjects reporting any EAC confirmed cardiovascular event was similar in both treatment groups (1.5% in the icodec group and 1.6% in the comparator group) (Table 68).

There were no clinically relevant differences between insulin icodec and daily basal insulin in the improvement or deterioration of ECG categories in the Phase 3a pool or in any phase 1 or phase 2 trial.

Updated results including data from the extension phases of ONWARDS 1 and ONWARDS 6 reported the same results, i.e. that adjudicated cardiovascular events, ECG findings and results from the MACE-meta-analysis did not overall indicate any increase in CV risk for patients treated with insulin icodec compared to daily basal insulin.
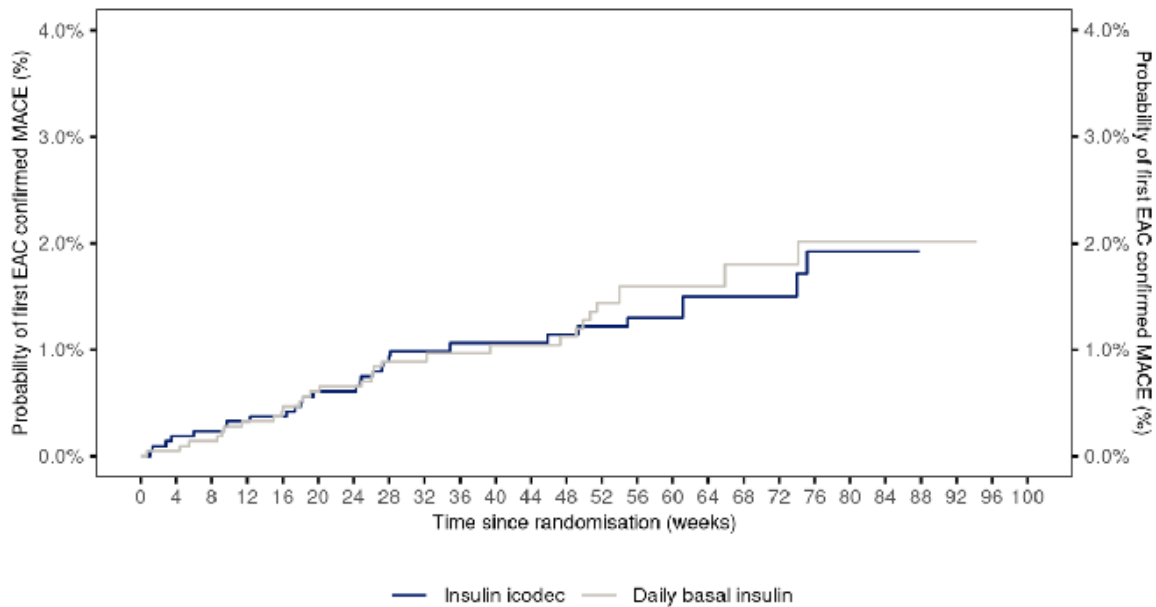
Table 68. EAC confirmed cardiovascular events – in-trial- summary – safety analysis set - phase 3a pool

	Insulin icodec			Daily basal insulin		
	N	(Adj.%)	E Adj.R	N	(Adj.%)	E Adj.R
Number of subjects	2170			2170		
PYO (years)	1707.1			1702.1		
Acute coronary syndrome	18	(0.8)	19 1.05	13	(0.6)	14 0.73
Acute myocardial infarction	17	(0.8)	18 1.01	12	(0.6)	13 0.69
STEMI	7	(0.3)	7 0.35	7	(0.3)	7 0.41
NSTEMI	9	(0.4)	10 0.61	5	(0.2)	6 0.27
Undetermined	1	(0.0)	1 0.05	0		
Hospitalisation for unstable angina pectoris	1	(0.0)	1 0.05	1	(0.0)	1 0.04
Cerebrovascular event	4	(0.2)	4 0.28	11	(0.5)	11 0.59
Stroke	4	(0.2)	4 0.28	11	(0.5)	11 0.59
Ischaemic stroke	3	(0.1)	3 0.23	11	(0.5)	11 0.59
Hemorrhagic stroke	1	(0.0)	1 0.05	0		
Undetermined stroke	0			0		
Heart failure	5	(0.2)	6 0.27	3	(0.1)	4 0.28
Heart failure hospitalization	5	(0.2)	6 0.27	3	(0.1)	3 0.20
Urgent heart failure visit	0			1	(0.0)	1 0.08
CV death	2	(0.1)	2 0.13	6	(0.3)	6 0.34
Undetermined cause of death	3	(0.1)	3 0.16	2	(0.1)	2 0.09

%: Percentage of subjects with one or more events, CV: Cardiovascular, E: Number of adverse events, EAC: Event adjudication committee, N: Number of subjects with one or more events, NSTEMI: Non-ST- segment elevation myocardial infarction, PYO: Patient years of observation (1 PYO = 365.25 days), R: Rate (number of adverse events per 100 PYO). STEMI: ST-segment elevation myocardial infarction. Adj.: Adjusted percentages and rates were calculated using the Cochran-Mantel-Haenszel method to account for differences between trials. In-trial status is defined based on the onset date as decided by the EAC. In-trial: Onset date on or after the day of randomisation and no later than the last subject-site contact or withdrawal/death date for subjects that withdraws/dies. Daily basal insulin: IDeg, IGlar U100, and IGlar U300. Phase 3a pool: ONWARDS 1-6, only main part of ONWARDS 1 and 6

The assessment of CV safety was based on a meta-analysis of independently confirmed adjudicated MACE events among the six phase 3 trials (ONWARDS 1-6). In the MACE meta-analyse MI and stroke events has not been distinguished between fatal and non-fatal outcomes.

Subjects treated with insulin icodec had a similar incidence of MACE when compared to those treated with a daily basal insulin analogue. The estimated hazard-ratio from the analysis of time to first EAC confirmed occurrence of MACE in the phase 3a pool, including the extension phases for ONWARDS 1 and ONWARDS 6, was similar in the insulin icodec group and daily basal insulin group (HR: 0.93; 95% CI [0.56;1.56]) (Figure 35). There was no apparent difference in distribution of the individual EAC confirmed MACE events between the two treatment groups.

Cumulative incidence estimate for first EAC confirmed MACE during in-trial period. EAC: Event adjudication committee, MACE: Major adverse cardiovascular events with adjudicated outcome of either CV death, myocardial infarction (acute myocardial infarction) and stroke (ischaemic, haemorrhagic or undetermined stroke). Phase 3a pool: ONWARDS 1-6.

Figure 35. Time to first EAC confirmed MACE - cumulative incidence plot - in-trial - SAS- phase 3a pool

Retinal disorders

Intensification of insulin therapy with abrupt improvement in glycaemic control have been associated with eye disorders such as temporary visual impairment (due to temporary alteration in the turgidity and refractive index of the lens) and temporary worsening of diabetic retinopathy. This is appropriately reflected in SmPC section 4.4.

In the Phase 3a pool (treatment/main-on treatment phases), there was no difference noted regarding reported diabetic retinopathy or maculopathy AEs between the treatment groups (5.1% insulin icodec group vs 5.3% in the daily basal insulin group). Specifically diabetic retinopathy was in the Phase 3a pool reported without any difference between the two treatment groups (~3% in both) (Table 69). However, in the double blinded ONWARDS 3 trial, performed in insulin naïve subjects, a larger proportion of the insulin icodec treated subjects reported diabetic retinopathy (5.1%; n=15) compared to the IDeg treated group (2.0%; n=6).

Table 69. Diabetic retinopathy or maculopathy (predefined MedDRA search) - adverse events by system organ class and preferred term- reported by ≥0.5% of subjects on insulin icodec or daily basal insulin - in-trial - summary - phase 3a pool

	Insulin icodec				Daily basal insulin			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Number of subjects	2170				2170			
PYO (years)	1707.11				1702.14			
Eye disorders								
Diabetic retinopathy	65	(3.0)	71	5.15	72	(3.3)	76	5.36
Macular oedema	13	(0.6)	14	1.02	5	(0.2)	5	0.30
Diabetic retinal oedema	6	(0.3)	6	0.50	10	(0.5)	11	0.74

%: Percentage of subjects with one or more events, E: Number of adverse events, N: Number of subjects with one or more events, PYO: Patient years of observation (1 PYO = 365.25 days), R: Rate (number of adverse events per 100 PYO). Adj.: Adjusted percentages and rates were calculated using the Cochran-Mantel-Haenszel method to account for differences between trials. In-trial: Onset date on or after the day of randomisation and no later than the last subject-site contact or withdrawal/ death date for subjects that withdraws/dies. Daily basal insulin: IDeg, IGlar U100, and IGlar U300.

Neoplasms

The nonclinical programme for insulin icodec revealed no safety concerns indicating any carcinogenic potential.

Across the insulin icodec phase 3a programme, the number of events and rate of AEs within the MedDRA search for neoplasms was 74 events in 62 subjects and 4.44 events per 100 PYO in the insulin icodec group, and 86 events in 66 subjects and 5.18 events per 100 PYO in the daily basal insulin group. The proportion of subjects with AEs was 2.9% in the insulin icodec group and 3.0% in the daily basal insulin group. Most of the neoplasms were non-serious and mild, and all were judged by investigator as unlikely related to trial product.

Pancreas cancer:

Across the insulin icodec phase 3a programme, there were 6 events of pancreas cancer reported with insulin icodec and 2 events reported with daily basal insulin. The events were all reported as serious adverse events considered unlikely related to insulin icodec and daily basal insulins, as judged by the investigator and by the applicant. Two (2) of the events in the insulin icodec arm and one (1) in the comparator arm had onset within the first 25 days of the trial; therefore, it is fully unlikely that insulin icodec had any role in their development. The overall number of cases is low, i.e. if the two cases with a TTO <25 days are excluded, 4 events in the insulin icodec group remain compared to two in the daily basal insulin group. In these few remaining cases confounding factors (medical history, concomitant treatments and long-standing diabetes) preclude proper causality assessments. It is worth noting that preclinical data did not indicate any increased risk of pancreas cancer, and there is no scientific rationale to suspect a different safety profile regarding pancreas cancer for insulin icodec compared to other insulins. Therefor no further evaluation is considered warranted in this regard.

Peripheral oedema

In the phase 3a pool (treatment/main on treatment phases), the rate (insulin icodec: 1.57 events per 100 PYEs vs daily basal insulin: 0.87 events per 100 PYEs) and proportion (insulin icodec: 1.1% vs daily basal insulin: 0.6%) of subjects reporting AEs related to Peripheral oedema was slightly higher in the insulin icodec treated group compared to the comparator group. All events were non-serious. The ADR "Peripheral oedema" is included in in SmPC section 4.8.

Medication errors

In the Phase 3a pool, medication errors were reported as an AE in 1.7% (n=37) of the subjects treated with insulin icodec without any clinically important difference compared to the daily basal insulin group (1.4%; n=31) (Table 70). However, in T1DM population (ONWARDS 6) a higher reporting rate of medication errors was noted in the insulin icodec group (5.5%) compared IDeg group (1.7%). In this trial a cluster of medication errors was noted in the populations switching from daily basal insulin administration to once weekly administration with insulin icodec. The medication errors were mainly reported in the period corresponding to the first and second dose of insulin icodec. A critical moment seemed to be at the second injection where the one-time additional dose was supposed to be removed. Level 1 and level 2 related hypoglycaemic episodes were reported within two weeks following the events of the medication error. This phenomenon was also noted in ONWARDS 2 and ONWARDS 4.

In clinical practice it is of importance to minimise this risk. In the SmPC the risk of medication errors when switching from daily or twice daily basal insulin to once weekly basal insulin is appropriately reflected in SmPC section 4.4. Medication errors during the switch from daily basal insulin is also included as an important potential risk in the RMP.

Table 70. Medication errors incl. misuse and abuse (predefined MedDRA search) – adverse events by system organ class and preferred term – on-treatment/main- on-treatment – summary – phase 3a pool

	Insulin icodec				Daily basal insulin			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Number of subjects	2170				2170			
PYE (years)	1681.23				1680.58			
Events	37	(1.7)	40	3.34	31	(1.4)	36	2.77
Injury, poisoning and procedural complications	36	(1.7)	39	3.26	30	(1.4)	35	2.73
Accidental overdose	14	(0.6)	15	1.24	4	(0.2)	5	0.41
Incorrect dose administered	6	(0.3)	6	0.52	5	(0.2)	7	0.52
Prescribed overdose	5	(0.2)	5	0.47	0			
Overdose	4	(0.2)	4	0.28	3	(0.1)	3	0.21
Medication error	2	(0.1)	2	0.16	3	(0.1)	3	0.25
Product administration error	1	(0.0)	1	0.09	2	(0.1)	2	0.12
Product dispensing error	1	(0.0)	1	0.09	0			
Underdose	1	(0.0)	1	0.08	5	(0.2)	5	0.36
Accidental underdose	1	(0.0)	1	0.08	0			
Extra dose administered	1	(0.0)	1	0.08	1	(0.0)	1	0.08
Wrong product administered	1	(0.0)	2	0.16	6	(0.3)	6	0.53
Wrong dose	0				2	(0.1)	2	0.16
Intentional overdose	0				1	(0.0)	1	0.08
Psychiatric disorders	1	(0.0)	1	0.08	1	(0.0)	1	0.04
Drug abuse	1	(0.0)	1	0.08	0			
Drug dependence	0				1	(0.0)	1	0.04

%: Percentage of subjects with one or more events, E: Number of adverse events, N: Number of subjects with one or more events, PYE: Patient years of exposure (1 PYE = 365.25 days), R: Rate (number of adverse events per 100 PYE). Adj.: Adjusted percentages and rates were calculated using the Cochran-Mantel-Haenszel method to account for differences between trials. On-treatment: Onset date on or after the first dose of trial product and no later than the first date of either the follow-up visit (FU2), the last date on trial product + 5 weeks for once daily insulin and + 6 weeks for once weekly insulin or the end-date for the in-trial period. Main-on-treatment: Onset date on or after the first dose of trial product and no later than the first date of either the end-date of the on-treatment period or the last planned visit in the main part of the trial. Daily basal insulin: IDeg, IGlar U100, and IGlar U300. Phase 3a pool: ONWARDS 1-6, only main part of ONWARDS 1 and 6.

2.6.8.3. Serious adverse event/deaths/other significant events

<u>Serious adverse events</u>

Overall, in the **T2DM pool**, serious adverse events were balanced between treatment groups (7.6-7.8%) (Table 57). The most reported SAE PTs in the insulin icodec group were COVID-19 pneumonia/COVID-19 /pneumonia (n=33 in total) followed by Acute myocardial infarction/coronary artery disease/myocardial infarction (n=23 in total).

In the **T1DM population** (ONWARDS 6 completed trial [0-52 weeks]) a slightly higher proportion of subjects and rates of SAEs were reported in the insulin icodec group (8.3%; rate 12.99 per 100 PYE) compared to the insulin IDeg group (6.8%; rate 8.08 per 100 PYE). The imbalance in number of SAEs is driven by more serious hypoglycaemic episodes reported by insulin icodec-treated patients (n=14 hypoglycaemic SAEs) compared to the IDeg group (n=3 hypoglycaemic SAEs).

<u>Fatal events</u>

Fatal events were balanced between the two treatment groups (0.6%). COVID-19 was the only PT reported in more than one subject (n=3) in the insulin icodec treatment group. No fatal COVID-19 event was reported in the daily basal insulin group. No death was reported in connection to hypo- or hyperglycaemias.

Overall, there was no indication of any differences regarding the cause of death as classified by the EAC for CV death, Undetermined cause of death or non-CV death.

2.6.8.4. Laboratory findings

Haematology parameters, biochemistry parameter and lipids were generally stable over time with both insulin icodec and daily basal insulin treatment. No clinically relevant change from baseline was seen during the on-treatment/main-on-treatment period in either treatment group. Neither was any difference between treatment groups seen for any of the evaluated laboratory investigations.

Weight gain is as expected considering the HbA1c lowering achieved during the trials and was noted across all trials and treatment groups in the Phase 3a pool. An exception is the daily basal insulin treatment group in ONWARDS 2 in which, for an unknown reason, a reduction was noted. Overall, the weight gain was slightly larger in the subjects treated with insulin icodec compared to the daily insulin treated subjects. The estimated change in body weight in ONWARDS 1 was 2.29 kg in the insulin icodec group vs 1.83 kg in the daily basal insulin group, in ONWARDS 2: 1.40 kg vs -0.30 kg, in OWARDS 3: 2.77 kg vs 2.32 kg, in ONWARDS 4: 2.73 vs 2.16 kg, in ONWARDS 5: 2.28 vs 1.45 kg and in ONWARDS 6 the change in baseline was 1.29 kg in the insulin icodec group vs 1.01 in the daily basal insulin group. To note is that 4 subjects in the insulin icodec group and one in the daily basal insulin group were withdrawn from the trials due to the AEs "weight increased".

Change in body weight was also a secondary endpoints in ONWARDS trials, see section on Clinical Efficacy above.

No difference between treatment groups were seen for **vital signs**.

2.6.8.5. Safety in special populations

Age

Overall, in the Phase 3a safety study pool (ONWARDS 1-6), 668 elderly subjects including 96 subjects ≥75 years <85 years and 4 subjects 85 years and above, have been exposed to insulin icodec. Most of the elderly ≥75 years were insulin naïve subjects with T2DM (n=68) and only 3 subjects ≥75 years were included in the T1DM population. There were too few patients over 85 years of age (n=4 in the insulin icodec group and none in the daily basal insulin group) to assess the safety profile in this age-group.

According to ICH E7 a minimum of 100 patients would usually allow for a detection of clinically important differences. Thus, the experience of use of insulin icodec in subjects ≥75 years is considered sufficient.

The minor differences in the overall safety profile in the elderly population (≥65 years) compared to the younger (<65 years) are noted in both treatment groups and are rather to be explained by diseases following natural aging.

Within the older age-group (≥75 years <85 years) a difference is noted between the two treatment groups regarding the proportions of subjects with AEs within the SOC cardiac disorders (insulin icodec: 14.3% [n=14] vs daily insulin: 5.8% [n=4]) and the SOC vascular disorders (insulin icodec: 19.3% [n=18] vs daily insulin: 10.2% [n=8]). On a PT level the frequencies of diarrhoea events differed between the two groups (insulin icodec: 11% [n=11] vs daily insulin: 1% [n=1]). These differences are not, at present, considered to be warranting any further evaluation or to be specified in the SmPC but should be followed with routine pharmacovigilance. However, elderly patients are in general a vulnerable population especially with reference to hypoglycaemia. Therefore, intensified glucose monitoring is of importance in this age group.

Renal impairment

The effect of renal impairment on the pharmacokinetics of insulin icodec has been evaluated in the clinical pharmacology Trial 4226 (see sections on Clinical Efficacy and Clinical Pharmacology above). In this single-dose phase 1 trial no safety concerns were raised.

In the phase 3a safety pool, in total 211 subjects in the insulin icodec group (9.7%) and 241 in the comparator group (11.1%) had moderate or severe renal function. No pronounced treatment difference in AEs by SOC, and by SOC and PT were observed across baseline renal function groups.

Hepatic impairment

The effect of hepatic impairment has been evaluated in the clinical pharmacology Trial 4570 (see sections on Clinical Efficacy and Clinical Pharmacology above). No new safety issues were identified in relation to insulin icodec in this trial.

In the phase 3a poll, a few subjects with impaired hepatic function were included (n=8 in the insulin icodec group and n=7 in the comparator group). The low number precluded a proper safety assessment in this subpopulation.

However, no difference of clinical importance was noted in the safety profile, including hypoglycaemic episodes, between patients with AST/ALT <75th or ≥75th percentile respectively (although, it is unclear how many of the subjects had elevated AST/ALT values [>ULN] at baseline). Overall, based on results from trial 4570 and ONWARDS 1-6, there is nothing indicating that the safety pattern in patients with hepatic impairment in general differs compared to the broader experience in the overall insulin icodec treated population. However, the risk for hypoglycaemia is potentially increased in subjects with hepatic impairment

due to a decreased ability to produce glucose from liver glycogen. Therefore, more frequent glucose monitoring is recommended in this subpopulation, and this is reflected in SmPC section 4.2.

Japanese population

Four (4) phase 3a trials (ONWARDS 1, 2, 4 and 6) included in total 429 Japanese subjects (205 in the insulin icodec group [9.4%] and 224 in the comparator groups [10.3%]).

The proportion of subjects reporting and the rate of severe hypoglycaemic episode (level 3) or clinically significant hypoglycaemic episodes (level 2) was lower (ONWARDS 1 and 2) or similar (ONWARDS 4 and 6) in the insulin icodec groups in the Japanese population as compared to the entire trial populations.

Across the ONWARDS trial 2, 4 and 6 except ONWARDS 1 (insulin naïve population) there was in the Japanese population, as in the entire population, an increased risk of severe clinically significant hypoglycaemic episodes when treated with insulin icodec as compared to the daily basal insulin.

Importantly, extension data for ONWARDS 1 (T1DM population) demonstrates that at week 52, there was a higher rate overall of severe or clinically significant hypoglycaemic episodes, including nocturnal, for insulin icodec compared to insulin degludec in the Japanese population than in the entire T1DM population (see section on Clinical Efficacy above).

Race, ethnicity, baseline HbA1c, duration of diabetes or baseline BMI

No pronounced treatment difference in AEs by SOC, and by SOC and PT was observed in the subgroups of race, ethnicity, baseline HbA1c, duration of diabetes or baseline BMI.

2.6.8.6. Immunological events

Anti-drug antibodies including antibody incidence and titres over time have been monitored in ONWARDS 2-4 and 6 and the Phase 2 trial 4383 anti-insulin icodec antibodies. In the remaining trials (i.e. ONWARDS 1 and ONWARDS 5), anti-insulin icodec antibodies were only assessed in the event of suspicion of systemic hypersensitivity reactions, in parallel with additional immunological analyses.

Immunology including Neutralising antibodies is also reflected in the section on Clinical Pharmacology above.

Antibody formation

In **insulin-naïve T2DM subjects** (ONWARDS 3 [Chinese population excluded] and Trial 4383), a high proportion of subjects developed treatment-induced anti-insulin icodec antibodies (77-82%). This frequency is markedly higher compared to the development of ADA during use of IGlar in trial 4383 (35%) and historical data for treatment with IDeg (Tresiba; 6.2%). It should be noted, however, that the up-to-date immunological assays usually are more sensitive with regard to the detection of ADA, which precluded direct comparisons in titres and frequencies with historical data. In subjects with **T2DM previously treated with insulin** a lower proportion of subjects developed treatment-induced antibodies (41-54%). In the **T1DM population** 33% developed anti-insulin icodec antibodies. The frequency in the T1DM is also higher as compared with historical data of ADA development for IDeg in T1DM (12%). Most of the icodec antibody positive subjects (in both populations) also had cross-reacting antibodies towards human insulin.

Antibody titres

The proportion of subjects who were ADA positive at baseline and developed increased titres during the trials (i.e. "treatment-boosted antibodies") varied between 11-37%, with the highest frequency in the T1DM population (ONWARDS 6). The overall mean titre peak of ADA differed between week 10 and week 18 across the trials.

Overall, no clinically relevant correlation between ADA titres and the efficacy parameters, "change of HbA1c from baseline to the end of treatment", "HbA1c at the end of treatment" or "higher weekly icodec dose (U/kg) during the last 2 weeks before end of treatment" was noted. Neither were any correlations between ADA titres and the safety parameters "rate of severe (level 3) or clinically significant (level 2) hypoglycaemic episodes", "injection site reactions" or "hypersensitivity" noted.

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

No clinical studies of drug interactions have been performed, which is acceptable given the product characteristics.

2.6.8.8. Discontinuation due to adverse events

In the phase 3 pool, the proportion of withdrawn subjects was low and similar (~1%) in the two treatment groups. Approximately 50% of the discontinuation adverse events were SAEs.

The only PTs, for AEs leading to permanent treatment discontinuation, reported by more than two subjects with insulin icodec were "weight increased" (4 AEs in the insulin icodec group and 1 AE in the daily basal insulin group) and urticaria (3 AEs in the insulin icodec group and none in the daily basal insulin group). There were no AEs reported with the PT of hypoglycaemia that led to permanent discontinuation of trial product. However, 4 subjects treated with insulin icodec (and one with insulin degludec) discontinued the trials due to hypoglycaemic events not reported as AEs.

2.6.8.9. Technical complaints

In the phase 3a pool, a total of 19 AEs were marked as related to technical complaints by the investigator, 11 events in 11 subjects in the insulin icodec group and 8 events in 7 subjects in the daily basal insulin group. However, according to protocol, if an AE is considered related to a technical complaint, a technical complaint form has to be filled out by the investigator in addition to the information given on the AE form. Only three (3) of the 19 AEs had a technical complaint form filled out, 1 of which was related to the bolus insulin pen-injector (Trial 4480) and 2 events related to basal insulin pen-injectors in the insulin icodec group (Trial 4480 and Trial 4479). For the remaining 16 events, no technical complaint form was filled out and the links between events and technical complaints appear to be data entry error. Only three (3) of the 19 AEs related to a technical complaint, had a form filled out. According to the applicant this seems to have been caused by entry errors, since the nature of these AEs does not indicate that they were indeed linked to a technical complaint.

The 2 AEs related to technical complaints for basal insulin in the insulin icodec group were mild or moderate in severity, both events were recovered or recovering, and they had the PTs of incorrect dose administered and injection site abscess.

2.6.8.10. Post marketing experience

Not applicable.

2.6.9. Discussion on clinical safety

In the Phase 3a pool, 2170 subjects were exposed to insulin icodec including 1880 subjects (142.31 PYE) with T2DM during the treatment/main-on-treatment phases and 290 subjects (300.16 PYE) with T1DM during the entire study period (52 weeks) of ONWARDS 6. The proposed safety population for the overall evaluation of insulin icodec is considered appropriate and is accepted. The trial ONWARDS 3 (insulin naïve T2DM) was a double blinded, double dummy trial. The remaining trials had open-label designs, which is a limitation for the evaluation of safety due to the risk of un-intended bias.

For both T2DM and T1DM the minimum number of subjects exposed to at least 12 months of treatment (n=614 for T2DM and n=249 for T1DM) is within the requirement for safety evaluation. Additional data from the extension phase of ONWARDS 1 (insulin naïve patients with T2DM), includes 465 subjects exposed to insulin icodec for $\geqslant$ 82 weeks.

Use of insulin icodec in newly diagnosed (not previously treated with basal insulin) subjects with T1DM has not been evaluated, and this fact is reflected in section 4.4 of the SmPC.

Adverse events: Overall, in the Phase 3a pool, there was no pronounced difference in the proportion of subjects reporting the most common AEs when comparing insulin icodec with the daily basal insulin group or the T2DM populations with the T1DM population. Serious adverse events (SAEs) in the T2DM pool were balanced between groups (~8%). Safety results from the extension phase (week 52-83) of ONWARDS 1 (insulin naïve T2DM population) is overall in line with the results from the main treatment period (0-52 weeks).

In the **T1DM population** (ONWARDS 6 complete trial [0-52 weeks]) a slightly higher proportion of subjects reported at least one SAE in the insulin icodec group (8.3%) as compared to the insulin IDeg group (6.8%). The imbalance in the number of SAEs was driven by more hypoglycaemic SAEs reported by insulin icodec-treated patients (n=14) compared to the IDeg group (n=3). Fatal events were balanced between groups (0.3%) in the phase 3a pool. No death was reported in connection to hypo- or hyperglycaemia.

Hypoglycaemic episodes: In the **T2DM population**, **severe (level 3) hypoglycaemic episodes** were reported in low proportions (0%-1.4%) and rates in the insulin icodec groups. There was no difference of clinical relevance compared to the comparator groups (0.4%-0.7%).

In the **T2DM population** the proportion of subjects reporting severe (level 3) or clinically significant (level 2) hypoglycaemic episodes in the insulin icodec group varied between 9% and 52%. As expected, the lowest reporting was noted in the insulin naïve population and the highest in the T2DM population previously treated with basal-bolus insulin.

Overall, in most of the T2DM populations, similar or only slightly higher incidences but higher rates of severe or clinically significant hypoglycaemic episodes were noted in the insulin icodec group as compared to the comparator groups.

In the **insulin naïve T2DM population** (ONWARDS 1,3 and 5) the proportion of subjects reporting any severe or clinically significant hypoglycaemic episodes in the insulin icodec groups compared to the comparators were 8.9%-11.8% and 6.1-10.6%, respectively. The rates of hypoglycaemic episodes were

higher in all insulin icodec groups compared to the comparators across these three trials (ONWARDS 1: 29.64 vs 16.08 events per 100 PYE; ONWARDS 3: 31.01 vs 14.61 per 100 PYE and ONWARDS 5: 18.56 vs 14.45 events per 100 PYE).

In the **T2DM population previously treated with basal insulin** both the proportion of subjects reporting and the rates of <u>severe or clinically significant hypoglycaemic episodes</u> were higher in the insulin icodec groups compared to the daily basal insulin group (14.1% vs 7.2% and 72.29 vs 27.49 episodes per 100 PYE). An exception in the pattern with higher proportions and rates of reported <u>severe or clinically significant hypoglycaemic episodes </u>was in the **T2DM population on a previous basal-bolus insulin** regimen where similar frequencies and rates were reported (51.1% vs 55.7% and 564.05 vs 562.36 episodes per 100 PYE).

The difference of mean number of reported severe or clinically significant hypoglycaemic episodes per subject over time between the insulin icodec and daily basal insulin groups occurred after the first 4-12 weeks (i.e. after the initial titration phases). Reassuringly, data from the extension of ONWARDS 1 demonstrates that neither the rate (episodes/100 PYE) nor the proportion (%) of subjects with at least one severe (level 3) or clinically significant (level 2) hypoglycaemic episodes increased in any of the two treatment groups during the 12-18 months' period compared to the first 12 months. The rate is, however, constantly higher in the insulin icodec group throughout the complete 18 months' study period.

Overall, in the T2DM trials no pronounced difference regarding reporting of **nocturnal** severe or clinically significant hypoglycaemic episodes were noted between subjects treated with insulin icodec and the comparators, respectively. However, in the T2DM population on a previous basal insulin regimen (ONWARDS 2) an imbalance was noted for reporting of **nocturnal** clinically significant hypoglycaemic episodes with a higher reporting of these events in the insulin icodec group (6.1% vs 3.4% rate: 20.61 vs 8.51 episodes per 100 PYE). Reassuringly, no severe nocturnal hypoglycaemic episode was recorded.

In the **T1DM population** hypoglycaemic episodes (despite classification) were overall reported in higher proportions of subjects compared to all the studied T2DM populations. This is expected due to an in general lower ability to counteract hypoglycaemia in the T1DM population. Data from the complete study period (52 weeks) in ONWARDS 6 demonstrated that the proportion of subjects with T1DM reporting severe (level 3) hypoglycaemic episodes was same in the insulin icodec and the comparator (IDeg) group (4%). However, the rate of severe hypoglycaemia was higher in the insulin icodec group compared to the IDeg group (18.66 vs 8.08 events per 100 PYE at week 52). The difference in rate was driven by one subject in the insulin icodec group that accounted for 61% of the severe hypoglycaemic episodes.

In the **T1DM trial** (ONWARDS 6), results for the complete 52-weeks study period demonstrated that both the proportions the rate of severe or clinically significant hypoglycaemic episodes were higher in the insulin icodec group compared to the IDeg treated group (90.7% vs 85.6% and rate 1700.10 vs 916.07 episodes per 100 PYE; estimated rate ratio 1.80 [1.48; 2.18]). The higher rate of hypoglycaemic events in the insulin icodec group is reflected also by higher proportion of subjects reporting ≥20 hypoglycaemic episodes compared to the IDeg group (14.8% vs 5.8%; data from the main 26-week study period). Nocturnal severe (level 3) or clinically significant (level 2) hypoglycaemic episodes were also reported at a higher proportion and with a higher rate among the insulin icodec treated subjects compared to the IDeg group (59.0% vs 47.9%; rate 289.85 vs 149.23 per 100 PYE; estimated rate ratio 1.89 [1.44; 2.48). Reassuringly, severe nocturnal hypoglycaemic episodes were reported similarly low in the two treatment groups (~1.4%).

In the **T1DM trial** (ONWARDS 6), the mean number of severe or clinically significant hypoglycaemic episodes per subject was comparable between treatment groups during the initial two weeks. Thereafter, the insulin icodec and insulin degludec curves of the mean number of severe or clinically significant hypoglycaemic

episodes started to diverge. The rates are approximately twice as high for the icodec group compared to the IDeg group throughout the complete 52-weeks study period. However, reassuringly the rate decreased from 1992.86 events per 100 PYE, at week 26 weeks, to 1700.1 events per 100 PYE at week 52. In the IDeg group, a corresponding pattern was noted with a decrease in rate from 1036.33 after 26 weeks to 916.07 events per 100 PYE after 52 weeks.

In the phase 3a trials, the median time to recovery from hypoglycaemic episodes in the insulin icodec group were longer (ONWARDS 1 and ONWARDS 2) or similar (ONWARDS 3-6) as compared to the daily basal insulin groups. Across all trials, a larger proportion of the insulin icodec SMPG-verified clinically significant (level 2) hypoglycaemic episodes had a duration >360 min (3%-9%) compared to daily basal insulin episodes (0-3%). A warning for the risk of prolonged hypoglycaemia episodes with insulin icodec is included in SmPC section 4.4.

Immunogenicity: High incidences of treatment induced anti-insulin icodec antibodies were noted in all T2DM and T1DM populations. The highest formations of anti-insulin icodec antibodies were noted in the insulin naïve T2DM subjects (70-82%). This frequency is markedly higher compared to the development of ADA in insulin naïve subjects during use of IGlar in trial 4383 (35%) and historical data for treatment with IDeg (Tresiba; 6.2%). In the T1DM population 33% developed ADA and a similar proportion (37%) had increased titres of already existing ADA. The frequency in the T1DM is also higher compared with historical data of ADA development for IDeg in T1DM (12%).

No correlation between ADA titres and the efficacy parameters 'changes of HbA1c from baseline to the end of treatment', 'HbA1c at the end of treatment' or 'higher weekly icodec dose (U/kg) during the last 2 weeks before end of treatment' was noted. Neither were any correlations between ADA titres and the safety parameters, rate of severe (level 3) or clinically significant (level 2) hypoglycaemic episodes, injection site reactions or hypersensitivity noted. The risk of ADA is considered sufficiently reflected in the SmPC sections 4.4, 5.1 and 5.2. Immunogenicity is also discussed in the section on Clinical Pharmacology above.

Injection site reactions: In the Phase 3a study pool (treatment/main-on treatment phases), a higher frequency of ISR were reported in the insulin icodec group (8.5%) compared to the IDeg group (4.4%) in the double blinded, double dummy trial ONWARD 3 (performed in insulin naïve T2DM). On a PT-level the main difference between the two groups was the unspecific PT "Injection site reaction" (3.1% in the insulin icodec group and 0.7% in the IDeg group). The remaining PTs were reported by 1-3 subjects. Reassuringly, most of the events in both treatment groups were mild (95%) and no event in either group was serious or severe. Only one case of lipodystrophy and no case of cutaneous amyloidosis was reported in the insulin icodec groups across the Phase 3a trials. The risk of ISR, lipodystrophy and cutaneous amyloidosis is sufficiently reflected in the SmPC.

Hypersensitivity reactions: An overall similar proportion of subjects with hypersensitivity events were reported for the two treatment groups both in the T1DM population (8.3-8.6%) and the T2DM population (3.1-3.8%). In both treatment groups few serious hypersensitivity adverse events were reported (0-0.1%). Hypersensitivity is sufficiently reflected in SmPC section 4.8.

Hyperglycaemia: The reporting of AEs related to hyperglycaemia during treatment with insulin icodec was low (0.5%) in the Phase 3a pool. No SAE of DKA events were reported.

Cardiovascular disorders: The results presented regarding CV safety, i.e. reported adjudicated cardiovascular events, ECG findings and results from the MACE meta-analysis (including data from the extension phases of ONWARDS 1 and 6, did not indicate any apparent increase in CV risk for patients treated with insulin icodec.

Medication Errors: A cluster of medication errors was noted in the populations switching from daily basal insulin administration to once weekly administration with insulin icodec (ONWARDS 2, 4 and 6) in the period corresponding to the first and second dose of insulin icodec. The risk of medication errors when switching from daily or twice daily basal insulin to once weekly basal insulin is adequately reflected in SmPC section 4.4. Medication errors during the switch from daily basal insulin and medication errors due to mix ups are included as important potential risks in the RMP.

Subgroups: A total of 100 subjects ≥75 years were included in the insulin icodec group in the Phase 3a pool. This is considered sufficient to allow for the detection of clinically important differences.

Only three (3) of the 100 subjects were subjects with T1DM. Some differences in AE reporting in the elderly population was noted.

The minor differences in the overall safety profile for the elderly population compared to the younger are noted in both treatment groups and are likely to be explained by diseases associated with natural aging. In the subjects ≥75 years a difference in the proportion of subjects with PTs was noted within the SOCs Cardiac disorders and Vascular disorders, respectively. There is no need, at present, for these to be further evaluated or specified in the SmPC. However, elderly patients is in general a vulnerable population especially with reference to hypoglycaemia. Therefore, intensified glucose monitoring is of importance in this population.

In the phase 3a pool only a few subjects with **hepatic impairment** were included in the insulin icodec group. Based on PK data, no dose adjustment is recommended for subjects with hepatic impairment.

Overall, based on results from the trial 4570 and ONWARDS 1-6, there is no indication that the safety pattern in patients with hepatic impairment in general differs from the broader experience in the overall insulin icodec treated population. However, the risk of hypoglycaemia is potentially increased in subjects with hepatic impairment due to a decreased ability to produce glucose from liver glycogen. Therefore, more frequent glucose monitoring is recommended and this is reflected in SmPC section 4.2.

No pronounced treatment differences in AEs were observed in the subgroups of race, ethnicity, baseline HbA1c, duration of diabetes, baseline BMI or renal impairment.

Long-term safety data will be gathered from the extension phase of ONWARDS 1 (insulin naïve T2DM) and will be available up to 78 weeks of treatment.

2.6.10. Conclusions on the clinical safety

Overall, the safety profile of insulin icodec is in accordance with what is expected for basal insulins and no new safety issues have been identified. However, there was a higher risk of hypoglycaemia compared to the comparators in both the T2DM and T1DM populations. This difference was especially pronounced in the T1DM population in which the incidence of hypoglycaemic episodes was higher as compared to the T2DM populations. Use of once weekly basal insulin implies increased difficulties to adjust the basal dose for external factors with a lower ability to counteract hypoglycaemia such as in subjects with T1DM. This might be an explanation for the difference noted in the described hypoglycaemic pattern in this population. In the T1DM population both the frequencies and especially the rates of hypoglycaemic episodes (all categories) were markedly higher in the insulin icodec treated group compared to the IDeg group. At the end of the 52-weeks treatment period the rate of severe (level 3) or clinically significant (level 2) hypoglycaemic episodes was approximately twice as high in the insulin icodec group as compared to the IDeg group. This was also

reflected by a higher proportion of subjects reporting ≥20 episodes compared to the IDeg group. However, the risk of hypoglycaemia did not increase over time during the complete trial (from baseline to 52 weeks) and data indicate that severe nocturnal hypoglycaemic episodes were reported similarly low in the two treatment groups (n=4 subjects in both treatment arms) during the 52-week study period.

For subjects with **T2DM** the risk of hypoglycaemia during use of insulin icodec is considered manageable with the current information in the SmPC. The higher risk of hypoglycaemia with insulin icodec in the **T1DM** population might be a limitation for treatment with insulin icodec in some patients. Based on the data submitted it is not considered possible to identify subjects with an increased risk for hypoglycaemia. Therefore, the SmPC sections 4.4 and 4.8 specifically reflect the higher frequency and rate of hypoglycaemic events compared to daily basal insulin for T1DM patients. Further, the SmPC includes a warning to the effect that insulin icodec should only be used in patients with T1DM for which a clear benefit of a once weekly administration is expected.

Medication errors: "Medication errors due to potential mix-up" and "Medication errors during switch from daily basal insulin" could both lead to under- or over-dosing of insulin resulting in life-threatening conditions, and have been included as important potential risks in the RMP. Post-marketing these events might increase. There is a potential risk that these events will increase in clinical practice. Additional risk minimisation activities in the form of a patient/carer's guide have been agreed in order to manage the safety concerns of "Medication errors due to mix-up" and "Medication errors during switch from daily basal insulin".

Pregnancy and breast-feeding: Non-clinical studies have not revealed any fetotoxic or teratogenic potential for insulin icodec. However, the inclusion of "pregnancy and lactation" as missing information in the RMP is agreed since clinical safety data in this population is lacking and considering that insulin icodec is a novel molecule. To note is also the fact that during pregnancy frequently insulin dose adjustments are needed and after the child is born the insulin requirement is reduced abruptly. Therefore, use of insulins icodec with its long-acting potential in this population is questioned. Use of insulin icodec during pregnancy and breast-feeding is sufficiently reflected in SmPC section 4.6.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 71. Summary of safety concerns (RMP version 0.4)

Summary of safety concerns	
Important potential risks	Medication error due to potential mix-up
	Medication error during switch from daily basal insulin
Missing information	Pregnancy and lactation

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

Table 72. Pharmacovigilance and risk minimisation activities by safety concern

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
None.		
Important potential risks		
Medication errors due to mix-up	*Routine risk communication:* • The risk of mix-ups is presented in Section 4.4 of the SmPC and Section 2 of the PL. *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • Instructions for avoidance of medication errors are described in Section 4.4 of the SmPC and Section 2 of the PL • Special precautions for disposal and handling of the pre-filled pen (FlexTouch®) are described in Section 6.6 of the SmPC • Recommendations in Section 4.4 of the SmPC and Section 3 of the PL indicates that patients with impaired vision require assistance from a person with good vision • Product appearance is described in Section 6 of the PL to prevent misidentification of medicine *Other risk minimisation measures beyond the Product Information:* • These include differentiation strategy; includes trade name, label text, colour branding of the carton, container label and cartridge holder. • This medicine is only available by prescription. *Additional risk minimisation measures:* Additional risk minimisation in the form of patient/carer's educational guide is distributed when insulin icodec is newly launched and made available for the first 2 years to help minimise the risk of medication errors due to mix-up (see Annex 6). The information will describe: • Instructions to strictly adhere to weekly dosing regimen. • Instructions to always check the insulin label before each injection. • Weekly dosing frequency prominently included on the four faces of the carton.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Standardised follow-up questions (see Annex 4A). **Additional pharmacovigilance activities:** None proposed.
Medication errors during switch from daily basal insulin	*Routine risk communication:* • The risk related to switching from daily basal insulin products is presented in Sections 4.2, 4.4, and 4.9 of the SmPC and Section 2 of the PL *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • Instructions for switching from other daily	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Follow-up questions (see Annex 4A). **Additional pharmacovigilance activities:** None proposed

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
	basal insulins to insulin icodec, including a dose calculation table presenting the recommended one-time additional dose and second dose based on the daily basal insulin dosing regimen, are presented in Section 4.2 of the SmPC • Patients must be instructed to check that they inject the correct dose, especially in the first 10 days of treatment (Section 4.4 of the SmPC). It is also indicated in Section 4.2 of the SmPC and Section 2 of the PL that the one-time additional dose is not to be continued with subsequent doses • Patients who are uncertain about the correct dose must be instructed to consult their physician for further guidance (Section 4.4 of the SmPC) • A recommendation to only begin a switch to insulin icodec from another insulin under medical supervision is included in Section 4.4. of the SmPC and Section 2 of the PL • In Section 3 of the PL, switching to insulin icodec is discussed with specific mention that a doctor should prescribe you the first and second dose, and that subsequent doses should be determined in consultation with a doctor • In Section 4.9 of the SmPC, specific warning is included concerning the risk for overdose if the one-time additional dose continues to be taken with subsequent dosing. • Recommendations in Section 4.4 of the SmPC and Section 3 of the PL indicates that patients with impaired vision require assistance from a person with good vision — ***Other risk minimisation measures beyond the Product Information:*** This medicine will only be available by prescription ***Additional risk minimisation measures:*** Additional risk minimisation in the form of patient/carer's educational guide is distributed when insulin icodec is newly launched and made available for the first 2 years to help minimise the risk of medication errors during switch from other basal insulin (see Annex 6). The information will describe: • Information on use of one-time additional dose when initiating Awiqli®. • Key differences between first dose and second dose. • Cautionary text on the carton "The pen shows the dose, One step equals 10 units".	
Missing information		
Pregnancy and breast-feeding	***Routine risk communication:*** • Lack of experience in this population is mentioned in Section 4.6 of the SmPC (Fertility, pregnancy and lactation). • It is acknowledged that, as a result of	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
	potential exposure during breast-feeding, a risk to the newborns/infants cannot be excluded (Section 4.6, SmPC) ***Routine risk minimisation activities recommending specific clinical measures to address the risk***: • In Section 2 in the PL, patients are encouraged to discuss with a doctor, nurse or pharmacist whether to begin therapy with insulin icodec while pregnant or breast feeding. • It is also advised that a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from insulin icodec therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman (Section 4.6, SmPC). ***Other risk minimisation measures beyond the Product Information:*** • This medicine will only be available by prescription.	None **Additional pharmacovigilance activities:** None proposed.

Abbreviations: EU-PI = European Union product information ; PL = product leaflet ; SmPC = Summary of Product Characteristics.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.4 is acceptable.

The applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

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

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Awiqli (Insulin icodec) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

Insulin icodec is intended to be used in the following indication:

"Treatment of diabetes mellitus in adults"

Insulin icodec is a basal insulin for once-weekly subcutaneous administration.

The extended half-life of insulin icodec is due to a strong but reversible binding to albumin. Thereby, a depot of essentially inactive insulin icodec is formed in the circulation and in the interstitial compartment, from which insulin icodec is slowly and continuously released. Insulin icodec is largely cleared by internalisation mediated by binding to and activation of the insulin receptor. Hence, the slow and steady glucose-lowering effect is due to reversible albumin binding, reduced insulin receptor binding and receptor-mediated clearance from the circulating insulin icodec depot. When insulin icodec binds to the human insulin receptor it results in the same pharmacological effects as human insulin.

3.1.1. Disease or condition

Diabetes mellitus is a metabolic disorder characterised by the presence of hyperglycaemia due to defective insulin secretion, insulin action or both. In both T1DM and T2DM, various genetic and environmental factors can result in the progressive loss of b-cell mass and/or function that manifests clinically as hyperglycaemia. Once hyperglycaemia occurs, patients with all forms of diabetes are at risk for developing chronic complications, particularly damage, dysfunction, and failure of various organs, including the heart, kidneys, and eyes, as well as blood vessels and nerves, although rates of progression may differ (ADA 2019). In the

latest edition of the International Diabetes Federation's Diabetes Atlas (2021), the estimated worldwide diabetes prevalence was 537 million and is predicted to increase further.

T2DM is characterised by peripheral tissue insulin resistance, impaired insulin secretion and/or increased hepatic glucose output due to glucagon dysregulation resulting in chronic hyperglycaemia. The pathogenesis is seemingly heterogeneous, involving environmental, lifestyle, and genetic factors (DeFronzo 2004, Leahy et al. 2005).

T1DM is a heterogeneous disorder characterised by T cell-mediated autoimmune destruction of insulin-producing beta cells in the pancreas. The destruction of beta cell function leads to insulin deficiency and the requirement of lifelong administration of exogenous insulin. The fundamental principle for insulin treatment of T1DM is to mimic normal physiological patterns as closely as possible. The current gold standard of care is based on intensive insulin therapy with multiple daily injections of prandial and basal insulin or continuous subcutaneous insulin infusion (DiMeglo et al. 2018, ADA 2019).

3.1.2. Available therapies and unmet medical need

In T2DM patients, the current treatment follows a stepwise approach comprising lifestyle changes in combination with pharmacological intervention. In asymptomatic individuals, the first line of treatment is always lifestyle changes such as diet and exercise, with the aim of reducing weight and improving insulin sensitivity. Such changes may also have a beneficial effect on lipids and blood pressure. Glucose-lowering agent monotherapy, primarily metformin as first-line therapy, is generally recommended as initial pharmacological therapy. Single agent therapy is followed by combination therapy with other oral antidiabetic drugs, GLP-1 receptor agonists and/or insulin as the disease progresses. On average, after failure of diet and exercise alone, patients with T2DM require a new intervention with glucose-lowering agents every 3-4 years in order to obtain/retain good glycaemic control (Danne et al. 2007, Pinhas-Haimel et al. 2007, Rosenblom et al. 2009, Zeitler et al. 2010, IDF 2011, Morales et al. 2011, EMA Diabetes Guideline 2012, Inzucchi et al. 2012, Inzucchi 2015, Araki et al 2019).

In T1DM patients, lifelong administration of exogenous insulin is required. New therapies are still required to further reduce the treatment burden, increase the number of treatment options, and ultimately provide improved glycaemic control. Treatment of diabetes needs to be highly individualised due to the heterogenous population (Danne et al. 2018, Silverstein et al. 2005). There is no unmet medical need for insulin icodec.

3.1.3. Main clinical studies

The efficacy data supporting this application are derived from the six confirmatory phase 3 studies, of which five trials in T2DM patients and one trial in T1DM patients. All studies were open-label, except for one T2DM study which was double-blinded. The efficacy was evaluated in insulin naïve T2DM patients, in T2DM patients previously treated with basal insulin and in T2DM and T1DM patients previously treated with basal-bolus insulin. All studies applied a treat-to-target design, except for one study in insulin naïve T2DM patients (ONWARDS 5), which was designed to mimic a clinical practice setting with fewer dedicated visits and routine assessment left to the treating physician. Insulin icodec was in this study used together with a dosing guide application under investigation. Two studies evaluated the effect up to 52 weeks, while the remaining 4 studies had a duration of 26 weeks.

Table 73. Key design elements of the 6 confirmatory phase 3 studies

Design elements	ONWARDS 1	ONWARDS 3	ONWARDS 5	ONWARDS 2	ONWARDS 4	ONWARDS 6
Population	Insulin naïve T2DM	Insulin naïve T2DM	Insulin naïve T2DM	T2DM patients (basal switch)	T2DM patients (basal-bolus regimen)	T1DM patients
Study design	Open-label Treat-to target	Double-blind Treat-to target	Open-label Design to mimic a clinical practice setting; to evaluate effectiveness	Open-label Treat-to target	Open-label Treat-to target	Open-label Treat-to target
Insulin icodec Starting dose	70 U	70 U	70 U Insulin degludec with DoseGuide application	Total daily basal insulin dose x 7 + one-time additional 50% dose	Total daily basal insulin dose x 7 + one-time additional 50% dose	Total daily basal insulin dose x 7 + one-time additional 50% or 100% dose*
Comparator	IGlar (100 U/mL)	IDeg (100 U/mL)	IGlar (100 U/mL, 300 U/mL) or IDeg (100 U/mL)	IDeg (100 U/mL)	IGlar (100 U/mL)	IDeg (100 U/mL)
Randomisation scheme	1:1	1:1	1:1	1:1	1:1	1:1
Treatment duration	52 weeks (+ 26 weeks extension)	26 weeks	52 weeks	26 weeks	26 weeks	26 weeks (+ 26 weeks extension)
Randomised and treated with study drug	984	588	1 085	526	582	582
Randomised and treated	492	293	542	262	291	291

with insulin icodec						
Background medication	Non-insulin anti-diabetic treatment (excluded sulfonylureas and glinides)	Non-insulin anti-diabetic drugs (sulphonylureas and glinides reduced by approximately 50%)	Non-insulin anti-diabetic drugs (sulphonylureas and glinides reduced by approximately 50%)	Non-insulin anti-diabetic drugs (excluded sulphonylureas and glinides)	Non-insulin anti-diabetic drugs (excluded sulphonylureas and glinides) + bolus insulin	Bolus insulin
HbA1c inclusion criteria	HbA1c: 7.0-11.0%	HbA1c: 7.0-11.0%	HbA1c: >7.0%	HbA1c: 7.0-10.0%	HbA1c: 7.0-10.0%	HbA1c: <10%

*One-time additional 50% dose: HbA_{1c} <8% or subjects who received insulin glargine U300 or twice daily basal insulin prior to randomisation). One-time additional 100% dose: $HbA_{1c} \geq 8\%$

3.2. Favourable effects

The primary hypothesis was that insulin icodec is non-inferior to a daily basal insulin comparator (insulin degludec or insulin glargine) in terms of HbA_{1c} change from baseline to week 26 (ONWARDS 2, 3, 4 and 6) or week 52 (ONWARDS 1 and 5) using a non-inferiority margin of 0.3%. The primary endpoint was met in all studies (ONWARDS 1:-0.19% [-0.36; -0.03], ONWARDS 2: -0.22% [-0.37; 0.08], ONWARDS 3: -0.21% [-0.34; -0.08], ONWARDS 4: -0.02% [-0.11; 0.15], ONWARDS 5: -0.38% [-0.66; -0.09] and ONWARDS 6 (0.05% [-0.13; -0.23]). In addition, statistical superiority was confirmed in insulin naïve T2DM patients (ONWARDS 1, 3 and 5) and T2DM subjects previously treated with basal insulin (ONWARDS 2). Extension data for ONWARDS 1 (at week 78) showed: ETD -0.11% [-0.22; 0.00] and ONWARDS 6 (at week 52): ETD: 0.17% [0.02; 0.31].

A multiple testing procedure was in place for the confirmatory secondary endpoint time spent in range 3.9-10.0 mmol/L in ONWARDS 1. Other secondary endpoints were not corrected for multiplicity.

For the key secondary endpoint in ONWARDS 1 (insulin naïve), insulin icodec led to statistically significantly more time spent in euglycaemic range (TIR) compared to daily basal insulin (4.27% [1.92: 6.62]), as demonstrated through continuous glucose monitoring. In basal switch and basal-bolus patients (ONWARDS 2, 4 and 6), there were no important differences for TIR between insulin icodec and daily basal insulin.

In T1DM patients, time spent in hypoglycaemic range <3.9 mmol/L for insulin icodec ranged from 1.20% to 2.65% (corresponding to 17.3-38.2 minutes in 24 hours) and for daily basal insulin from 0.83% to 2.26% (corresponding to 12.0-32.6 minutes in 24 hours). Time spent <3.0 mmol/L was between 0.27-0.73% (corresponding to 3.9-10.5 minutes in 24 hours) for insulin icodec and 0.21-0.61% (corresponding to 3.0-8.8 minutes in 24 hours) for daily basal insulin. In T1DM patients, time spent <3.9 mmol/L and <3.0 mmol/L, respectively, was 3.86% and 1.02% (corresponding to 55.6 and 14.7 minutes in 24 hours), respectively, for insulin icodec and 2.90% and 0.68% (corresponding to 41.8 and 9.8 minutes in 24 hours), respectively, for insulin degludec.

In T2DM patients, FPG reduction was comparable between treatment arms. In T1DM patients, the reduction in FPG from baseline to end of treatment was -0.84 mmol/L for insulin icodec and -1.87 mmol/L for insulin degludec; ETD: 1.03 [0.48; 1.59].

Weekly basal insulin doses were numerically higher with insulin icodec compared to daily basal insulin in all studies, except for ONWARDS 3. In patients on basal-bolus regimen, ETR of weekly total insulin dose (basal + bolus insulin) was 0.92 [0.85; 0.99] (ONWARDS 4) and 0.96 [0.90; 1.03] (ONWARDS 6) for insulin icodec vs daily basal insulin, of which weekly bolus insulin dose was 0.77 [0.70; 0.86] (ONWARDS 4) and 0.82 [0.74; 0.90] (ONWARDS 6) for insulin icodec vs daily basal insulin.

Across the studies, numerically higher weight gain was observed in the insulin icodec group compared to the daily basal insulin group, with an estimated treatment difference in change in mean body weight ranging from 0.28 kg to 1.70 kg between treatment groups.

In T2DM patients (ONWARDS 2 and 5), insulin icodec led to greater improvement in PRO scores compared to daily basal insulin. Change from baseline in DTSQs score at the end of treatment was 1.25 [0.41; 2.10] (ONWARDS 2) and 0.78 [0.10; 1.47] (ONWARDS 5) for insulin icodec vs daily basal insulin. In T1DM patients (ONWARDS 6), improvement in PRO scores was greater for daily basal insulin compared to insulin icodec (ETD -1.09 [-1.85; -0.34] for insulin icodec vs insulin degludec).

In a prespecified analysis, a greater portion of insulin naïve and basal switch T2DM patients (40.5-52.6%) compared to daily basal insulin patients (31.6-42.6%) achieved target HbA_{1c} <7% without hypoglycaemia. In basal-bolus T2DM subjects, the rates were comparable between the treatment groups. In T1DM patients, the responder rates of achieving HbA_{1c} target <7% without hypoglycaemia was 9.6% for insulin icodec and 16.7% for insulin degludec.

3.3. Uncertainties and limitations about favourable effects

The T1DM trial enrolled rather few subjects (n=582) and data up to 52 weeks of treatment with insulin icodec indicate a somewhat lower glucose reducing effect compared to insulin degludec. The weekly dosing could be a benefit in some patients who have difficulties adhering to daily treatment regimens. However, considering that patients with type 1 diabetes still have to take daily bolus insulin injections, the population for which this is a benefit may be rather limited.

For ONWARDS 4 and ONWARDS 6, statistical conclusions are accepted based on the primary HbA1c non-inferiority analysis since the predefined confirmatory testing strategy included no secondary hypotheses.

3.4. Unfavourable effects

Hypoglycaemic episodes

In the **T2DM population**, severe hypoglycaemic episodes were reported in 0%-1.4% in the insulin icodec groups and 0.4%-0.7% in the comparator groups. No nocturnal severe hypoglycaemic episodes were reported in the T2DM population.

In the **insulin naïve T2DM population** (treatment/main on-treatment phases ONWARDS 1-5) the proportion of subjects reporting severe or clinically significant hypoglycaemic episodes in the insulin icodec groups compared to the comparators were 8.9%-11.8% and 6.1-10.6%, respectively. The rates of hypoglycaemic episodes were higher in all insulin icodec groups compared to the comparators across these

three trials (ONWARDS 1: 29.64 vs 16.08 events per 100 PYE; ONWARDS 3: 31.01 vs 14.61 per 100 PYE and ONWARDS 5: 18.56 vs 14.45 events per 100 PYE). Data from the extension phase (0-78 weeks) of ONWARDS 1, demonstrated that the rate of severe (level 3) or clinically significant (level 2) hypoglycaemia did not increase over time but was at the end of the complete study (week 78) still twice as high in the insulin icodec group as compared to the daily basal insulin group (29.65 vs 15.78 episodes per 100 PYE).

In the **T2DM population previously treated with basal insulin** both the proportion of subjects reporting and the rates of severe or clinically significant hypoglycaemic episodes were higher in the insulin icodec groups compared to the daily basal insulin group (14.1% vs 7.2% and 72.29 vs 27.49 episodes per 100 PYE). An exception in the pattern with higher proportions and rates of reported severe or clinically significant hypoglycaemic episodes was in the **T2DM population on a previous basal-bolus insulin** regimen where similar frequencies and rates were reported (51.1% vs 55.7% and 564.05 vs 562.36 episodes per 100 PYE).

Nocturnal severe or clinically significant hypoglycaemic episodes were, in the insulin icodec groups, reported by 0%-2.0% in the insulin naïve T2DM population, 6.1% in subjects with T2DM previously treated with daily basal insulin and 18.6% in subjects with T2DM previously treated with basal-bolus insulin. In the T2DM population on a previous basal insulin regimen, a higher reporting of these episodes was noted in the insulin icodec group (6.1% vs 3.4% rate: 20.61 vs 8.51 episodes per 100 PYE). In the remaining T2DM trials "Nocturnal severe or clinically significant hypoglycaemic episodes" was reported in slightly higher proportions in the comparator groups.

In the **T1DM population** (complete 52-week trial of ONWARDS 6) the proportions of subjects reporting severe hypoglycaemic episodes were similar in the insulin icodec and the comparator (IDeg) groups (~4%). Severe nocturnal hypoglycaemic episodes were also reported similarly in the two treatment groups (~1.4%).

The proportions of subjects and the rate of reported severe or clinically significant hypoglycaemic episodes in the T1DM population were higher in the insulin icodec group compared to the IDeg treated group (52-week-data: 90.7% vs 85.6% and rate 1700.10 vs 916.07 episodes per 100 PYE; estimated rate ratio 1.80 [1.48; 2.18]). The proportion of subjects that reported ≥20 "Severe or clinically significant hypoglycaemic episodes" was higher in the insulin icodec group compared to the IDeg group (15% vs 6% [26-weeks data]). Nocturnal severe or clinically significant hypoglycaemic episodes were also reported at a higher proportion and with a higher rate among the insulin icodec treated subjects compared to the IDeg group (52-weeks data: 59.0% vs 47.9%; rate 289.85 vs 149.23 per 100 PYE; estimated rate ratio 1.89 [1.44; 2.48]).

In the phase 3a trials the median time to recovery from SMPG verified hypoglycaemic episodes in the insulin icodec group were longer (ONWARDS 1 and ONWARDS 2) or similar (ONWARDS 3-6) as compared to the daily basal insulin groups. Across all Phase 3 trials (both T1DM and T2DM) a larger proportion of the insulin icodec SMPG-verified clinically significant (level 2) hypoglycaemic episodes had a duration of >360 min (3%-9%) compared to daily basal insulin episodes (0-3%).

Injection site reactions

Across all trials in the Phase 3a pool (treatment/main-on-treatment phases) except ONWARDS 3, the frequencies of subjects reporting ISR were 0.3%-1.2% and without any difference compared to the comparator group. In the double blinded, double dummy performed in insulin naïve T2DM (ONWARDS 3) a higher frequency of ISR were reported in the insulin icodec group compared to IDeg group (8.5% vs 4.4%). Most (95%) of the events in both treatment groups across all Phase 3 a were mild and no event in either group was serious or severe. One case of lipodystrophy and no case of cutaneous amyloidosis was reported in the insulin icodec groups across the Phase 3a trials.

Hypersensitivity reaction

In the Phase 3a pool (treatment/main-on-treatment phases), ~4% of subjects reported hypersensitivity reactions in the insulin icodec and the comparator groups. The most reported PTs in the insulin icodec group were rash (0.6%) and eczema (0.5%). Hypersensitivity SAEs were reported by two subjects (0.1%) in the insulin icodec group and one subject in the comparator group. In the T1DM population a higher proportion of subjects reported hypersensitivity events compared to the T2DM population (8.3% vs ~3%) without any difference compared to the daily basal insulin group (8.6%). The most reported PTs in the T1DM population (ONWARDS 6) were in both treatment groups "Medical device site rash" (~2%). No serious hypersensitivity reactions were reported in the T1DM population.

Immunological events – antibody formation

In insulin-naïve T2DM subjects, 77%-82% of the subjects developed treatment-induced anti-insulin icodec antibodies (ADA). In subjects with T2DM previously treated with basal insulin or basal-bolus insulin lower proportions of subjects developed treatment-induced antibodies (54% and 41%, respectively). In the T1DM population 33% developed anti-insulin icodec antibodies and in 37% treatment with insulin icodec boosted already existing ADAs to increased titre levels. Most of the icodec antibody positive subjects also had cross-reacting antibodies towards human insulin.

Overall, no clinically relevant correlation between ADA titres and the efficacy parameters, "change of HbA1c from baseline to the end of treatment", "HbA1c at the end of treatment" or "higher weekly icodec dose (U/kg) during the last 2 weeks before end of treatment" was noted. Neither were any correlations between ADA titres and the safety parameters, "rate of severe (level 3) or clinically significant (level 2) hypoglycaemic episodes", "injection site reactions" or "hypersensitivity" noted.

Medication errors

In the Phase 3a pool (treatment/main-on-treatment phases), a medication error event was reported by 1.7% (40 events in 37 subjects) in the insulin icodec group and 1.4% (36 events in 31 subjects) in the daily basal insulin group. A cluster of these medication errors (n=25 of 40) concerned switching from daily basal insulin administration to once weekly administration with insulin icodec (ONWARDS 2, 4 and 6). This resulted in level 1 and level 2 related hypoglycaemic episodes.

Use in elderly

Overall, in the Phase 3a safety study pool (ONWARDS 1-6), 668 elderly subjects including 96 subjects ≥75 years <85 years and 4 subjects 85 years and above, were exposed to insulin icodec. Most of the elderly ≥75 years were insulin naïve subjects with T2DM (n=68). Three (3) subjects ≥75 years were included in the T1DM population. In the older age-group (≥75 years <85 years) a difference is noted between the two treatment groups regarding the proportions of subjects with AEs within the SOC cardiac disorders (insulin icodec: 14.3% [n=14] vs daily insulin: 5.8% [n=4]) and the SOC vascular disorders (insulin icodec: 19.3% [n=18] vs daily insulin: 10.2% [n=8]). On a PT level the frequencies of diarrhoea events differed between the two groups (insulin icodec: 11% [n=11] vs daily insulin: 1% [n=1]).

3.5. Uncertainties and limitations about unfavourable effects

The potential risk of prolonged hypoglycaemia is requested to be monitored in future PSURs.

"Medication errors during switch from daily basal insulin" and "medication errors due to potential mix-up" have been included in the RMP as important potential risks.

3.6. Effects Table

The Efficacy table below includes endpoints adjusted for multiplicity.

Table 74. Effects table for Awiqli

Effect	Short Description	Unit	Insulin icodec	Daily basal insulin	Uncertainties/ Strength of evidence
Favourable Effects					
T2DM population					
HbA1c	Mean change in HbA1c from baseline	%	-1.55 [1] -1.55 [2] -0.93 [3] -1.57 [4] -1.16 [5] -1.68 [6] -0.47 [7] -0.37 [8]	-1.35 [1] -1.44 [2] -0.71 [3] -1.36 [4] -1.18 [5] -1.31 [6] -0.51 [7] -0.54 [8]	**Strengths of evidence related to benefits** • Treatment with insulin icodec provided statistically superior HbA1c reduction in T2DM insulin-naive subjects and basal only subjects; insulin icodec provided non-inferior HbA1c reduction in T2DM basal-bolus subjects and T1DM basal-bolus subjects. • In ONWARDS 1, TIR from week 48-52 for insulin icodec was confirmed to be statistically superior compared to insulin glargine. **Limitations and uncertainties related to benefits** • Patients with hepatic impairment were excluded from the studies.
Time in euglycaemic range (TIR) 3.9-10.0 mmol/L	Observed mean for last 4 weeks of treatment (week 48-52)	%	71.94 [1]	66.90 [1]	• Limited data are available for people ≥75 years of age or older (<5% trial population).
T1DM population					
HbA1c	Mean change in HbA1c from baseline	%	-0.47 [7] -0.37 [8]	-0.51 [7] -0.54 [8]	**Strengths of evidence related to benefits** • Treatment with insulin icodec provided non-inferior HbA1c reduction inT1DM basal-bolus subjects up to 26 weeks. **Limitations and uncertainties related to benefits** •Data up to 52 weeks of treatment with insulin icodec indicate a somewhat lower glucose reducing effect compared to insulin degludec (HbA1c treatment difference 0.17, 95% CI 0.02; 0.31).

Effect	Short Description	Unit	Insulin icodec	Daily basal insulin	Uncertainties/ Strength of evidence
Unfavourable Effects					
Hypoglycaemia T2DM **Insulin naïve up to 52 weeks**[1,4,6] Severe (level 3) or clinically significant (level 2) hypoglycaemic episodes Incidence (%) Rate (per 100 PYE)			8.9-11.8 18.56-31.01	6.1-10.6 14.45-16.08	
Hypoglycaemia T2DM **Insulin naïve week 78**[2] Severe (level 3) or clinically significant (level 2) hypoglycaemic episodes Incidence (%) Rate (per 100 PYE)			12.4 29.65	14.2 15.78	
Hypoglycaemia T2DM **Previous basal insulin treated**[3] Severe (level 3) or clinically significant (level 2) hypoglycaemic episodes Incidence (%) Rate (per 100 PYE)			14.1 72.29	7.2 27.49	
Hypoglycaemia T2DM **Previous basal and bolus treated**[5] Severe (level 3) or clinically significant (level 2) hypoglycaemic episodes Incidence (%) Rate (per 100 PYE)			51.1 564.05	55.7 562.36	
Hypoglycaemia T1DM 26 weeks [7] Severe (level 3) or clinically significant (level 2) hypoglycaemic episodes Incidence (%) Rate (per 100 PYE)			85.2 1992.86	76.2 1037.33	Estimated rate ratio at week 26: 1.89 [1.54;2.33]

Effect	Short Description	Unit	Insulin icodec	Daily basal insulin	Uncertainties/ Strength of evidence
Hypoglycaemia T1DM 52 weeks[8] Severe (level 3) or clinically significant (level 2) hypoglycaemic episodes Incidence (%) Rate (per 100 PYE)			90.7 1700.10	85.6 906.07	Estimated rate ratio at week 52: 1.80 [1.48; 2.18].
Injection site reactions Pooled Phase 3a data[9] Incidence (%) Rate per 100 PYE			1.9 6.04	1.7 3.97	95% of the ISR events were mild. No severe or serious cases were reported.
Injection site reactions Insulin naïve T2DM (double blinded) [4] Incidence (%) Rate per 100 PYE			8.5 36.28	4.4 12.86	97% of the ISR in the insulin icodec group and 100% in the comparator group were mild. No severe or serious cases were reported.
Hypersensitivity reactions Pooled Phase 3a data[9] Incidence (%) Rate per 100 PYE			3.8 6.20	4.4 7.41	86% were reported as mild and 0.1% of the events were reported as serious. The most common PT were rash (0.6%) and eczema (0.5%)
Development of treatment induced insulin-icodec antibodies Incidences (%)		82.1[10] 54.2[3] 41.0[5] 32.6[8]		unk unk unk unk	Neutralising antibodies has not been evaluated in the phase 3 trials.

Notes: (**1**) ONWARDS 1 (week 52), (**2**) ONWARDS 1 (week 78), (**3**) ONWARDS 2, (**4**) ONWARDS 3, (**5**) ONWARDS 4, (**6**) ONWARDS 5, (**7**) ONWARDS 6 (26 weeks), (**8**) ONWARDS 6 (week 52), (**9**) pooled Phase 3a data (ONWARDS 1-6); (**10**) phase 2 trial 4383 performed in insulin naïve T2DM.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Diabetes is a chronic and progressive metabolic disorder. T1DM and advanced T2DM with decreased beta-cell function require insulin replacement therapy. When treating hyperglycaemia, there is always a balance between the goal of achieving good metabolic control and the risk of hypoglycaemia. Due to differences in pathogenesis, the risk of hypoglycaemia differs between T1DM and T2DM as well as between individuals, depending on genetic and lifestyle factors. Despite technological advances with regards to insulin administration and blood glucose monitoring, compliance could be a challenge for some individuals. The introduction of a basal insulin that needs to be administered less often than once daily may offer an

improvement for some individuals; however, the prolonged effect may also increase the risk of hypoglycaemia and hamper the possibility to adjust insulin doses. This may not be a problem in well controlled patients but may be an issue in some patient groups (e.g. patients with hypoglycaemic unawareness or recurrent severe hypoglycaemic episodes).

For the evaluation of efficacy, the primary aim of the pivotal studies was to show that treatment with insulin icodec was non-inferior to daily basal insulin with respect to reduction of HbA1c. This goal was met in all pivotal studies in patients with T2DM, including the studies with a 52-week duration. In addition, statistical superiority as compared to comparators was demonstrated in insulin naïve and basal switch T2DM patients. It is considered that a relevant glucose lowering effect has been documented in patients with T2DM up to a treatment duration of 52 weeks.

With respect to patients with T1DM, non-inferiority compared to once daily insulin was shown at week 26 with respect to change in HbA1c. However, there was a trend towards reduced efficacy over time considering that data up to 52 weeks of treatment with insulin icodec indicate a somewhat lower glucose reducing effect as compared to insulin degludec at the end of the study.

The most important unfavourable effect is the risk of hypoglycaemic episodes, both in T1DM and T2DM. In patients with type 2 diabetes, the incidence rate of level 2 or level 3 hypoglycaemic episodes was higher for insulin icodec compared to daily basal insulin in 4 out of 5 studies. However, the proportion of subjects with severe (level 3) hypoglycaemic episodes, including severe nocturnal hypoglycaemia, was low and there was no difference compared to daily basal insulin.

In T1DM patients, the frequencies and rates of hypoglycaemic episodes, including severe and nocturnal level 2 and 3 episodes, were higher compared to IDeg. It is somewhat reassuring that the risk of hypoglycaemia did not increase over time during the complete trial (from baseline to 52 weeks) and time below range was similar compared to IDeg. However, considering that patients with T1DM still have to take daily bolus insulin injections, the benefit of weekly dosing may be limited. Further, long-acting insulin may not be optimal in T1DM patients without endogenous insulin production.

3.7.2. Balance of benefits and risks

In patients with **T2DM**, a relevant glucose-lowering effect has been documented for a treatment duration of 52 weeks. Long-term safety and tolerability have been characterised up to 78 weeks of treatment (insulin naïve subjects). There is a moderately increased risk of hypoglycaemia as compared to daily basal insulin. The rate of hypoglycaemic episodes did not increase over time and there were few episodes of severe hypoglycaemia with no differences between treatment groups. This risk is considered manageable with adequate routine risk minimisation and is outweighed by the benefits associated with a weekly administration resulting in fewer injections.

The benefit/risk balance of insulin icodec in patients with **T1DM** is more uncertain. The glucose-lowering effect in T1DM patients is considered of clinical relevance even if it is a concern that the effect seems to diminish over time, but the benefit of a weekly dosing is less obvious and the risk of all categories of hypoglycaemia is increased as compared to IDeg.

However, there may be some patients with T1DM that benefit from a weekly posology and for whom this benefit outweighs the risk. It is not considered possible to identify these patients by the submitted data. It will rather be a decision for the prescriber, and a **warning** has been included in the SmPC to the effect that insulin icodec should only be used in patients with T1DM for which a clear benefit of a once weekly

administration is expected. Further, the higher frequency and rate of hypoglycaemic events compared to daily basal insulin for T1DM patients and the seemingly reduced efficacy over time for insulin icodec in T1DM patients is reflected inf the SmPC.

3.7.3. Additional considerations on the benefit-risk balance

Additional risk minimisation activities in the form of a patient/carer's guide have been agreed in order to manage the safety concerns of "Medication errors due to mix-up" and "Medication errors during switch from daily basal insulin".

3.8. Conclusions

The overall benefit/risk balance of Awiqli is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Awiqli is not similar to Amglidia within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Awiqli is favourable in the following indication(s):

Treatment of diabetes mellitus in adults

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and

interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall provide an education guide prior to launch targeting to all patients who will be treated with Awiqli. The educational guide is aimed at increasing awareness about the introduction of the one-time additional dose and describing the key points of use to minimise the risk of medication errors due to mix-up and during switch from daily basal insulin to once-weekly Awiqli in diabetes mellitus.

The educational guide contains information and instructions related to the following key elements:
Medication errors due to switch from daily basal insulin:
- Information on use of one-time additional dose when initiating Awiqli.
- Key differences between first dose and second dose of Awiqli.

Medication errors due to potential mix-up:
- Instructions to strictly adhere to weekly dosing regimen as prescribed by the healthcare provider.
- Instructions to always check the insulin label before each injection to avoid accidental mix-ups between Awiqli and other products.
- Instructions to always use the dose recommended by the healthcare provider.
- Instructions to always use the dose counter and the dose pointer to select the dose. Do not count the pen clicks to select the dose.
- Instructions to check how many units were selected before injecting the weekly insulin.
- Instructions to patients who are blind or have poor vision to always get help/assistance from another person who has good vision and is trained in using the insulin device.

The MAH shall agree on the final content of the education guide together with a communication plan, with the National Competent Authority in each Member State prior to distribution of the educational guide in the Member State.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that Insulin icodec is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.