18 September 2025
EMA/CHMP/290792/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kyinsu

International non-proprietary name: insulin icodec / semaglutide

Procedure No. EMEA/H/C/006279/0000

Note

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

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List of abbreviations

EMA	European Medicines Agency
EC	European Commission
EU	European Union
GLP	1 glucagon like peptide 1
GLP	1 RA glucagón like peptide 1 receptor agonist
CV	cardiovascular
T2D	type 2 diabetes
ADA	American Diabetes Association
EASD	European Association for the Study of Diabetes
SGLT2i	sodium glucose cotransporter 2 inhibitors
CVD	cardiovascular disease
CKD	chronic kidney disease
COMBINE	refers jointly to project NN1535 phase 3 studies
FDR	fixed dose regiment
GMP	good manufacturing practice
GLP	good laboratory practice
GCP	good clinical practice
OECD	Organisation for Economic Co operation and Development
WCB	working cell banks
MCB	master cell bank
ALP	Achromobacter Lyticus Protease
PQ	performance qualification
ICC	initial cell clone
EPC	end of production cell
LEC	late extended culture
IPCs	in process controls
PV	process validation
PPQ	process performance qualification
LC	MS/MS liquid chromatography tandem mass spectrometry
IEF	capillary isolectric focusing
CD	circular dichroism
ATR FTIR	attenuated total reflection Fourier transform infrared spectroscopy
RP	UHPLC phase ultra high performance liquid chromatography
UV	ultraviolet
RP	UHPLC reverse phase ultra high performance liquid chromatography
SE	UHPLC size exclusion ultra high performance liquid chromatography
TAMC	Total Aerobic Microbial Count
TYMC	Total Yeast and Mould Count
HCP	host cell proteins
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
PRM	primary reference material
SRM	secondary reference material
HMWP	High molecular weight proteins
PC	process characterisation
PJ	process justification
MS	mass spectrometry
DSC	differential scanning calorimetry
SAXS	small angle X ray scattering
NMR	nuclear magnetic resonance
CG	MALS Composition gradient multiangle light scattering
GSPRs	General safety and Performance Requirements
CQAs	critical quality attributes
IR absorbance	infrared absorbance
PDE	permitted daily exposure
WFI	water for injection
CFU	colony forming unit
PDE limits	permissible daily exposure limits
TSE	transmissible spongiform encephalopathy
IR	insulin receptor
PK	pharmacokinetics

MAA	marketing authorisation application
LOCI	luminescent oxygen channelling immunoassay
ADA	antidrug antibody
RIA	radioimmunoassay
LOCI	Luminescence Oxygen Channelling Immunoassay
TK	toxicokinetic
DRF	dose range finding
EPAR	European Public Assessment Report
NOAEL	No Observed Adverse Effect Level
DART studies	Developmental and Reproductive Toxicology Studies
ERA	environmental risk assessment
U	units
mg	milligrams
kg	kilograms
EFD study	embryo fetal development study
RMP	risk management plan
IgE	Immunoglobulin E
NONMEM	nonlinear mixed effects modelling tool
PBPK	physiologically based pharmacokinetic
Kd	dissociation constant
kDa	kilo Daltons
AUC	total plasma exposure
PopPK	population pharmacokinetics
PBPK	physiology based pharmacokinetic
AE	adverse events
L	Liter
Mmol	millimole
BMI	body mass index
FPG	fasting plasma glucose
FAS	full analysis set
ANCOVA	analysed using an analysis of covariance
ePID	electronic patient interactive devices
T2DM	type II diabetes mellitus
TIR	Time in range
TBR	Time below range
PY	patient names
PYE	patient years of exposure
MedRA	Medical Dictionary for Regulatory Activities
GI	gastrointestinal
TBL	total bilirubin
SAE	serious adverse reaction
AESI	Adverse Event of Special Interest
PTs	preferred terms
SOC	system organ class
GIAE	Gastrointestinal adverse events
CVOT	cardiovascular outcome trial
MEs	medication errors
s.c.	subcutaneous
PhV	pharmacovigilance
aRMM	additional risk minimisation measure

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novo Nordisk A/S submitted on 7 October 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Kyinsu, 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 adults with type 2 diabetes mellitus insufficiently controlled on basal insulin or glucagon-like peptide 1 (GLP-1) receptor agonists as an adjunct to diet and exercise in addition to oral antidiabetic medicinal products. For study results with respect to combinations, effects on glycaemic control, and the populations studied, see sections 4.4, 4.5 and 5.1.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 10(b) of Directive 2001/83/EC – relating to applications for fixed combination products.

The application submitted is for a fixed combination medicinal product.

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0312/2021 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 not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

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
25 February 2021	EMA/SA/0000050205	Rosalia Ruano Camps and Clemens Mittmann
23 February 2023	EMA/SA/0000114169	Hrefna Gudmundsdottir and Armin Koch
14 September 2023	EMA/SA/0000134324	Elmer Schabel and Martin Walter

The applicant received scientific advice on three occasions, as mentioned in the table above for the

development of Kyinsu for treatment of type 2 diabetes mellitus. The scientific advice pertained to the following non-clinical and clinical aspects:

- Applicability of non-clinical data from development of mono-components to support initiation of phase 3 programme
- Planned clinical pharmacology programme; proposed Phase 3 programme to support indication 'for treatment of T2DM': cardiovascular (CV) risk assessment, patient exposure, dosing and titration algorithm, treatment duration, endpoints, safety database, strategy to investigate anti-drug antibody development, testing to demonstrate superiority in terms of hypoglycaemia risk, estimand strategy, handling of missing data, definition of trial periods and non-inferiority margin; extrapolation of the results of the clinical comparability study of semaglutide (approved) vs. semaglutide (new) to insulin icodec/semaglutide (Kyinsu) due to a manufacturing change in the semaglutide finished product

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: Kristina Nadrah

The application was received by the EMA on	7 October 2024
The procedure started on	31 October 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 January 2025
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	3 February 2025
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 February 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 May 2025
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	30 June 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	24 July 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	14 August 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	17 July 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting	18 September 2025

a marketing authorisation to Kyinsu on	

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Kyinsu is intended to be used in the following indication:

"Treatment of adults with type 2 diabetes mellitus insufficiently controlled on basal insulin or glucagon-like peptide 1 (GLP-1) receptor agonists as an adjunct to diet and exercise in addition to oral antidiabetic medicinal products. For study results with respect to combinations, effects on glycaemic control, and the populations studied, see sections 4.4, 4.5 and 5.1."

Kyinsu is a fixed dose combination for weekly subcutaneous administration of insulin icodec and semaglutide. Insulin icodec is a once-weekly basal insulin and semaglutide is a once-weekly GLP-1 agonist, both approved for treatment of adults with type 2 diabetes.

2.1.2. Epidemiology and risk factors

Type 2 diabetes mellitus is characterised by insulin resistance, impaired insulin secretion, and increased hepatic glucose output due to glucagon dysregulation resulting in chronic 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. Estimates were not separated by diabetes type; however, the overwhelming majority of people with diabetes in 2021 were type 2 diabetes and the increases to 2045 are projected to be mainly type 2 diabetes (IDF 2021).

2.1.3. Aetiology and pathogenesis

The pathogenesis of T2D seems to be heterogeneous, involving environmental, lifestyle, and genetic factors leading to chronic hyperglycaemia caused by peripheral tissue insulin resistance, impaired insulin secretion due to abnormal beta-cell function and abnormal glucose metabolism in the liver. The majority of people with T2D do not meet the recommended glycaemic targets required to reduce long term micro- and macrovascular complications. The microvascular disorders associated with diabetes are retinopathy, nephropathy and neuropathy and the macrovascular complications of diabetes are cardiovascular, cerebrovascular, and peripheral vascular disease.

2.1.4. Clinical presentation, 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

The consensus statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) for treatment of T2D emphasises individualised care and a holistic

approach encompassing lifestyle changes as well as pharmacotherapy, while balancing the risks and benefits of each intervention. The person-centred diabetes care should be achieved by managing glycaemic control, weight, cardiovascular risk factors, and the need for cardiorenal protection, with equal importance. Metformin has for many years been the recommended first-line glucose-lowering therapy for the management of type 2 diabetes. However, there is ongoing acceptance that other approaches may be appropriate. The benefits of GLP-1 RA and SGLT2i for cardiovascular and renal outcomes have been found to be independent of metformin use, and thus these agents should be considered in people with established or high risk of CVD, HF, or CKD, independent of metformin use. Due to the progressive nature of the disease, many people with T2D will in addition to lifestyle modification and treatment with one or more oral antidiabetic agents require the addition of one or more injectable agents, including insulin and/or GLP-1 RA. Treatment intensification increases the complexity and the burden, which are known to negatively impact persistence and adherence. Furthermore, insulin treatment is associated with increased risk of hypoglycaemia and weight gain, which also contributes to poor adherence and therapeutic inertia, i.e., failure to timely initiate or intensify treatment when treatment goals are not met. GLP-1 RA reduces body weight and improves glycaemic control. The combination of a basal insulin analogue and GLP-1 RA may be a way to reduce the burden and complexity of treatment (ADA/EASD 2022).

2.2. About the product

The fixed-ratio combination of insulin icodec (700 U/mL) and semaglutide (2 mg/mL) is indicated for the treatment of type 2 diabetes mellitus insufficiently controlled on basal insulin or GLP-1 agonists to improve glycaemic control as an adjunct to diet and exercise in addition to oral antidiabetic medicinal products.

The fixed-ratio combination is intended to be administered subcutaneously once weekly at any time of the day.

The recommended starting dose of Kyinsu is 40 dose steps (40 units of insulin icodec and 0.114 mg of semaglutide). The dose is titrated to target. The recommendation is to not exceed 350 dose steps weekly (350 U insulin icodec and 1 mg semaglutide).

2.3. The development programme/compliance with guidance/scientific advice

Development programme

The development program includes two clinical pharmacological studies and three phase 3a confirmatory efficacy and safety studies (COMBINE studies). The phase 3a studies included a total of 2,653 patients. The three studies were of 52 weeks duration.

The participants in the COMBINE studies were people with T2D inadequately controlled on daily basal insulin or on GLP-1 RA, respectively. Patients with mild to moderate renal impairment were included in the studies. All three studies were open-label, and both treatment arms were with or without OADs.

COMBINE 1 and 3 evaluated the once weekly fixed dose regiment (FRC) of insulin icodec/semaglutide in patients inadequately controlled on daily basal insulin therapy. Once weekly insulin icodec was used as the comparator in COMBINE 1 and daily insulin glargine in combination with insulin aspart was used as the comparator in COMBINE 3. COMBINE 2 was designed to evaluate the FRC in insulin naïve patients inadequately controlled with GLP-1 RA. Semaglutide was used as a comparator.

The development program is in all essentials in line with the Guideline on clinical development of fixed combination medicinal products (EMA/CHMP/158268/2017). The design of COMBINE 1 and 2 are both similar to an 'add-on indication', as outlined in the FRC guideline. COMBINE 1 was designed to support the use of the FRC in patients insufficiently controlled on basal insulin by adding a GLP-1 agonist. COMBINE 2 was designed to support the use of the FRC in patients insufficiently controlled on GLP-1 RA therapy with the addition of basal insulin. In COMBINE 3, a fixed combined treatment of basal insulin and GLP-1 RA was compared with a basal-bolus insulin regimen. Given that GLP-1RAs enhances the endogenous post-prandial insulin release, the possibility of adding a GLP-1 RA as an alternative to prandial bolus insulin has been discussed in current diabetes guidelines. Therefore, this study design was considered to be of interest.

Compliance with CHMP Guidance

A scientific advice has been received from the CHMP (EMA/SA/0000050205) in February 2021 on non-clinical and clinical aspects of the development of a fixed combination of insulin icodec/semaglutide. The scientific advice pertained to the following clinical aspects: indication, study design, choice of estimand and handling of missing data. In general, given scientific advice regarding clinical aspects was followed and implemented in the clinical program with some exceptions:

- The applicant has chosen an open-label design due to differences in posology of FRC insulin icodec/semaglutide versus the comparators (starting dose titration scheme). The CHMP advice did not consider an open-label design to be appropriate, and the applicant was encouraged to mask the studies.
- With regard to the primary non-inferiority hypothesis in study 4593, the applicant was advised by the CHMP to approach the intercurrent events with a hypothetical strategy. This advice was not followed.
- The CHMP advice expressed the disadvantage of only one fixed dose ratio of semaglutide/icodec developed. Adjusting the dose to the insulin icodec requirement (treat to target) may not result in the optimal dose of semaglutide for every patient.

2.4. General comments on compliance with GMP, GLP, GCP

Good manufacturing practice (GMP): The EMA Compliance and Inspection Service has reviewed the manufacturer information in the context of this application and determined that no pre-approval inspections to verify GMP compliance are deemed necessary. All relevant sites have valid manufacturing authorisations or valid GMP certificates as appropriate. In conclusion, GMP compliance has been adequately confirmed.

Good laboratory practice (GLP): The nonclinical studies (i.e. a 13-week repeat-dose toxicology study in rats and a local tolerance study in minipigs) to support this FDC application were conducted in accordance with GLP regulations and were conducted in an Organisation for Economic Co-operation and Development (OECD) member country or in a country part of the OECD Mutual Acceptance of Data process.

Good clinical practice (GCP): No need for a GCP inspection of the clinical trials included in this dossier has been identified.

2.5. Quality aspects

2.5.1. Introduction

Kyinsu is a fixed dose combination of insulin icodec and semaglutide, both produced in *Saccharomyces cerevisiae* by recombinant DNA technology. They are known active substances contained in the centrally authorised medicinal products:

- Awiqli (EMEA/H/C/005978) for insulin icodec (same marketing authorisation holder);

- Ozempic (EMEA/H/C/004174) and Wegovy (EMEA/H/C/005422) for semaglutide (same marketing authorisation holder).

The finished product is formulated with zinc acetate, glycerol, phenol, metacresol, sodium chloride, sodium hydroxide, hydrochloric acid and water for injections.

Kyinsu is presented as a solution for subcutaneous injection in a cartridge which is integrated into a multi-dose pre-filled pen referred to as PDS290 or FlexTouch which is used in other centrally authorised medicinal products from the same applicant/marketing authorisation holder.

A cartridge contains:

- 300 units of insulin icodec and 0.86 mg of semaglutide in 0.43 mL solution;

- Or 700 units of insulin icodec and 2 mg of semaglutide in 1 mL solution;

- Or 1 050 units of insulin icodec and 3 mg of semaglutide in 1.5 mL solution.

1 mL solution contains 700 units of insulin icodec and 2 mg of semaglutide, corresponding to a strength of (700 units + 2 mg)/mL.

For each configuration, the pre-filled pen is presented without staked needle (provided separately) or is co-packaged with 6 or 9 disposable NovoFine Plus needles.

2.5.2. Active substance

2.5.2.1. Insulin icodec

General information

Insulin icodec is an analogue of insulin human where Thr^{B30} has been omitted, Tyr^{A14} has been substituted with Glu, and Tyr^{B16} and Phe^{B25} have been substituted with His. A C20 fatty acid sidechain derivative is added to the peptide backbone via the amino group in the side chain at Lys^{B29}. The predicted molecular weight (MW) is 6380 Da. Insulin icodec binds to and activates the human insulin receptor.

Full Module 3 quality documentation for the insulin icodec active substance is included with this application. The quality documentation for insulin icodec active substance used for Kyinsu finished product shares many insulin icodec active substance documents from Awiqli.

Manufacture, process controls and characterisation

Manufacturers

The manufacturer of the active substance is Novo Nordisk A/S, Kalundborg, Denmark. The sites for Master Cell Bank (MCB) storage, WCB storage and quality control are listed. All sites involved in manufacture and control of the active substance operate in accordance with EU GMP.

Description of manufacturing process and process controls

Insulin icodec is manufactured in *Saccharomyces 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 process are depicted.

A brief outline of the overall process is shown and separate flow charts for each of the four process parts, including operational parameters and in-process tests are provided. This is acknowledged.

The applicant defines the propagation and fermentation process as one step. The main purpose of 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. The purification process is divided into 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 to LysB29 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 are provided.

The manufacturing steps are the same as for the approved insulin icodec 700 U/mL, except for The revised description is found acceptable. A batch size of insulin icodec in incoming material is possible in the current equipment.

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. This is supported by data from stability studies performed at accelerated conditions.

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.

Control of materials

The cell bank is the same as for Awiqli. Section S.2.3 is identical but some additional supportive stability data has been added.

Source, history and generation of cell substrate

The origin of the parental cell and the initial cell clone (ICC) strain is described. The strain with the insulin icodec precursor expression plasmid and the expression construct with the gene of interest and how it is regulated has been described in sufficient detail. All raw materials used during transformation, selection and preservation of the ICC strain were of certified non-animal origin. This is endorsed.

Cell bank system

A two-tiered system of MCB and WCB is used. The manufacture and characterisation of the cell banks are adequately described. The genetic and phenotypic stability of the expression system has been confirmed for the MCB, WCB, end-of-production cell (EPC) and late extended culture (LEC).

The cell bank characterisation consisted of, microbial purity, strain identity, sequencing, viability, plasmid rearrangement, copy number, frequency and phenotype. Cell bank stability is carried out on a regular basis. The cells are stored at two separate sites at -80°C and regularly monitored for stability. This is acceptable.

A protocol for establishment of working cell banks has been submitted with media and reagents, in-process controls and characterisation according to specification, also tests like plasmid rearrangement, copy number and frequency is performed, this is acceptable.

Media and solutions and control of raw materials

Raw materials used for media and solutions are listed, for purification, recovery and propagation and fermentation. They are all stated to be of non-animal or human origin. For most parts they are pharmacopeial, type of test, method of analysis and acceptance criteria are shown. Media and solutions used in purification, recovery and propagation and fermentation are quantitatively described. The information provided is found acceptable.

Acylating agent

The acylating agent is manufactured over synthetic steps. The acylating agent is in the insulin icodec manufacturing process. An overview of the route of synthesis for acylating agent was provided. Specifications for the proposed starting materials have been sufficiently justified by presenting results from purging studies and satisfactory batch analysis data.

Control of critical steps and intermediates

The control strategy for the insulin icodec active substance manufacturing process is described in this section. The applicant uses the term in-process controls (IPCs) 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. Criticality assignment is further addressed and assessed in sections 3.2.S.2.6 and 3.2.S.4.5.

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

Furthermore, stability studies for the intermediates are presented.

The differences in section 3.2.S.2.4 - Retest Period for the acylating Agent as compared to the approved product Awiqli concern inclusion of additional long-term stability study data and a request for extension of the shelf-life.

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. The term Process Validation used by the applicant is equivalent to Process Performance Qualification (PPQ). 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.

Since the manufacture of 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

Insulin icodec is currently intended for two different finished products – Awiqli and Kyinsu. The difference is adequately defined and justified. Throughout development, three active substance processes have been used. The main changes between processes are described, and comparability between active substance batches from Process A to Process C and optimised Process C has been demonstrated. It is noted that different statistical tests are used for the three methods to evaluate bioactivity. Even though the statistical approach is not justified, data for all batches are presented and batches manufactured by the different processes are found comparable.

The process justification studies are at large the same as for the approved product. This is found acceptable.

Acylating agent

The differences in justification of specification for the acylating agent as compared to the approved product Awiqli (highlighted in blue above) concern some results from the reduction studies made, which have been recalculated due to the lower maximum daily dose of insulin icodec for Kyinsu. These minor changes, which correspond to an increased safety margin for the impurities concerned, do not affect the assessment of this dossier section.

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.

Characterisation

The batches used for characterisation of insulin icodec are the same as those used for characterisation of the approved Awiqli. This is found acceptable since the manufacturing processes are similar and comparability of active substance has been demonstrated.

Primary sequence was characterised by high resolution liquid chromatography-mass spectrometry. The masses of intact insulin icodec and the reduced chains agreed with the calculated masses. Primary sequence was confirmed by liquid chromatography tandem mass spectrometry (LC-MS/MS) of the reduced A- and B-chain. Representative MS/MS-data is included in the dossier and the position of the sidechain at LysB29 is confirmed. Furthermore, the disulphide linkage was confirmed by non-reduced Glu-C peptide mapping. In conclusion, the results from the LC-MS/MS and peptide mapping experiments confirm the expected peptide sequence, the position of the sidechain and the presence of disulphide bridges.

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Bioactivity was evaluated using the Insulin pAkt (phosphorylated protein kinase B) reverse phase bioassay. 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 pAkt bioassay. The choice of the pAkt 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 further supports the biological functionality of insulin icodec.

The correlation between the insulin icodec Bioactivity as determined by the Insulin pAkt cell-based bioactivity assay and the content of the main peak and related substances determined by reverse phase ultra high-performance liquid chromatography (RP-UHPLC) 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 as observed by reverse phase and size exclusion ultra-high performance liquid chromatography (RP-UHPLC and SE-UHPLC) are described. The substances/impurities were identified by mass spectrometry and peptide mapping LC-MS/MS. *In vitro* bioactivity of the components purified for characterisation was determined relative to insulin icodec using the Insulin pAkt bioassay. The characterisation of product-related substances and impurities is found extensive and the correlation between the peaks observed in the RP-UHPLC chromatogram and the product-related substances and impurities is described.

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.

The differences in section 3.2.S.3.2 – Impurities in acylating agent as compared to the approved product (highlighted in blue above) concern some results from the reduction studies made, which have been recalculated due to the lower maximum daily dose of insulin icodec for Kyinsu. These minor changes, which corresponds to an increased safety margin for the impurities concerned, do not affect the assessment of this dossier section.

The information presented regarding the origin and fate of acylating agent related impurities (acylating and non-acylating), process related impurities, and theoretical related impurities are considered acceptable. The control of these impurities is also considered acceptable.

Specification, analytical procedures, reference standards, batch analysis, and container closure

Specifications

Active substance specification for insulin icodec, including methods to evaluate identity, product-related substances and impurities, content, high molecular weight proteins, bioactivity, residual protease activity, loss on drying, bacterial endotoxins, appearance, host cell proteins, Total Aerobic Microbial Count (TAMC) and Total Yeast and Mould Count (TYMC). The specification is the same as that for the approved insulin icodec 700 U/mL product, except for that Residual Protease Activity which has been added and for the Bioactivity specification which limit is different. For compendial methods, references are made to the Ph. Eur. For non-compendial method, the type of method used for analysis is stated and in-house method numbers are defined.

The level of host cell proteins (HCP) is tested in-process. This is found acceptable.

Residual protease activity may be present in trace amount in insulin icodec. Insulin icodec is stable towards proteolytic degradation and not impacted as demonstrated in stability studies. However, in Kyinsu, insulin icodec is mixed with the active substance semaglutide which is sensitive towards protease degradation. The acceptance criterion for bioactivity is found acceptable. In conclusion, the active substance specification is found acceptable.

Analytical procedures and reference standards

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 is submitted. 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 details, and chromatograms are shown, where applicable. System suitability tests and acceptance criteria are adequately described. In conclusion, the method descriptions are found acceptable.

Validation reports for all in-house methods, except for the appearance method, are provided. 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 and results obtained for individual samples. Chromatograms are shown for the chromatographic methods. Relevant validation characteristics have been evaluated. In conclusion, the analytical procedures have been acceptably validated according to ICH Q2(R1).

Batch analyses

Results from batch analyses of insulin icodec active substance manufactured during development are presented. In total, batch analyses data from 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 active substance.

Reference standard

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 insulin icodec active substance, produced by Process B. The selected batch is considered acceptable. A provisional shelf-life is proposed both for the 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 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.

Three former PRM batches and one former SRM batch 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.

Container closure system

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 specification is presented for the inner bag, and batches of the inner bag are confirmed to comply with the specification.

Stability

All documents submitted in Section 3.2.S.7 are new for Kyinsu as compared to the already approved Awiqli.

The stability program presented for insulin icodec active substance involves long-term and accelerated stability studies. Three batches manufactured for phase 3 clinical trials are referred to as the primary batches. This is found acceptable, since comparability between these batches and the commercial batches has been demonstrated. Four batches manufactured by the commercial process, i.e. the three PV batches and one additional batch, referred to as supportive batch, are also included in the study. All batches are stored in containers representative of those used for commercial batches.

Long-term stability data is provided. In addition, accelerated stability studies were performed. In conclusion, no change over time is noted during accelerated conditions.

Based on the obtained stability data, the proposed shelf-life, 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. 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 levels were influenced by extreme conditions and that the RP-HPLC and SE-UHPLC methods 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 program. 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.

2.5.2.2. Semaglutide

General information

Semaglutide is a long-acting analogue of human glucagon like-1 peptide i.e. an Aib^{8}, Arg^{34}-GLP-1(7-37) analogue substituted on the ε-amino group of the lysine residue in position 26 with an (S)-22,40-dicarboxy-10,19,24-trioxo-3,6,12,15-tetraoxa-9,18,23-triazatetracontan-1-oyl side chain. The side chain consists of two 8-amino-3,6-dioxaoctanoic acid (ADO) spacers, one γ-glutamic acid (Glu) spacer, and a fatty diacid (1,18-octadecanedioic acid). Semaglutide is produced using recombinant DNA technology in yeast (*Saccharomyces cerevisiae*) and chemical modification.

Full Module 3 quality documentation for semaglutide active substance is included in the Kyinsu dossier. The applicant states that the Module 3 documentation for semaglutide is identical to Ozempic and Wegovy. Each section of the CTD module 3.2.S is summarised below. In conclusion, the information provided on semaglutide active substance in Sections 3.2.S.1 – 3.2.S.7 is found acceptable also for Kyinsu.

Manufacture, process controls and characterisation

Manufacturers

The manufacturer of the active substance is Novo Nordisk A/S, Kalundborg, Denmark. The sites for MSB storage, WCB storage and quality control are listed. The information on active substance manufacturing sites is found acceptable. All sites involved in manufacture and control of the active substance operate in accordance with EU GMP.

Description of manufacturing process

Semaglutide is manufactured in *Saccharomyces cerevisiae* cells. The manufacturing process of the semaglutide active substance consists of a fermentation process in yeast cells, a recovery process, a purification process for semaglutide precursor, a modification process, and the purification of semaglutide. All the manufacturing steps are adequately described and explained.

The fermentation process is run as a continuous process, in which the semaglutide precursor is produced continuously in the fermenter, and culture broth is withdrawn continuously. The harvested culture broth is split into several batches at delivery to recovery. The subsequent steps in recovery and purification (including modification) are all performed as batch processes, and unique batch numbers are assigned at designated steps

In addition to the active substance itself, three other intermediates are isolated and storage conditions and shelf life are defined.

The final active substance is dried and placed in containers and stored at -20°C. The active substance is stored in the purification plant and shipped from this site to the site for formulation and filling within Denmark. The active substance is transferred in thermo transportation boxes, and the time of transportation is logged. The shipping of the active substance is handled according to written procedures.

Overall, the description of the manufacturing process is found acceptable. Storage, shipping and batch numbering is adequately described. The active substance manufacturing process is identical to that of the already approved products Ozempic and Wegovy.

Control of materials

Detailed descriptions of control of the raw materials used during the active substance manufacturing process have been provided in section 3.2.S.2.3 of the dossier. The descriptions are considered adequate.

The construction of the expression plasmid and the source and history of strain, and the generation of *Saccharomyces cerevisiae* strain producing the extended semaglutide precursor is described in detail. The cell bank system (MCB, WCB) is explained and characterisation of MCB, WCB as well as end-of-production cells and late extended cultures is reported. Stability results are available. The results comply with the specification acceptance criteria for the MCB and WCB.

No animal-derived substances are used in the production of semaglutide.

The acylating agent is both well-characterised and controlled by specifications.

Control of critical steps and intermediates

Detailed descriptions of the critical operational parameters and critical in-process tests performed during manufacturing process of the semaglutide active substance, and the synthesis of the acylating agent has been presented in section 3.2.S.2.4 of the dossier. The proposed in-process tests are considered acceptable.

During the recovery and purification process of the manufacturing of semaglutide active substance, there are three steps where the intermediate is stored in a solid form and stored frozen. Stability studies have been provided, and the provided data demonstrates that the intermediates are stable and well within specification limits. The proposed shelf-lives of the intermediates are found acceptable.

A control strategy for the acylating agent including a specification covering relevant impurities has been established and is considered appropriate and sufficient to ensure that the quality of the semaglutide active substance is not adversely affected. Additionally, stability studies have been performed on three acylating agent batches. The data demonstrates that the agent is very stable and based on the data a re-test period is acceptable.

Process validation

The manufacturing process design consists of process characterisation (PC) and process justification (PJ). This is followed by PV, confirming that the semaglutide manufacturing process is capable of consistently producing semaglutide of the required quality in commercial scale.

For Process B, the fermentation and recovery process are adopted from the approved oral semaglutide process which was validated back in time. Therefore, the process validation (PV) has been carried out and reported in two separate parts. Both parts of the PV were performed in production scale and carried out in Building JC, site Kalundborg, Denmark, to confirm that the manufacturing process is capable of producing semaglutide consistently and reproducibly in commercial scale. The PV design has been based on consecutive batches on each step. The batches are appropriately defined in the dossier.

The results from the PVs of the critical and non-critical operational parameters, critical in-process tests, and the results of the semaglutide active substance specification tests were all consistent for the fermentation, recovery, and purification batches and all acceptance criteria were fulfilled. The results support consistent and adequate production of semaglutide active substance. The process is considered validated.

The evaluation of impurity reduction was carried out at a manufacturing scale, covering representative production batches from the PV of Process B. Selected product-related and process-related impurities were analysed during the PV. Process steps were monitored, reduction factors calculated, and in-process acceptance criteria set.

Based on the presented data from testing of PV batches, it can be concluded that the impurity removal/reduction throughout the semaglutide active substance manufacturing process has been confirmed. The semaglutide active substance manufacturing process has demonstrated to be robust and to consistently reduce the content of impurities to below the acceptance limits.

Manufacturing process development

Comparability of active substance manufactured by Process B and the previous process (Process A) has been demonstrated with respect to the expected structural and physical/chemical characteristics of semaglutide. The impurity profile is comparable; no new impurities were observed in the semaglutide active substance and stability trends are comparable. In conclusion, comparability has been demonstrated throughout manufacturing process development. This is found acceptable.

Characterisation

Elucidation of structure and other characteristics

The structural aspects and physicochemical properties of semaglutide have been adequately described. The results of the structural characterisation of semaglutide have confirmed the expected and theoretical structure, and the physico-chemical characteristics have all been investigated. The

hydrophobic properties evaluated by RP-HPLC and the hydrodynamic size evaluated by SE-HPLC were confirmed.

Biological activity

The testing of specific bioactivity of semaglutide related impurities isolated from the active substance and degradation products from the active substance.

The specific bioactivity of active substance and finished product, tested in stability studies show that the specific bioactivity as well as purity of semaglutide active substance and finished product are very stable. It appears for both active substance and finished product that there is a direct correlation between the specific bioactivity and the main peak content of semaglutide, which is unaffected by the purity of the sample.

Impurities

The applicant has satisfactory presented the potential product and process related impurities which can arise during the manufacture of active substance. Impurities in semaglutide active substance and potential degradation products of semaglutide have been identified and characterised.

The product related impurities present in the process have been characterised and relevant controls have been introduced. Appropriate in-process controls have been established to ensure that the levels of product related impurities are under continuous control (see section S.2.5).

In summary, the proposed control of product related and process related impurities in the manufacturing process and in the final active substance is considered to be adequate for ensuring the pharmaceutical quality of the active substance manufactured.

The results of the forced degradation study show that active substance and finished product generally are susceptible to degradation under extreme conditions.

RP-HPLC chromatograms for placebo samples were compared with RP-HPLC chromatograms for the active substance and finished product samples. The comparison shows that no significant interfering components from the degraded placebo solutions co-elute with the semaglutide or degradation product peaks. Additionally, the ability of the RP-HPLC method to detect all or the majority of the degradation products formed in semaglutide active substance and finished product subjected to forced degradation was evaluated. Based on these investigations it can be concluded that the RP-HPLC method show satisfactory selectivity and ability to detect the degradation of semaglutide active substance and finished products after subjection to extreme conditions.

All the degraded samples were also subjected to SE-HPLC analysis. The results show that the semaglutide monomer can be satisfactorily separated from the HMWP.

As for the testing of biological activity of semaglutide and major impurities of semaglutide, it can with the forced degradation studies also be concluded that there is a direct correlation between the measured bioactivity and the main peak content, independent of purity.

Potential product and process related impurities in the manufacturing process for acylating agent and the potential acylating agent related semaglutide impurities formed during manufacturing of the active substance have been adequately described and characterised.

Specification, analytical procedures, reference standards, batch analysis, and container closure

Specification

Active substance specification for semaglutide including methods to evaluate appearance, identity, content, hydrophilic impurities, impurities, high molecular weight proteins, specific bioactivity, bacterial endotoxins, TAMC, loss of drying and host cell proteins is presented. The specification is the same as that for Wegovy and Ozempic, i.e. the methods included in the active substance specification and the specification limits are identical. For compendial methods, references are made to the Ph. Eur. For non-compendial method, the type of method used for analysis is stated and in-house method numbers are defined. This is found acceptable.

It is noted that bioactivity will be tested on one out of ten batches or one batch per campaign, whichever comes first.

Analytical procedures

The tests for loss on drying, bacterial endotoxins and TAMC are stated to comply with Ph. Eur. This is found acceptable. The non-pharmacopoeia analytical procedures in the active substance specification are adequately described in the dossier.

Pharmacopoeia procedures have been verified to be suitable for semaglutide active substance, and non-pharmacopoeia procedures have been validated according to ICH guidelines. Validation summaries of the non-pharmacopoeia procedures are provided. This is found acceptable.

Batch analyses

Results from batch analyses of semaglutide active substance manufactured using Process B are presented. 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 active substance.

Reference standard

The reference standard system consists of a semaglutide primary reference material (PRM) and a semaglutide secondary reference material (SRM). The same reference materials are used for the approved semaglutide products Ozempic and Wegovy. The release results for semaglutide PRM and SRM all comply with the presented release specifications. PRM and SRM are therefore considered suited for their intended use.

The results from the characterisation studies of PRM also confirms that the primary reference material is suited for its intended use, as it is demonstrated that the identity and structure is that of semaglutide.

New reference materials will be established according to the protocols for establishment of PRM and SRM that are included in the dossier. The information provided in these protocols are considered sufficient.

In conclusion, the active substance specification is found acceptable.

Container closure system

The semaglutide active substance, which is a solid active substance, is stored in container closure systems. Stability samples are stored in equivalent containers of reduced size.

The information provided on the containers for active substance is considered sufficient. In view of the nature of the active substance (dry powder) and the storage temperature the risk of interactions is considered very low.

Stability

The shelf-life claim is based on long-term and accelerated stability studies. Three semaglutide active substance batches manufactured by Process B are referred to as the primary batches. The three PV batches for Process B and four batches manufactured by Process A are also included in the study. All batches are stored in containers representative of those used for commercial batches.

All the presented stability data are within the acceptance criteria, both at long-term conditions, and accelerated conditions. The data show no changes over time. Since comparability between Process A and Process B batches has been demonstrated, a shelf-life of for the semaglutide active substance is found acceptable.

2.5.3. Finished medicinal product

Description of the product and pharmaceutical development

Description of the product

Kyinsu is an integral drug-device combination product containing 700 units/mL of insulin icodec and 2 mg/mL of semaglutide. There are three sizes (variants): 0.43 mL, 1mL and 1.5 mL. The volumes are provided in a Type I glass cartridge with a plunger (chlorobutyl) and a laminated rubber sheet (bromobutyl) contained in a pre-filled multidose disposable PDS290 (FlexTouch) pen made of polypropylene, polyoxymethylene, polycarbonate-acrylonitrile butadiene styrene and acrylonitrile butadiene styrene. The pre-filled pen is either co-packaged with 6 or 9 NovoFine Plus needles or is without needle and in this case the disposable needle should have a length of up to 8 mm.

The finished product is formulated with compendial excipients: zinc acetate, glycerol, phenol, metacresol, sodium chloride, sodium hydroxide, hydrochloric acid and water for injections. The finished product is a clear, colourless or almost colourless, isotonic solution with a pH of approximately 7.4.

The cartridges and rubber closures are stated to be compliant with appropriate Ph. Eur. monographs for primary containers and closures as described in section P.7. There are no novel excipients and there are no materials of human or animal origin. An acceptable device description is found in line with EMA/CHMP/QWP/BWP/259165/2019.

Pharmaceutical development

Finished product

The finished product composition has remained unchanged throughout clinical phase 1 and phase 3; thus, the composition of commercial finished product is identical to the composition used in the clinical programme.

An overview of finished product batches used in pivotal non-clinical studies and clinical trials is provided, the corresponding active substance batches for both insulin icodec and semaglutide are listed.

Insulin icodec

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. The hexameric nature of the insulin icodec oligomers in Kyinsu finished product is

ensured by the lower and upper specification limits for zinc. It is acknowledged that the applicant has extensive prior knowledge of insulin icodec.

Semaglutide

Correlation between content and bioactivity has been demonstrated for both insulin icodec and semaglutide, this is accepted. The impurity profile is comparable to already approved insulin icodec and semaglutide finished product. The impurities of Kyinsu finished product are stated to be well-known as from already approved products. These have been clinically qualified by phase 3 clinical trials (P.5.5.). It is agreed that compatibility has been demonstrated between insulin icodec and semaglutide.

Device

The applicant has described the intended use of the medical device part and the functionality and suitability for use with the medicinal product. The therapeutic indication and the relevant target patient population is also described. The PDS290 Kyinsu pen-injector is based on other marketed PDS290 pen-injectors approved with different types of Novo Nordisk insulin products (e.g. Tresiba, Fiasp, Awiqli) and with semaglutide (e.g. Ozempic). The differences are limited to colours of outer plastic components, the piston rod, cartridge holder and cap due to cartridge size difference (applicable to 3 mL variant only), residual scale on cartridge holder, max dose stop, increment and indicator, and indication for use.

It is acknowledged that the device-constituent suitability is supported by prior experience from the PDS290 pen-injector design from marketed products and phase 3 clinical trial products.

A Notified Body Opinion was provided, confirming full compliance of the FlexTouch pen with the relevant General safety and Performance Requirements (GSPRs) of the Medical Device Regulation.

Control strategy

A summary of the control strategy is provided for the drug-device combination product Kyinsu PDS290 and defines critical quality attributes (CQAs) for action profile, dosage form and delivery, physical, chemical, biological/microbiological attributes with rationales for control and references to further information in the dossier. The CQAs are stated to be based on general scientific knowledge, development, manufacturing, clinical experience, stability and characterisation of insulin icodec and semaglutide active substances as well as prior knowledge from the applicant's already marketed insulin products. It is acknowledged that the applicant has extensive prior knowledge with these substances. The approach and identified CQAs are assessed as acceptable and in-line with ICH Q8. The elements of the control strategy are discussed, critical manufacturing steps, control of process and active substance, excipients, container closure system, the finished product specification, device and assembly controls, facilities and equipment, continued process verification and maintenance of the validated state.

Manufacturing process development – device assembly

The manufacturing process for the Kyinsu 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 Kyinsu PDS290 used for phase 3 clinical trials and for commercial manufacturing with exception for scale-up.

Manufacturing process development – finished product

Kyinsu finished product is provided in a 1.5 ml cartridge with different nominal volumes (0.43, 1 and 1.5 mL), referred to as variants.

The composition of the Kyinsu finished product has been the same from clinical phase 1 trial to clinical phase 3 to the commercial Kyinsu and no changes in the container closure system have been introduced during clinical trials. This is endorsed. The applicant has provided an acceptable overview of process changes during development that essentially amounts to scale and sites for finished product.

A comparability study on phase 3 and commercial finished product batches originating from different sites, batch sizes and variants has been performed in-line with ICH Q5E. finished product batches used in clinical phase 3 trials were compared. Impurity profiles were examined side-by-side using RP-UHPLC, SE-UHPLC) and LC-MS, with presented chromatograms. The samples were stored at +5°C from respective date of manufacture and then further stored at +30°C. The results were within predefined acceptance criteria and the chromatograms, were visually comparable. Stability indicating impurities were observed in the accelerated studies. No new impurities were seen in the batches manufactured in the commercial facility compared to batches from the phase 3 facilities. The levels of impurities found across facilities, batch sizes, and variants were comparable. It is acknowledged that the results support comparability

Container closure system

Data on the finished product contacting cartridge part is presented here. Information on the entire device is found in section 3.2.P.7.

The 1.5 mL cartridge is made of colourless glass. The rubber plunger meets the requirements for type 1 rubber Ph. Eur. The cartridges are siliconised prior depyrogenation.

Compatibility with the rubber components of the container closure system with respect to sorption and precipitation in solution is addressed through the stability studies with the primary pilot scale batches of Kyinsu finished product.

The potential for 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), this is endorsed. 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.

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.

Analysis of functional performance and control strategy

Performance requirements have been tested according to ISO 11608-1:2022 (Needle-based injection systems). The general design requirements, testing strategy, test methods description and batch information is presented. The testing strategy with bracketing and bridging to insulin icodec finished product is found justified. The transport simulation and the testing conditions are described. Tolerances and acceptance criteria from ISO 11608-1, ANSI/AAMI HE75:2009 or user capability studies have been used. A results summary concludes passed for all ISO 11608-1 requirements and data from the studies is presented in appendices.

Microbial attributes

Kyinsu finished product must be preserved against microbial contamination as the product is intended for multiple use. The choice of a preservatives for finished product is based on the applicants prior experience with other insulin finished products.

The integrity of the container closure system was tested (Ph. Eur.) on cartridges filled with media.

Results for Kyinsu bulk formulation with preservatives at or below the lower specification limits of preservatives are also presented with acceptable results.

Compatibility

Kyinsu finished product was shown to be compatible with the 1.5 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.

Manufacture of the product and process controls

Manufacturing process and process controls - finished product

All sites involved in manufacture and control of the finished product operate in accordance with EU GMP.

Schematic flow diagrams are provided with IPCs for the formulation and sterile filtration of the finished product. No claim for reprocessing has been made.

The other individual manufacturing steps are controlled by monitoring and registering of the total time. This approach is found acceptable.

Procedures are controlled by weight. Pre-treatment, sterilization and depyrogenation of cartridges, caps and plungers are briefly described, in line with the requirements of the sterilisation guideline, EMA/CHMP/CVMP/QWP/850374/2015, this is acceptable. The final finished product formulation is filtered through two sterile filters (0.2 µm), filter materials has been validated. The first filtration is just after formulation, the second at point of filling. Bioburden sampling is performed before each sterile filtration step and results must comply with the control limits specified in 3.2.P.3.4. It is further stated by the applicant in 3.2.P.3.3 that the first sterile filter is integrity tested before and after use and that the second filter is tested after use only. It is acknowledged that this is a matter of GMP.

Non-critical parameters

Some process parameters are classified as non-critical when kept within established ranges. The ranges are derived from at-scale process characterisation studies, thus, equipment dependant. This is also reflected in the change management protocol for an additional finished product manufacturing site.

Manufacturing process and process controls – assembly of device

The assembly process flow and process controls system are satisfactorily described in this section with subassembly steps.

Process justification

It is stated by the applicant that a risk assessment has been performed according to the principles of ICH Q9 to identify the CQAs. A process description and summary are provided to justify the critical process parameters and in-process limits for Kyinsu finished product. In this part only the scalable part of the process is discussed. Non-scalable parameters were studied during the formulation process.

As scalable CQA for the manufacturing of Kyinsu finished product, were established with data presented.

Process characterisation

The finished product batches included originated from several different active substance batches which is endorsed. Mixing studies demonstrating homogeneity with challenged limits are presented. This is accepted.

Chemical stability was confirmed for the active substances, insulin icodec and semaglutide. Data was provided on hydrophilic and hydrophobic substances and impurities, HMWP, phenol, m-cresol, Zink and pH. Acceptance criteria were derived from respective specification. The approach and results are found acceptable.

Process validation

Ten batches in total were included in the validation, four of the 1.5 mL variant and three each for the 1 and 0.43 mL respectively. Homogeneity was further demonstrated for all ten batches.

In-process control and testing according to specifications were all performed with acceptable results. The process validation covers three variants (0.43 mL, 1 mL and 1.5 mL) provided in 1.5 mL cartridge and manufactured. The data confirmed the integrity of quality attributes in a controlled and reproducible manner. This is acceptable. Product specific qualification reports on the sterile filters used are found in section 3.2.R and are in line with EMA/CHMP/CVMP/QWP/850374/2015 Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container. Acceptable information on media fills is found in section 3.2.A.1, filling parameters are tabled, the media fills were performed with aseptic processing times from end of filtration to end.

Further information is found in 3.2.P.2.4 analysis of functional performance and control strategy. Three batches were tested each for the 1.5 mL, the 1 mL and the 0.43 mL variant. All results were pass.

Product specification, analytical procedures, batch analysis

Specifications and analytical procedures

There are separate specifications proposed for 0.43 mL, 1 mL and 1.5 mL variants of Kyinsu finished product with differences only in extractable volume. The finished product specifications include methods to evaluate identity, content, macroscopy, pH, product-related substances and impurities, high molecular weight proteins, a few process-related impurities, bacterial endotoxins, sterility and particulate matter.

Dose accuracy and is also included in the specifications. This is endorsed.

The test panel is acceptable. References are made to the Ph. Eur. for compendial methods.

Analytical procedures during development for Kyinsu finished product are listed with method identifiers, enabling traceability. The analytical method development is acceptably described. The analytical procedures are further described and validated in accordance with ICH Q2 (R1) where applicable, otherwise following a standard (dose accuracy, ISO11608-1) or suitability is confirmed with relevant pharmacopeia. Procedures and chromatograms are provided. This is acceptable.

Data from 28 batches is presented, from non-clinical studies, clinical trials (clinical pharmacology trials, phase 1 trials and phase 3 trials), production scale test, process characterisation, process validation and stability studies. Results were within specifications and are acceptable.

The major degradation products found in the finished product have been identified and are also detected in the active substance. All impurities potentially formed in the finished product manufacturing process are at a low level and do not increase during storage. This is accepted.

Justification of specifications

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 non-quantitative and qualitative parameters without a systematic change, the specification is found acceptable with exception for questions raised. For quantitative parameters with a change during storage a calculation of degradation trends was performed. The applicant has provided a list over batches (n=18) used for statistical calculations. The batches are late development batches covering both long-term and accelerated storage conditions. The calculations apply to content of insulin icodec, content of semaglutide, HMWP, hydrophilic and hydrophobic impurities and substances. The lower shelf-life limit is calculated from the lower release limit adding the calculated expected degradation/change during long-term storage using the estimate by the Allen formula stated to reflect the degradation/changes, the uncertainty of the degradation rates (slopes) and the analytical variation. The estimate covers up to 36 months long-term storage.

The Arrhenius equation is used for calculation of the expected degradation/change during the in-use period. The estimate covers the proposed in-use period of 8 weeks for 1.5 mL or 1 mL variants or 6 weeks for the 0.43 mL variant 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. A table is provided, listing release limits and estimated degradation during long-term storage and in-use periods. An additional table is presented showing the absolute weekly exposure to HMWs, hydrophilic and hydrophobic impurities and substances. The mean and maximum exposures in clinical trials are shown and compared to the proposed shelf-life specification.

Batch analysis

Data were provided for batches and are satisfactory.

Reference standard

Documentation in relation to the primary and secondary insulin icodec reference materials is the same as for the authorised products Awiqli and Ozempic.

Characterisation of impurities

In alignment with ICH Q3D, a risk assessment has been performed to determine the relevance of inclusion of elemental impurities in the finished product and to establish appropriate controls to ensure the quality of the product. The strategy to limit elemental impurities in the finished product is based on the principles of risk management as described in ICH Q9. The total risk of exceeding the PDE for elemental impurities was evaluated. To verify the assumptions given in the risk assessments, analytical screenings of three batches of finished product were performed. The results obtained from both risk assessment and analytical screenings show that the level of elemental impurities in the finished product were all well below the threshold of 30% of the PDE limits stated in ICH Q3D. No control measures are needed and consequently, specific tests for elemental impurities are not included in the specification.

A risk assessment regarding the potential presence of nitrosamines was provided. The applicant evaluated the following compounds to be relevant for the assessment of risk of nitrosamines in the finished product based on principles in ICH M7: active substance and manufacturing process, including starting materials and intermediates, excipients and raw materials, primary packaging materials, finished product and manufacturing process. The evaluation of the risk of potential nitrosamine contamination has been based on knowledge of the respective manufacturing processes and statements from suppliers when relevant. In conclusion, negligible risks of nitrosamine presence were

identified. It is concluded that no risk of presence of nitrosamines is identified and therefore, nitrosamine impurities are not included in the specification.

Container closure

Kyinsu finished product is a drug device combination product consisting of insulin icodec 700U/ml and semaglutide 2 mg/ml provided in a 1.5 ml size cartridge assembled into the PDS290 icodec pen injector. Nominal fill volumes of Kyinsu are 1.5 mL, 1 mL and 0.43 mL.

The PDS290 icodec pen-injector is a multidose, disposable, prefilled pen-injector intended for insulin icodec/semaglutide finished product. The dosing is defined as dose step (DS) and 1 active substance contains 1 U insulin icodec and 0.0029 mg semaglutide. The Kyinsu PDS290 delivers 10 active substance per increment, with a maximum dose stop of 350 active substance for the 1.5 mL and 1 mL variants, and 300 active substance for the 0.43 mL variant. 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 Kyinsu 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. This is found acceptable.

The components in contact with Kyinsu finished product 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 an exploded view are also provided including information on dimensions of the different parts of the device. A detailed schematic view of sub and final assembly of PDS290 Kyinsu pen injector has been provided by the applicant. This is found acceptable.

The secondary packaging is based on a protective cardboard box.

Three different presentations including pack sizes of one pen-injector with or without NovoFine Plus disposable needles for each of the variants are planned to be marketed.

The applicant has provided a summary of usability evaluation in section 3.2.R, and this is further assessed in the clinical assessment report.

Stability of the product

The claimed shelf life for the finished product is 3 years when stored at 2 °C - 8 °C.

The applicant has submitted stability data for batches of the proposed three variants of Kyinsu finished product: 0,43 ml (300U + 0.86 mg), 1 ml variant (700 U +2 mg) and 1.5 ml (1050 U +3 mg). 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.

Preservative efficacy testing was performed on the 1.5 ml variant of Kyinsu finished product in cartridge at the long-term storage condition (one batch) and in use stability studies (one batch for each variant) and the results are provided in section 3.2.P.8.3. The results from the preservative efficacy study are reported as complies. As stated by the applicant, comply with the preservative efficacy test according to USP, JP and Ph Eur. This is endorsed.

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

The applicant has submitted stability data at long-term storage for 36 months (3 years) for the 0.43, 1- and 1.5-mL presentations. A shelf life of 3 years is accepted.

The shelf life for the finished product of 3 years when stored at 2 °C - 8 °C is acceptable.

In-use stability

Two in-use stability studies at 30°C for up to 9 weeks have been performed, one for the single cartridge and one for the pre-filled pen. All variants of cartridge/fill volume s are covered, and the studies were performed shortly after production, during shelf life and at 24 months. The batches of pre-filled pen were manufactured at Novo Nordisk A/S, site Bagsværd and site Måløv. This is however considered acceptable since acceptable comparability has been demonstrated with product manufactured in the intended commercial production facility Novo Nordisk A/S, site Hillerød.

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 support the intended in-use period of eight weeks for the 1.5 mL and 1 mL variants, and six weeks for the 0.43 mL variant, respectively. The results from chemical and physical testing complied with acceptance criteria. Comparable trends were seen between the variants as well as between Kyinsu PDS290 and Kyinsu finished product (cartridge). 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.

Photostability

Photostability studies were performed according to ICH Q1B on Kyinsu finished product in 0.43 ml, 1.5 ml, and 1 ml variants in the primary container closure systems, Kyinsu in the pen injector PDS290 with the cap on and Kyinsu finished product in primary container wrapped in aluminium foil (reference samples). After exposure to light, the cartridge test samples and Kyinsu PDS290 test samples were compared to the reference samples. According to the photostability data submitted by the applicant the Kyinsu 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 for Kyinsu finished product The photostability data supports further the storage conditions mentioned in the SmPC.

The proposed in-use period of eight weeks for the 1.5 mL and 1 mL variants, and six weeks for the 0.43 mL variant when stored at or below 30°C as well as the storage condition "Keep the cap on the pen in order to protect from light "are justified based in the in-use stability and photostability studies respectively.

Adventitious agents

There are no raw materials or excipients of human or animal origin used in the manufacture of insulin icodec or semaglutide active substance or finished product. *Saccharomyces cerevisiae* does not support propagation of mammalian virus. It is concluded that the Kyinsu finished product is safe with regards to both virus and transmissible spongiform encephalopathy (TSE) agents in accordance with the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01).

2.5.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The dossier is found to be appropriately structured.

Full module 3 quality documentation for the insulin icodec active substance and the semaglutide active substance is included with this application. In conclusion, information on development, manufacture and control of insulin icodec and semaglutide active substance has been presented in a satisfactory way and is found acceptable.

The finished product part is found acceptable. Stability data provided support the claimed shelf life of 36 months.

From a quality perspective, the marketing authorisation application is considered approvable.

2.5.5. Conclusions on the chemical, pharmaceutical and biological aspects

The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The manufacturing process of the active substances adequately described, controlled and validated. The active substances are well characterised and appropriate specifications are set. The manufacturing process of the finished products has been satisfactorily described and validated. The quality of the finished products is controlled by adequate test methods and specifications. Adventitious agents' safety including TSE have been sufficiently assured.

Overall, the quality of Kyinsu is considered acceptable when used in accordance with the conditions defined in the SmPC. Physico-chemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

In conclusion, based on the review of the quality data provided, the marketing authorisation application for Kyinsu is considered approvable from the quality point of view.

2.5.6. Recommendation(s) for future quality development

None.

2.6. Non-clinical aspects

2.6.1. Introduction

Kyinsu consist of two active substances insulin icodec and semaglutide both developed and approved for treatment of type 2 diabetes mellitus. Insulin icodec is an insulin analogue engineered to have an extended pharmacodynamic action following a single subcutaneous dose and that is suitable for once-weekly administration. Its molecular mode of action at the insulin receptor (IR) is the same as for human insulin. Insulin icodec have three backbone mutations (A14E, B16H and B25H), one deletion (B30) and a protractor attached at B29K using Ado-Ado-γGlu as a linker to a C20 fatty diacid were introduced into the human insulin sequence. These modifications enable insulin icodec to bind strongly to albumin and give it a low affinity for the insulin receptor thereby resulting in slow clearance and a high circulating level which acts as an inactive depot from which a slow and continuous PD response can be realised. Insulin icodec with the brand name Awiqli is approved for treatment of diabetes mellitus in adults. Semaglutide is a long-acting human GLP-1 receptor (GLP-1R) agonist, which specifically activates the GLP-1R. Semaglutide has been engineered to have a low clearance and

thereby a long elimination half-life of approximately one week in humans, making the compound suitable for once-weekly administration. Semaglutide under the brand name Ozempic is approved as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus.

2.6.2. Pharmacology

No new non-clinical pharmacological studies with insulin icodec/semaglutide (Kyinsu) have been conducted. This is acceptable since the pharmacology of the insulin icodec and semaglutide as single agents has been extensively evaluated to support their respective approvals for treatment of diabetes mellitus in adults and as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus. In short, the pharmacological evaluation of the monotherapies show that icodec insulin binds specifically to the insulin receptor (IR) with the desired agonist effects and that semaglutide is effective in lowering blood glucose levels as well as modulating satiety and giving rise to decreased food intake and have a body weight lowering effect. Further to this, there are clinical data that supports the fixed-dose combination of insulin icodec/semaglutide.

2.6.3. Pharmacokinetics

The pharmacokinetics to support the present application of insulin icodec/Semaglutide (Kyinsu) were included a 6-week DRF and a 13-week rat repeat dose toxicity studies with daily s.c. administration and three non-GLP single dose PK studies in pigs which included PK interactions between insulin icodec and semaglutide. The strains used included the Sprague Dawley rat and LYD pigs (crossbred of Danish Landrace, Yorkshire and Duroc pigs). No further pharmacokinetic studies with Kyinsu were conducted which is considered accepted since the pharmacokinetic properties of the mono-components Icodec insulin and Semaglutide have been extensively evaluated for their respective MAA approvals.

2.6.3.1. Analytic methods

The PK assay used for the rat toxicity studies was a luminescent oxygen channelling immunoassay (LOCI) to measure insulin icodec and a liquid chromatography and a tandem mass spectrometry detection (LC-MS/MS) assay to measure semaglutide. For ADA measurement of insulin icodec and semaglutide two separate validated radioimmunoassay's (RIA) using [125I]-labelled insulin icodec and [125I]-labelled semaglutide, respectively, were used. The PK assays in non-GLP studies in pigs used a non-validated LOCI similar to the one described above for rat plasma samples. The bioanalytical methods used were the same methods used for the mono-components insulin icodec and semaglutide and are considered appropriate and deemed correctly validated for quantitation of plasma detection of Icodec insulin and semaglutide, and antibodies against Icodec insulin and semaglutide in rats.

2.6.3.2. Repeat-dose pharmacokinetics in rats

The toxicokinetic (TK) data relating to the Kyinsu formulation has been generated in two toxicology studies, a non-GLP 6-week dose range finding (DRF) study and a 13-week GLP toxicity study in rats with daily administration. Generally, in these studies the exposure of insulin icodec and semaglutide after administration of Kyinsu was similar between the sexes. A dose proportionality (C_{max} and AUC) for both icodec insulin and semaglutide was seen in the 6-weeks study. However, this was not obvious in the 13-weeks study in that the high dose group showed no dose proportionality at week 14. In both studies approximately a 2-3 times accumulation of insulin icodec and the T_{max} ranged from 1.5 to 12 hours and from 4 to 12 hours, for insulin icodec and semaglutide, respectively.

2.6.3.3. Single–dose plasma pharmacokinetics in pigs

Different Kyinsu formulations with the presence of various zinc concentrations, albumin, or a short-chain fatty acid derivative (fatty acid ligand NNC0143-0000-3277) were evaluated in 3 non-GLP single-dose PK pig studies. Generally, no obvious differences compared to the separate formulations of insulin icodec and semaglutide was recorded of the PK parameters measured except T_{max} and C_{max}. From these studies it can be concluded that different zinc ranges affect the C_{max} of insulin icodec (but seemingly not the C_{max} of semaglutide), albumin seems to lower the C_{max} and higher C_{max} and an earlier T_{max} semaglutide is achieved in combination with insulin icodec. The addition of albumin clearly shows an impact on the kinetics profile due to competition of binding sites for albumin.

2.6.4. Toxicology

A full non-clinical toxicology evaluation has been completed for the mono-components insulin icodec and semaglutide. Detailed assessments of the toxicology of the individual components are included in the European Public Assessment Report (EPAR) for Awiqli (insulin icodec; https://www.ema.europa.eu/en/documents/assessment-report/awiqli-epar-public-assessment-report_en.pdf) and Ozempic (semaglutide; https://www.ema.europa.eu/en/documents/assessment-report/ozempic-epar-public-assessment-report_en.pdf).

In addition to the completed non-clinical toxicology programs for approved mono-components, the applicant conducted a 6-week DRF study in rat, a 13-week s.c. repeat-dose study in rat, and a local tolerance study in minipigs to support the current application for the combination (insulin icodec/semaglutide).

2.6.4.1. Single dose toxicity

Single-dose toxicity studies have not been performed for Kyinsu or for Insulin icodec as mono-components. Single dose toxicity studies in mice and rats have been performed for semaglutide (described in the EPAR for Ozempic).

2.6.4.2. Repeat dose toxicity

Repeat dose toxicity of Kyinsu was evaluated in a 6-week DRF study and a 13-week GLP study, both in rat. In both studies, major findings were clinical signs of hypoglycaemia, blood/plasma glucose lowering, minimal to slight hypertrophy of the Brunner's glands in the duodenum, and axonal degeneration of the sciatic nerve that were considered adverse. Additional findings in the 13-week study were slight atrophy of the mammary glands in males and testicular tubular degeneration.

Tubular degeneration of the testes and atrophy of the mammary glands persisted to the end of the recovery period in previously dosed males. All other treatment-related findings showed full recovery.

Except for the mammary gland finding, all important observations have been described after dosing either insulin icodec or semaglutide as mono-components and most are considered secondary to hypoglycaemia induced by insulin-treatment of normoglycemic rats.

The NOAEL in the 13-week GLP study was established at 31.5 nmol/kg/day insulin icodec and 0.015 mg/kg/day semaglutide, corresponding to 2.9x and 1.2x the clinical exposure, respectively. This was lower than when the mono-components were administered (the NOAEL for insulin icodec alone in a 26-week repeated dose study in rats was established at 80 and 60 nmol/kg/day in males and females, respectively, and NOAEL for semaglutide was at 0.60 mg/kg/day).

2.6.4.3. Genotoxicity

No genotoxicity studies were performed with Kyinsu.

2.6.4.4. Carcinogenicity

No studies were performed with the Kyinsu combination product. Carcinogenic potential has been evaluated for the mono-components.

Semaglutide is associated with thyroid C-cell tumours in rodents (considered a class effect of GLP-1 receptor agonists and suggested to be likely rodent specific) and insulin has a well-known growth promoting activity. Insulin icodec was not associated with an increased carcinogenic potential in a 52-week rat study when compared to human insulin (see EPARs of Awiqli and Semaglutide).

2.6.4.5. Reproductive and developmental toxicity

No DART studies were performed with the Kyinsu combination product. Reprotoxicity of semaglutide has been described in non-clinical studies with the monocomponent. This is reflected in the SmPC of Kyinsu, where it is stated that it should not be used during pregnancy and that women of childbearing potential must use effective contraception during and up to two months after treatment.

2.6.4.6. Toxicokinetic data

The toxicokinetic data for Kyinsu are described in Pharmacokinetics. Anti-drug antibodies had no effect on exposure in antibody positive animals as compared to antibody negative animals.

2.6.4.7. Local tolerance

Local tolerance was assessed in the repeat-dose studies in rat applying dilutions of Kyinsu and in a dedicated study in minipig applying the "to be marketed" drug product. Local reactions to 4.2 mmol/L + 2 mg/mL Kyinsu were mild and comparable to that of the vehicle or saline.

2.6.4.8. Antigenicity

Formation of antibodies towards insulin icodec and semaglutide after administration of Kyinsu was measured in the 6-week DRF study in rat. The observed antibody development for semaglutide was not different from that observed when tested as a mono-component. For insulin icodec, when tested as a mono-component, a high percentage of rats developed antibodies (69% of main study animals) in an 8-week rat study, while only 8% developed antibodies in a 26-week study. In the present 6-week DRF study, the incidence (25%) was in between those of the two insulin icodec studies. When comparing effect on blood glucose, plasma glucose and exposure between antibody positive and negative animals, the antibodies towards Insulin Icodec are not considered neutralizing, as the effect on blood/plasma glucose and/or exposure are comparable.

2.6.5. Ecotoxicity/environmental risk assessment

No ERA studies have been submitted. This is acceptable as both Insulin icodec and Semaglutide are non-natural peptides that are excreted in <10% of the dose given (table 7). The ERA was stopped at Phase I in accordance with EMEA/CHMP/SWP/4447/00 Rev. 1.

Substance (INN/Invented Name): Insulin icodec			
CAS-number: 1188379-43-2			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	<-2.7 (pH7 and pH9) Shake flask method	Potential PBT: N
Substance (INN/Invented Name): Semaglutide			
CAS-number: 910463-68-2			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	<-2.39 Shake flask method	Potential PBT: N

2.6.6. Discussion on non-clinical aspects

Kyinsu is a fixed dose combination of two active substances, insulin icodec and semaglutide, both developed and approved as mono-components for treatment of type 2 diabetes mellitus. No new non-clinical pharmacological studies with Kyinsu have been conducted which is considered acceptable based on that the pharmacology of the insulin icodec and semaglutide as single agents has been extensively evaluated to support their respective MAA (see EPARs for Ozempic and Awiqli).

The pharmacokinetics of Kyinsu were included in a 6-week DRF and a 13-week rat repeat dose toxicity study with daily s.c. administration and in 3 single-dose PK studies in pigs. Overall, no obvious gender differences in exposure occurred and a dose proportionality was confirmed (at least in the 6-week study). The pig studies showed that the addition of albumin has an impact on the kinetics profile due to competition of binding sites for albumin.

The general toxicity of Kyinsu was assessed in a 6-week DRF study and a 13-week repeat-dose toxicity study, both in rats. The local tissue reaction after single or repeated s.c. administration was evaluated using a pig model and as an integrated part of the repeated-dose studies. The toxicology of the combination showed no meaningful differences from what would be expected based on the knowledge of the individual components, although the NOAEL in the 13-week rat study was lower than what has been established for the mono-components. Slight atrophy of the mammary glands, as noted in a few males in the 13-week rat study, had not been reported previously for the mono-components but may be attributed to decreased weight as reduced weight gain has been associated with atrophy of the mammary gland in male rodents. The applicant has submitted a summary on toxicology of the individual components, these are not assessed in this AR (for the CHMP assessment, see EPARs for Ozempic and Awiqli).

The NOAEL in the repeated dose toxicity study of the combination product Kyinsu was limited by tolerability related to glucose lowering, as was the case also in repeated dose toxicity studies of Insulin icodec as mono-component. At NOAEL for Kyinsu, the levels (Caverage) of semaglutide and Insulin icodec were 0.041x and 0.75x the NOAELs established for the mono-components, respectively. The low animal-to-human exposure ratio for semaglutide (1.2x) in the Kyinsu study is therefore not considered of concern. Also, the exposure ratio for insulin icodec was lower in the study with the combination product (2.9x) than in the repeated dose study with the mono-component (3.8x in females, 5.7x in males). This is likely explained by the known pharmacological effect of semaglutide in decreasing food consumption and thereby reducing the rat's ability to compensate for the lowered blood glucose induced by the pharmacological effect of insulin icodec. The clinical relevance of this in humans with diabetes is likely limited.

Induction of ADAs towards insulin icodec in 25% of the animals after administration of Kyinsu in the non-GLP 6-week rat study was in line with the high frequency of ADAs detected in repeat dose toxicity studies of insulin icodec alone. In general, these have been considered non-neutralizing since exposure resulted in the expected decrease in blood glucose levels, and ADA formation is not considered to have

significantly influenced the outcome of the studies.

Reprotoxicity of semaglutide has been described in non-clinical studies with the mono-component. In a rat EFD study, major skeletal and visceral malformations were observed, including effects on long bones, ribs, vertebrae, tail, blood vessels and brain ventricles. In cynomolgus, increased pregnancy loss and slightly increased incidence of foetal abnormalities were observed at clinically relevant exposures. The clinical relevance of these findings is unknown, but a potential risk for humans is mitigated through the labelling in SmPC section 4.6, where it is stated that Kyinsu should not be used during pregnancy and that women of childbearing potential must use effective contraception during and up to two months after treatment. Any further risk mitigation measures are not warranted.

Carcinogenicity is a possible area of concern for Kyinsu, as semaglutide is associated with thyroid C-cell tumours in rodents (considered a class effect of GLP-1 receptor agonists and suggested to be likely rodent specific) and insulin has a well-known growth promoting activity. A theoretical risk for an enhancing effect of insulin icodec on the carcinogenic potential of semaglutide could be depicted. There are, however, no meaningful ways to address this theoretical risk in nonclinical models. Medullary thyroid cancer is listed in the RMP as potential risk. Insulin icodec was not associated with an increased carcinogenic potential in a 52-week rat study when compared to human insulin.

Insulin icodec and semaglutide are non-natural peptides excreted in <10% of the dose given. Therefore, Kyinsu is not expected to pose a risk to the environment.

2.6.7. Conclusion on the non-clinical aspects

There are no objections to marketing authorization of Kyinsu from a non-clinical point-of-view.

2.7. Clinical aspects

2.7.1. Introduction

GCP aspects

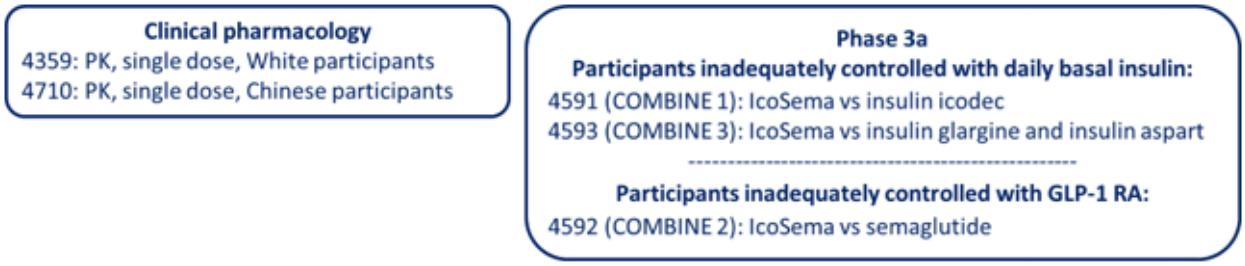
The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the EU 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 Kyinsu includes data from five clinical studies in the Kyinsu development programme: 2 clinical pharmacology studies and 3 phase 3a confirmatory efficacy and safety studies (COMBINE studies) (**Figure 1**).

Figure 1 Overview of Kyinsu clinical development programme



Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

2.7.2. Clinical pharmacology

Kyinsu is a fixed-ratio combination product (700 U/mL insulin icodec + 2 mg/mL semaglutide) for once-weekly subcutaneous injection. The ratio between the two active drug substances remains the same as the dose increases or decreases.

The clinical pharmacology file of the fixed ratio combination is referring to data from the monocomponents.

The insulin icodec/semaglutide (Kyinsu) clinical programme included two clinical pharmacology studies (studies 4359 and 4710) comparing single-dose PK properties of insulin icodec/semaglutide (Kyinsu) versus mono-components in participants with T2D (Table 1). A population PK analysis was performed using pooled data from the two clinical pharmacology studies and two phase 3a studies (participants with T2D studies NN1535-4591 and NN1535-4592).

Table 1. Overview of study design

Study ID	Population	Study design	Dosing	Comparator
4359	T2D White	RND, DB, CO, SD	Fixed dose, 175 U/0.5 mg	Insulin icodec, semaglutide
4710	T2D Chinese	RND, DB, CO, SD	Fixed dose, 40 U/0.11 mg	Insulin icodec, semaglutide

Abbreviations: CO: crossover; DB: double-blinded; RND: randomised; SD: single dose; T2D: type 2 diabetes.

2.7.2.1. Pharmacokinetics

Analytical methods

PK data in serum is available from studies 4359, 4710, 4591 and 4592. Three cross-validated bioanalytical methods for quantification of insulin icodec in human serum were used across the development, with the main site being at Celerion, Switzerland. For quantification of semaglutide in human plasma, two assays covering different range were developed and used across the development, with the main site being at Celerion, Switzerland.

The methods used for quantification of insulin icodec were similar: insulin icodec was quantified by a specific Luminescence Oxygen Channeling 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 photosensitizer present in the donor beads is excited to generate chemiluminescence proportional to the concentration of insulin icodec. For quantification of semaglutide, LC-MS/MS was used.

The immunogenicity of insulin icodec and semaglutide was assessed using a multi-tiered strategy including screening, confirmation, titer determination and cross-reactivity to human insulin (for insulin icodec) or GLP-1 (for semaglutide). The neutralising potential of antidrug antibodies (ADA) was not determined. In all studies, except for studies 4710 and 4593 (and study 4592 for semaglutide), systematic ADA sampling was performed. However, in all studies, 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 Celerion, with the exception of samples from Chinese subjects from studies 4591 and 4592 (at Wuxi).

The Celerion and WuXi assays are identical (including critical reagents), but have different assay parameter, thus their results are not pooled for studies 4591 and 4592. The Celerion and WuXi ADA method included an acid pre-treatment step prior to PEG precipitation, followed by binding to a radioactive tracer, PEG precipitation and radioactivity counting in the precipitate. For confirmation, excess unlabelled drug was added, while excess human insulin (for insulin icodec) or GLP-1 (for semaglutide) was added to assess cross-reactivity. The validation both at Celerion and WuXi followed current guidelines and white papers. At screening, 100 ng/mL of anti-insulin icodec antibody tolerated at least 1000 nM of insulin icodec. Drug tolerance in the confirmation assay was tested at WuXi only. There, for 100 ng/mL of positive control, 283 nM of insulin icodec were tolerated. 100 ng/mL of anti-semaglutide antibody tolerated 0.63 nM of semaglutide.

Pharmacokinetic data analysis

In most clinical pharmacology studies, standard non-compartmental methods have been used. In Phase 3 studies, PK data was sampled with sparse sampling designs and analysed using a population PK (PopPK) approach as described below.

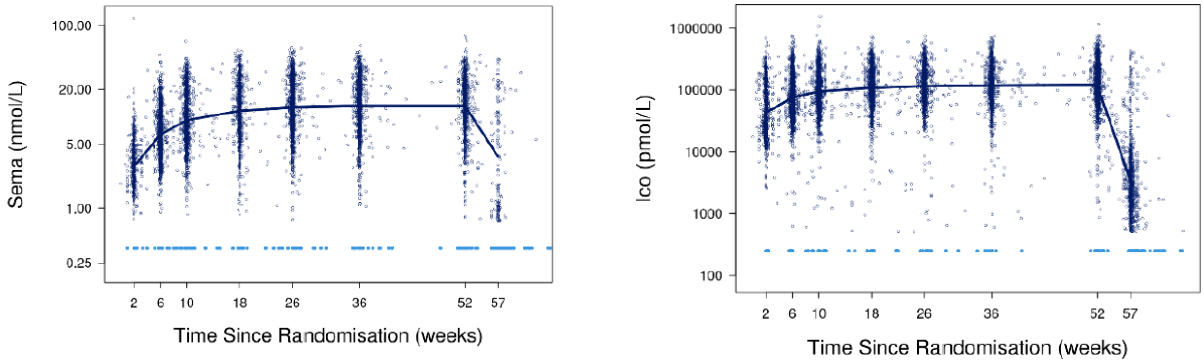
Population pharmacokinetic analysis

A PopPK analysis was performed with the objective to describe the population PK characteristics of Kyinsu for the treatment of type 2 diabetes.

Pooled PopPK datasets were used for the PopPK analysis including 4 studies in Type 2 diabetes patients including clinical pharmacology studies with rich PK sampling design (Studies 4359 and 4710) as well as Phase 3 studies with sparse PK sampling designs (Studies 4591 [COMBINE 1] and 4592 [COMBINE 2]).

The semaglutide PopPK dataset included 10246 PK observations from 1367 patients. The insulin icodec PopPK dataset included 14027 insulin icodec PK observations from 1669 patients. The PK observations vs time since randomization are shown in Figure 2.

Figure 2. Concentration data versus time since randomization for semaglutide and insulin icodec.



Abbreviations: Sema: semaglutide. Ico: insulin icodec. Dark blue points indicate individual values above LLOQ. Light blue points indicate individual values below LLOQ. Lines indicate geometric mean.

The analyses were carried out in NONMEM 7.5 using the first-order conditional estimation method with interaction. For semaglutide, a 2-compartment model with first-order absorption and elimination was used. For insulin icodec, a 1-compartment model with first-order absorption and elimination was used.

For the covariate analysis, a confirmatory full model approach 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) was used.

The following covariate-parameter relationships were explored:

- CL/F: age (grouped as 18-64 years, 65-74 years and ≥75 years), body weight, ethnicity, race, sex, ADA*
- V/F: body weight
- KA: treatment arm, formulation
- Relative bioavailability: injection site (thigh, abdomen, deltoid), drug product (pre-change drug product, post-change drug product), renal function (normal, mild impairment, moderate impairment)

*: For insulin icodec, the effect of antibody level on PK was evaluated based on antibody titre using five categories (antibody negative, 1st, 2nd, 3rd, 4th quartile of peak titre). For semaglutide, the effect of antibody level was explored graphically (using eta-vs-covariate plots for CL/F) by comparing antibody negative and antibody positive status, since very few patients had ADAs (0.8%).

All covariates apart from body weight were implemented as categorical covariates. Body weight was implemented using a power model.

The effect of mono-component formulation differences on KA was estimated only for semaglutide (no change in mono-component formulation for insulin icodec).

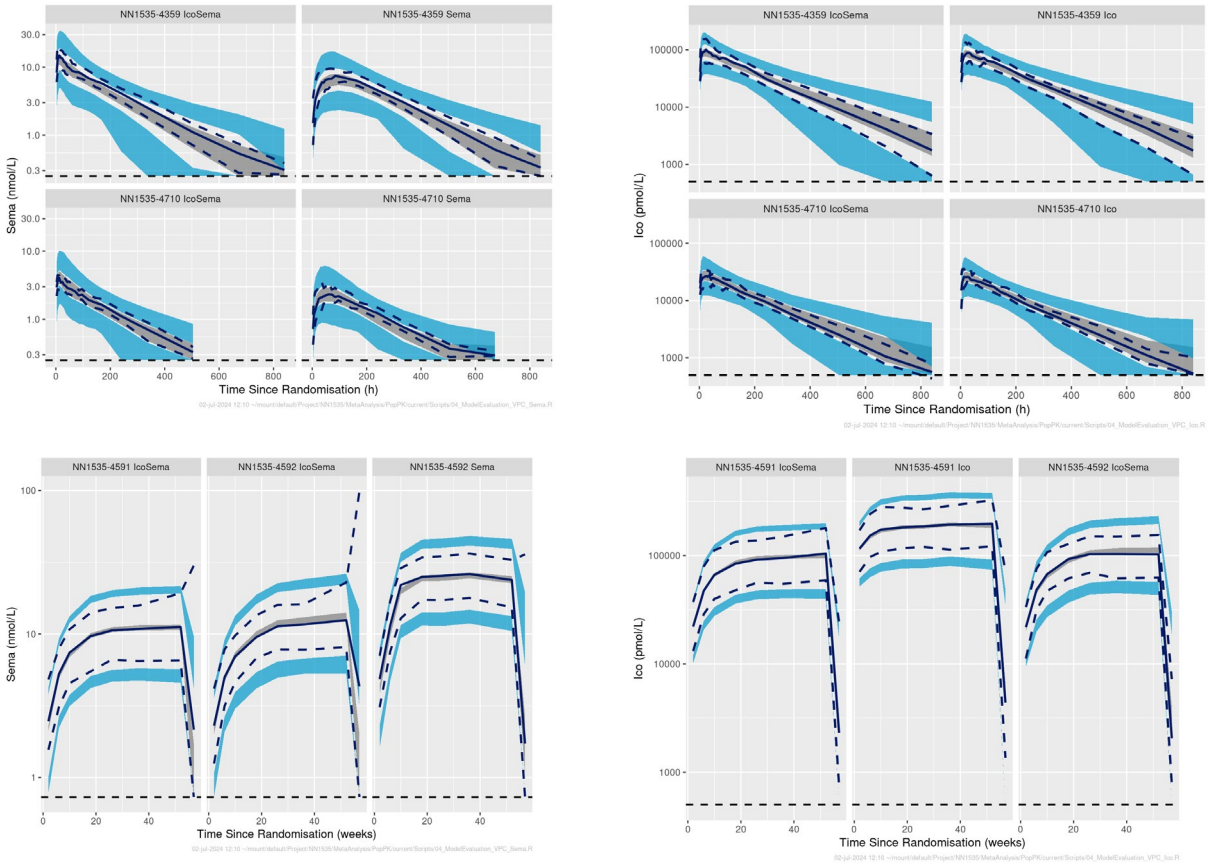
Furthermore, to appropriately fit the pooled semaglutide data from phase 1 and phase 3, a covariate effect of phase on the apparent volumes of distribution, Vc/F and Vp/F, was included.

The effect of drug product on relative bioavailability was only supported by data from the Kyinsu arm.

The model checking and validation included standard goodness-of-fit plots and a visual predictive checks (VPCs) as illustrated for the final models in Figure 3.

Figure 3. Final model: prediction-corrected VPC, stratified by study and treatment.

Semaglutide | Insulin icodec



Abbreviations: Sema: Semaglutide. Ico: Insulin icodec. 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 and treatment.

Parameter estimates for the final semaglutide model are provided in Table 2. The final semaglutide model included the following covariates:

- Treatment arm on relative bioavailability and KA
- Formulation on KA
- Body weight on clearance- and volume terms with estimated allometric exponents
- Japanese race on CL/F
- Renal function on relative bioavailability
- Phase on Vc/F and Vp/F

The most important, and only clinically relevant, covariate for predicting exposure was body weight, with exposure decreasing with increasing body weight.

Table 2 Final PK model: parameter estimates – semaglutide

Parameter	Unit	Estimate	95% CI lower limit	95% CI upper limit	RSE (%)	IIV (CV%)	Shrinkage (%)
Absorption rate constant (KA)	1/h	0.0281	0.0225	0.0337	10.2	NA	NA
Clearance (CL/F)	L/h	0.0464	0.0452	0.0476	1.29	24.4	6.82
Central volume of distribution (Vc/F)	L	2.54	2.03	3.06	10.3	60.2	27.2
Intercompartmental clearance (Q/F)	L/h	0.406	0.357	0.455	6.18	NA	NA
Peripheral volume of distribution (Vp/F)	L	6.45	5.8	7.09	5.08	NA	NA
Treatment on F (IcoSema)	NA	1.06	1.03	1.09	1.4	NA	NA
Treatment on KA (IcoSema)	NA	3.32	2.7	3.94	9.52	NA	NA
Formulation on KA (Sema)	NA	0.549	0.43	0.668	11.1	NA	NA
Body weight exponent on CL/F and Q/F	NA	0.852	0.78	0.923	4.27	NA	NA
Body weight exponent on Vc/F and Vp/F	NA	0.886	0.746	1.03	8.1	NA	NA
Race covariate on CL/F (Japanese)	NA	1.11	1.08	1.14	1.47	NA	NA
Renal function on F (Mild impairment)	NA	0.937	0.911	0.963	1.43	NA	NA
Renal function on F (Moderate impairment)	NA	0.88	0.826	0.933	3.12	NA	NA
Phase on Vc/F and Vp/F (phase 1/phase 3)	NA	1.44	1.35	1.52	2.99	NA	NA
Proportional error in phase 1	CV%	15.4	NA	NA	NA	NA	2.56
Additive error in phase 1	nmol/L	0.0448	NA	NA	NA	NA	2.56
Proportional error in phase 3	CV%	23.3	NA	NA	NA	NA	10.6
Additive error in phase 3	nmol/L	0.38	NA	NA	NA	NA	10.6

Parameter estimates for the final insulin icodec model are provided in Table 3. The final insulin icodec model included the following covariates:

- Treatment arm on relative bioavailability and KA
- Injection region on relative bioavailability
- Body weight on CL/F and V/F with estimated allometric exponents
- The age group 65≤ to <75 years on CL/F
- Hispanic ethnicity on CL/F
- Japanese race on CL/F
- Sex on CL/F
- Renal function on relative bioavailability
- ADA on CL/F

The most important, and only clinically relevant covariate for predicting exposure was body weight, with exposure decreasing with increasing body weight.

Table 3 Final PK model: parameter estimates – insulin icodec

Parameter	Unit	Estimate	95% CI lower limit	95% CI upper limit	RSE (%)	IIV (CV%)	Shrinkage (%)
Absorption rate constant (KA)	1/h	0.199	0.176	0.223	6.12	NA	NA
Clearance (CL/F)	L/h	0.043	0.0415	0.0446	1.83	23	8.77
Volume of distribution (V/F)	L	9.73	9.39	10.1	1.74	34	11.5
Injection region on F (Abdomen)	NA	0.97	0.94	0.999	1.55	NA	NA
Treatment on F (IcoSema)	NA	1.04	1.01	1.06	1.33	NA	NA
Treatment on KA (IcoSema)	NA	1.1	0.979	1.22	5.57	NA	NA
Body weight exponent on CL/F	NA	0.751	0.684	0.819	4.58	NA	NA
Body weight exponent on V/F	NA	0.835	0.741	0.929	5.75	NA	NA
Age group covariate on CL/F (65<= to <75 years)	NA	0.976	0.951	1	1.31	NA	NA
Eth1nicity covariate on CL/F (Hispanic)	NA	0.926	0.888	0.964	2.09	NA	NA
Race covariate on CL/F (Japanese)	NA	1.04	1.01	1.07	1.53	NA	NA
Sex covariate on CL/F (Male)	NA	1.04	1.01	1.06	1.41	NA	NA
Renal function on F (Mild impairment)	NA	0.934	0.911	0.958	1.28	NA	NA
Renal function on F (Moderate impairment)	NA	0.835	0.8	0.871	2.19	NA	NA
Antibody group covariate on CL/F (3rd quartile/Negative AB)	NA	0.962	0.93	0.994	1.7	NA	NA
Antibody group covariate on CL/F (4th quartile/Negative AB)	NA	0.867	0.835	0.899	1.87	NA	NA
Proportional error in phase 1	CV%	14.7	NA	NA	NA	NA	2.4
Additive error in phase 1	pmol/L	0	Fixed	Fixed	Fixed	NA	NA
Proportional error in phase 3	CV%	26.8	NA	NA	NA	NA	10.2
Additive error in phase 3	pmol/L	0	Fixed	Fixed	Fixed	NA	NA

Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

For semaglutide, although treatment arm was not considered clinically relevant, it had a large influence on the semaglutide absorption (higher semaglutide C_{max} for Kyinsu than for semaglutide monotherapy). The developed PopPK models were used to compare the semaglutide C_{max} difference between products (combination [insulin icodec/semaglutide] vs semaglutide monotherapy), at steady state.

At steady state, the PopPK model predicted that the semaglutide C_{max} was ~1.3- to 1.5-fold higher for Kyinsu than semaglutide monotherapy which is lower than the observed difference according to the single dose clinical pharmacology studies 4710 and 4359 (~1.5- to 2-fold).

Physiologically-based pharmacokinetic model

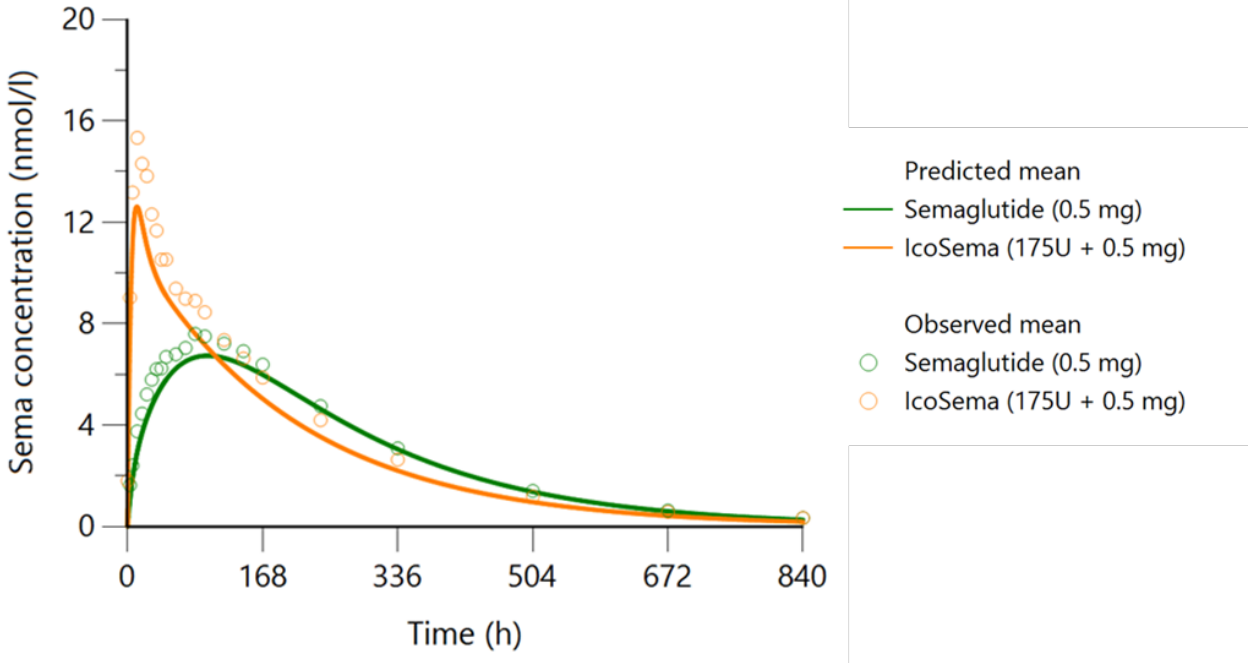
A physiologically-based pharmacokinetic (PBPK) model was developed to better understand the interplay between formulation and the affinity for albumin in the subcutis and the impact on the shape of the PK profile following subcutaneous administration of Kyinsu and semaglutide monotherapy.

A mechanistic, mathematical model was used to simulate the subcutaneous absorption profile of semaglutide with and without the presence of insulin icodec in the formulation. The model was based on absorption physiology, albumin content and dynamics in subcutis, and dissociation constant (Kd) values for albumin binding of insulin icodec and semaglutide (figure 9).

Absorption pathways from the subcutis are size dependent such that molecules <20 kDa are primarily absorbed fast via the endothelial cells whereas larger molecules are absorbed via the slow lymphatic flow. After extravasation from the blood, albumin (67 kDa) is returned via the lymph. Accordingly, unbound semaglutide (4 kDa) is considered to be absorbed via the fast route, whereas semaglutide bound to subcutaneous albumin is transported slowly in the lymph.

The mechanistic model adequately replicated the mean PK profiles of semaglutide from trial NN1535-4359, where a higher C_{max} and earlier T_{max} was observed for semaglutide in the Kyinsu formulation, compared to when given semaglutide alone (9).

Figure 4. Mean observed and model-predicted serum concentration of semaglutide administered alone or in the IcoSema formulation (trial NN1535-4359).



Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

Model input: Albumin concentration in subcutis of 300 µM (40-50% of that in blood), dissociation constant (Kd) values for albumin binding of semaglutide (1 µM) and insulin icodec (0.1 µM), respectively. Lymphatic absorption rate 0.025 h-1, fast absorption rate 0.14 h-1. Semaglutide disposition PK model for T2D with a mean body weight of 96.2 kg. Dilution in s.c. depot 2-fold.

Absorption

Bioavailability

Two single-dose cross-over studies (4359 and 4710) was provided comparing PK properties of insulin icodec and semaglutide in subjects with type 2 diabetes when given as a fixed ratio combination and as mono-components. The PK properties following administration of Kyinsu versus monocomponents were comparable in studies 4359 (White participants) and 4710 (Chinese participants) with similar total plasma exposure (AUC) of both insulin icodec and semaglutide and similar C_{max} of insulin icodec but a higher C_{max} of semaglutide. The higher C_{max} of semaglutide following administration of Kyinsu compared to semaglutide alone was observed in both studies.

The applicant suggest that the higher C_{max} and earlier t_{max} of semaglutide when administered as Kyinsu compared to semaglutide alone could be explained by competitive binding for albumin between insulin icodec and semaglutide in subcutaneous tissue following injection.

In **study 4359**, the total plasma exposure (AUC) of insulin icodec and semaglutide when administered as a fixed ratio of Kyinsu (175U/0.5 mg) was comparable with separate single dose administrations of insulin icodec and semaglutide. For insulin icodec, the C_{max} was similar when administered as Kyinsu compared to separate administration of insulin icodec. However, for semaglutide, C_{max} was higher (2-fold) and occurred earlier following Kyinsu administration compared to semaglutide alone.

At steady-state, total exposure (AUC) is assumed to be similar to AUCinf after single-dose and was comparable for both insulin icodec and semaglutide when administered as fixed combination compared to monocomponents. Prediction of C_{max} of semaglutide at steady-state using Pop-PK modelling showed similar results as following single-dose with a higher C_{max} following administration of the fixed dose combination compared to administration of semaglutide as a monocomponent but a lower ratio for C_{max} at steady-state (1.5) compared to single-dose (2.0).

In **study 4710** in Chinese subjects, the total plasma exposure (AUC) of insulin icodec and semaglutide when administered as a fixed ratio of Kyinsu was comparable with separate single dose administrations of insulin icodec and semaglutide. For insulin icodec, the C_{max} was similar when administered as Kyinsu compared to separate administration of insulin icodec. However, for semaglutide, C_{max} was higher (1.4-fold) and occurred earlier following Kyinsu administration compared to semaglutide alone. Prediction of C_{max} of semaglutide at steady-state using Pop-PK modelling for Study 4710 indicated a lower difference at steady-state (1.3-fold higher) than following a single dose.

Bioequivalence/ Comparability

No bioequivalence study has been performed.

The manufacturing process for the insulin icodec drug substance and semaglutide drug substance used for Kyinsu was changed and the change in manufacturing process for semaglutide was introduced during conduct of two of the phase 3a studies. Hence, both semaglutide B and semaglutide J (included in the to-be-marketed formulation) were administered in studies NN1535-4591 and NN1535-4592. The impact of the manufacturing change on semaglutide exposure in studies 4591 and 4592 has been evaluated in the population PK analysis and the results showed that the change in manufacturing process had no clinically relevant effect on semaglutide exposure. In addition, a comparability study (NN9535-4820) comparing semaglutide B and J was submitted and the results of this study indicated clinical comparability and thus extrapolation of semaglutide to the to be-marketed Kyinsu based on a population pharmacokinetic analysis.

Influence on absorption of injection site

The impact of injection regions on insulin icodec and semaglutide exposure following insulin Kyinsu administration was assessed by population PK analysis. For Kyinsu, the results of the Pop-PK analysis showed comparable exposure of insulin icodec and semaglutide following Kyinsu administration in the thigh, the abdomen and the upper arm. This was similar to previous data from the monocomponents.

Distribution

Both insulin icodec and semaglutide bind strongly but reversibly to albumin in the bloodstream corresponding to a plasma protein binding of >99% for both compounds.

The mean volume of distribution (V_z/F) was 8-10 L for both insulin icodec and semaglutide in participants with T2D, and it was similar whether administered as Kyinsu or as mono-components.

Elimination

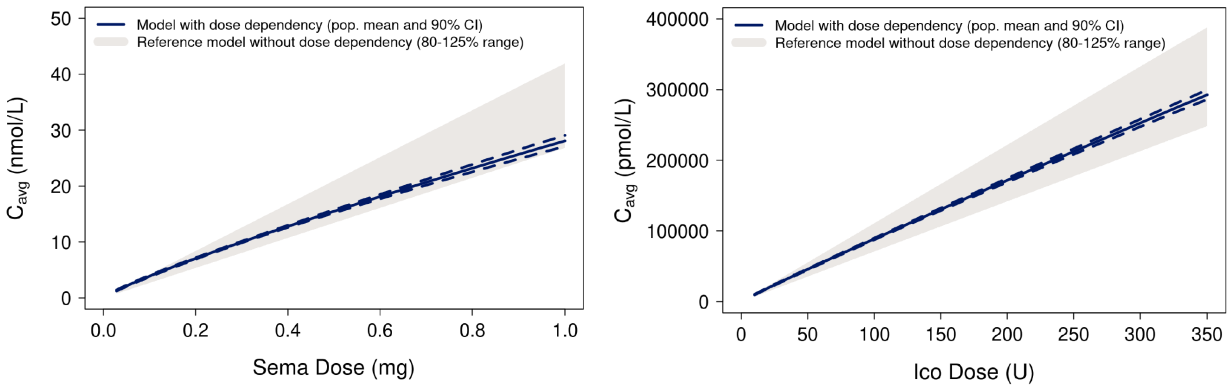
The terminal plasma half-life of insulin icodec and semaglutide is approximately 6-7 days after single subcutaneous dose of Kyinsu. This is in the same range as the half-lives following administration of the mono-components, insulin icodec and semaglutide.

Dose proportionality and time dependencies

Dose proportionality was evaluated using a PopPK approach (see Section "Population pharmacokinetic analysis" for additional details concerning the PopPK model development). Dose-proportionality was assessed with 2 population PK models; one assuming dose-proportionality and one assuming dose-dependent PK (dose was included as a power model on relative bioavailability).

The dose proportionality assessment suggests that there were no clinically relevant deviations from dose proportionality for semaglutide or insulin icodec as a component of Kyinsu within the observed dose range (Figure 5).

Figure 5. Dose proportionality assessment IcoSema component.



Abbreviations: Pop: Population; Sema: Semaglutide; Ico: Insulin icodec; U: Units; CI: Confidence interval. Solid and dotted lines represent mean and 90% CI of Cavg versus dose for the dose-dependent model. The shaded area represents the 80%–125% exposure range of the dose-proportional model. Data from IcoSema arms only. IcoSema=fixed dose regiment insulin icodec/semaglutide.

No new data on time-dependency has been submitted.

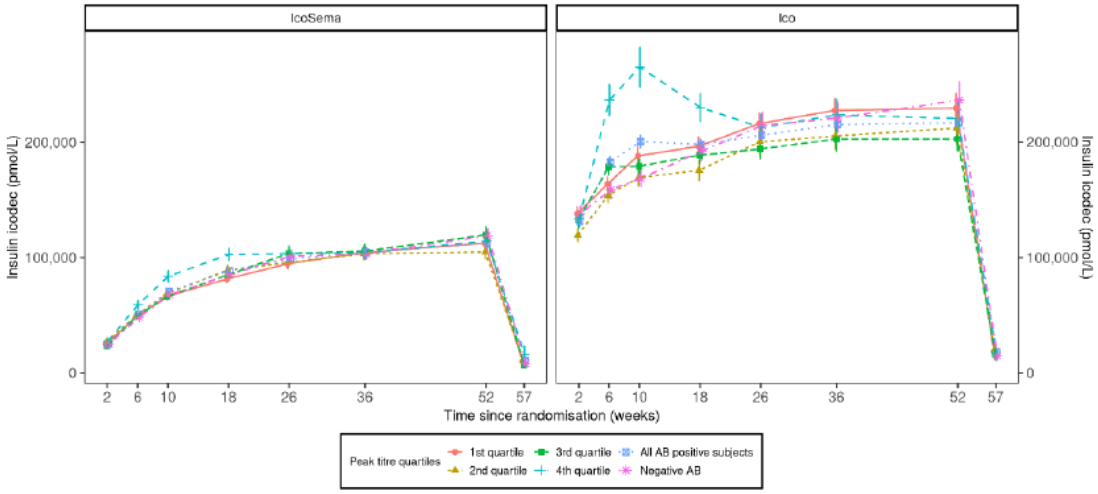
Immunogenicity

The relationship between anti-insulin icodec antibody titres and pharmacokinetic properties of insulin icodec was assessed in study 4591 and 4592. Overall, PK properties were similar between groups, with a trend towards higher exposure with higher ADA titers (figure 11).

Based on the PopPK model, ADA was a statistically significant covariate on CL/F (the 3rd quartile based on ADA titres among subjects with ADA positivity had 3.8% lower CL/F and the 4th quartile based on

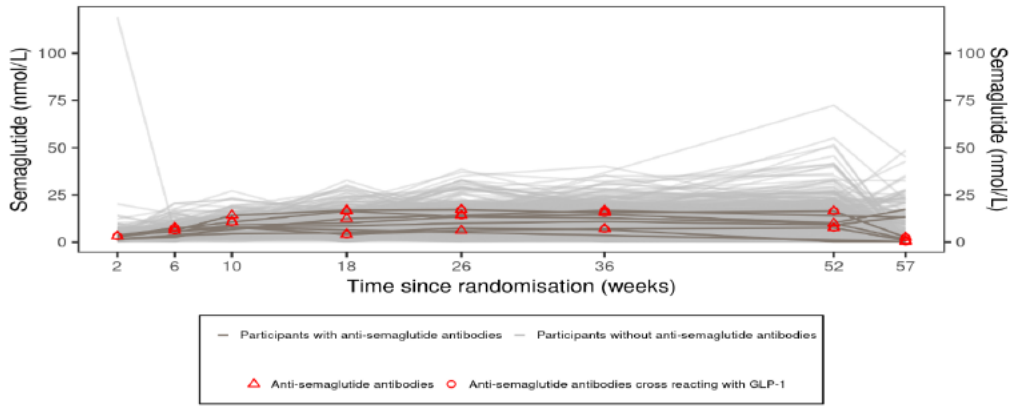
ADA titres among subjects with ADA positivity had 13.5% lower CL/F than ADA negative subjects and subjects with ADA positivity with titres in the 1st and 2nd quartiles). ADA was not a clinically relevant covariate according to the PopPK analysis.

Figure 6. Icodec concentration by treatment week and quartiles of peak anti-insulin icodec antibody titres post baseline – without China mainland – mean plot – in study – safety analysis set – 4591



Anti-semaglutide antibody formation was generally low and positive anti-semaglutide antibodies were only shown for study 4591. Thus, the potential impact of anti-semaglutide antibodies on PK of semaglutide was evaluated by comparing the semaglutide plasma concentrations over time in participants with or without anti-semaglutide antibodies (figure 12).
The impact of ADA was also evaluated in the PopPK analysis, but ADA was not considered a clinically relevant covariate.

Figure 7. Semaglutide concentration by occurrence of anti-sema antibodies – in study – without China mainland – on-treatment – spaghetti plot – 4591



Target population

All clinical PK data for Kyinsu is from Type 2 diabetes patients (the target population). Thus, all the PK data presented in the current Section 3.3.1. represents the target population. This includes NCA data from the dedicated clinical pharmacology studies 4359 and 4710 (see Section "Absorption") as well as the Population PK analysis, which was based on Study 4359, Study 4710, COMBINE 1 and COMBINE 2 (see Section "Population pharmacokinetic analysis").

No Kyinsu data in healthy volunteers has been provided by the applicant.

Variability between patients was quantified in the PopPK analysis where the inter-individual variability in CL/F were 24.4%CV and 23.0%CV for semaglutide and insulin icodec, respectively.

The steady-state exposures of semaglutide and insulin icodec in the Kyinsu combination were derived using the PopPK model. For semaglutide, the geometric mean Cavg at steady state was 15 nmol/L (61.9%CV) and the geometric mean C_{max} was 21 nmol/L (61.7%CV). For insulin icodec, the geometric mean Cavg at steady state was 136089 pmol/L (59.7%CV) and the geometric mean C_{max} was 179620 pmol/L (59.8%CV).

Special populations

The impact of special populations on the Kyinsu PK profile was generally explored using a PopPK approach.

Renal impairment was not a clinically relevant covariate on semaglutide or insulin icodec PK. For semaglutide, the PopPK dataset included 49.2% patients with normal renal function, 42.1% with mild renal impairment and 8.7% with moderate renal impairment. For insulin icodec, the PopPK dataset included 47.9% patients with normal renal function, 41.9% with mild renal impairment and 10.2% with moderate renal impairment.

The PK properties in participants with hepatic impairment have been investigated for the mono-components and are considered applicable for Kyinsu as well. Based on the data from the mono-components, dose-adjustments of Kyinsu are not necessary in patients with varying degrees of hepatic impairment.

Sex, ethnic factors and age were not clinically relevant covariates on semaglutide or insulin icodec PK.

Body weight was a clinically significant covariate for semaglutide and insulin icodec (included on clearance- and volume terms) where the exposure decreased with increasing weight. For semaglutide, the PopPK dataset had a mean wight of 86.4 kg (SD: 17.5 kg) and ranged from 40.7 to 155.3 kg. For

insulin icodec, the PopPK dataset had a mean weight of 85.1 kg (SD: 17.3 kg) and ranged from 40.7 to 155.3 kg.

Number of subjects with PK observations in different age groups including elderly subjects are presented in Table 4 (participants in studies with insulin icodec PK sampling) and Table 5 (participants in studies with semaglutide PK sampling).

Table 4. Number of participants with insulin icodec PK samples by study and age group

Study	18<= to <65 years	65<= to <75 years	75<= to <85 years	85<= years	Total
4359	30	0	0	0	30
4710	20	0	0	0	20
4591 COMBINE 1	780	410	87	6	1283
4592 COMBINE 2	210	110	18	0	338
Total	1040	520	105	6	1671

Table 5. Number of participants with semaglutide PK samples by study and age group

Study	18<= to <65 years	65<= to <75 years	75<= to <85 years	85<= years	Total
4359	31	0	0	0	31
4710	20	0	0	0	20
4591 COMBINE 1	380	222	36	3	641
4592 COMBINE 2	450	195	32	0	677
Total	881	417	68	3	1369

Pharmacokinetic interaction studies

No new interaction studies have been performed for the fixed combination, data for the individual compounds are referred to.

There was a change in the semaglutide PK observed when administered as Kyinsu with a higher C_{max} (up to 2-fold following single-dose and 1.5-fold at steady-state) and an earlier t_{max} compared to administration of semaglutide alone.

2.7.2.2. Pharmacodynamics

Insulin icodec/semaglutide (Kyinsu) is a fixed ratio combination product for once-weekly subcutaneous injection. It comprises the basal insulin, insulin icodec (Awiqli, a once-weekly basal insulin approved for

the treatment of diabetes), and the GLP-1 receptor agonist, semaglutide (Ozempic, a once-weekly s.c. injection approved for treatment of type 2 diabetes mellitus).

Mechanism of action

Insulin icodec is an insulin analogue with a fatty acid chain attached to the peptide backbone via a spacer. The slow and steady glucose-lowering effect of insulin icodec is mainly due to reversible albumin binding as well as reduced insulin receptor binding and receptor-mediated clearance from the circulating insulin icodec depot. The molecular mode of action of insulin icodec is the same as for human insulin.

Semaglutide is a GLP-1 RA with a fatty acid chain attached to the peptide backbone via a spacer. The extended effect of semaglutide is mainly due to reversible albumin binding and reduced susceptibility to DPP-4 degradation. GLP-1 is known to affect glycaemic control by stimulating secretion of insulin and reducing secretion of glucagon in a glucose-dependent manner. Semaglutide reduces body weight and body fat mass through lowered energy intake, involving an overall reduced appetite. Semaglutide had a beneficial effect on plasma lipids and lowered systolic blood pressure in clinical studies. These effects have also been established for once-weekly semaglutide s.c. in people with T2D.

Primary and secondary pharmacology

The development program investigating the pharmacodynamic profile of Kyinsu is in general considered adequate. The pharmacodynamic properties of the mono-components, insulin icodec and semaglutide, have been addressed in the individual development programmes.

An analysis of the relationship between change from baseline in HbA_{1c} and exposure to insulin icodec and semaglutide (as reflected by model-derived C_{avg} at steady state) in studies 4591 and 4592 was carried out to investigate the contribution of the individual drug components to the overall glycaemic control obtained with Kyinsu.

The rationale for the chosen starting dose and titration scheme in the clinical studies was based on data from PK single dose studies 4359 and 4710. In study 4359 with Kyinsu at 175 dose steps (corresponding to 175 U insulin icodec/0.5 mg semaglutide), the subjects experienced more GI AEs with Kyinsu (73%) than with 0.5 mg semaglutide alone (43%). In study 4710 with a lower starting dose of 40 dose steps (corresponding to 40 U insulin icodec/0.114 mg semaglutide), the incidence of GI AEs was 26% and for Kyinsu and 20% for semaglutide 0.114 mg. To compensate for the peak profile of semaglutide and associated GI AEs, a titration scheme with a lower starting dose of 40 DS (corresponding to 40 U insulin icodec/0.114 mg semaglutide) was selected for the phase 3a COMBINE programme.

No data on secondary pharmacology has been provided.

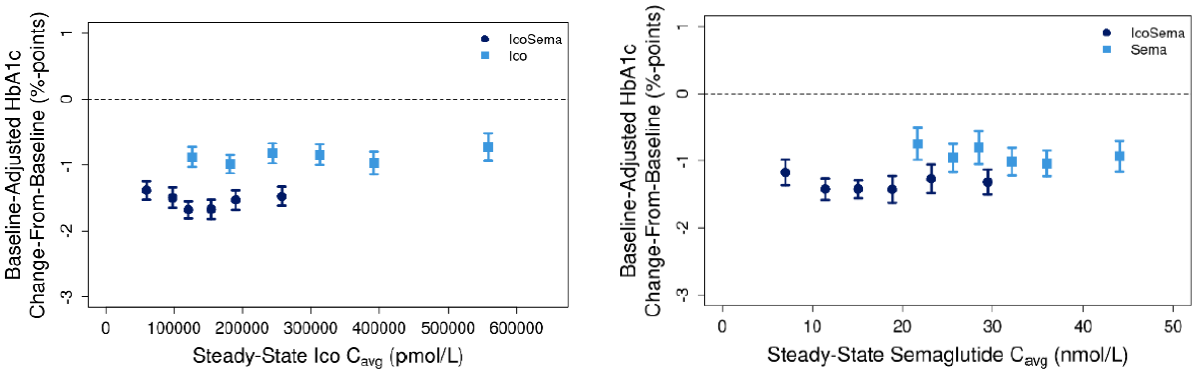
2.7.2.3. Pharmacokinetics/pharmacodynamics (PK/PD)

An analysis of the relationship between change from baseline in HbA_{1c} and exposure to insulin icodec and semaglutide in **studies 4591** (Kyinsu versus insulin icodec) and **4592** (Kyinsu versus semaglutide) was carried out to investigate the contribution of the individual drug components to the overall glycaemic control obtained with Kyinsu.

The contribution of semaglutide was evaluated based on COMBINE 1 where data from 1281 patients contributed to the exposure-response analysis. The contribution of insulin icodec was evaluated using COMBINE 2 where data from 676 patients contributed to the exposure-response analysis. Estimated effects of the components on HbA1c are shown as change from baseline plotted against exposure in terms of quantiles of Cavg values for each component, respectively in Figure 8. The reduction in HbA1c

was consistently greater with Kyinsu than with the corresponding mono-component, across the entire exposure range demonstrating a contribution of the semaglutide and insulin icodec component, respectively, to the overall efficacy of Kyinsu regardless of exposure.

Figure 8. Exposure-response relationship for HbA1c and insulin icodec.



Abbreviations: Ico: Insulin icodec; U: Units. Symbols with error bars are geometric mean observations with 95% CIs using 6 quantiles per arm. Data from COMBINE 1.

2.7.3. Discussion on clinical pharmacology

Pharmacokinetics

Methods

Validation of all methods with available validation reports was performed following current guidelines and shows that the methods are adequately validated, including long term stability, and cross-validation between the methods. The lack of interference with other insulins and semaglutide was assessed at clinically relevant concentrations. Study sample analysis was adequate.

The ADA methods were adequately validated following current guidelines and white papers. The selection of cutpoints in the validation and study sample analysis were overall adequate. The lack of data on the neutralising potential is acceptable. The assays used in case of hypersensitivity are considered fit for purpose.

Absorption

The PK properties following administration of Kyinsu versus monocomponents were comparable in studies 4359 (White participants) and 4710 (Chinese participants). The higher C_{max} of semaglutide following administration of Kyinsu compared to semaglutide alone was observed in both studies. The C_{max} was up to 2-fold higher following single-dose and estimated to 1.5-fold higher at steady-state.

The applicant has a theory that the higher C_{max} and earlier t_{max} of semaglutide when administered as Kyinsu compared to semaglutide alone could be explained by competitive binding for albumin between insulin icodec and semaglutide in subcutaneous tissue following injection. A physiology-based pharmacokinetic (PBPK) model was submitted with the aim of understanding the interplay between formulation and the affinity for albumin in the subcutis and the impact on the shape of the PK profile following subcutaneous administration. Overall, this analysis contributed to better understanding of potential mechanisms behind the observation that the semaglutide C_{max} is higher in the Kyinsu combination than semaglutide monotherapy. Bearing this in mind, the analysis is viewed as exploratory and was considered to have rather limited impact on the overall benefit-risk assessment.

Bioequivalence/comparability

For a fixed-dose combination containing two known active substances the Guideline on clinical development of fixed-combination medicinal products states that bioequivalence should be demonstrated between the free combination of the individual monocomponents and the marketing formulation (fixed combination), but since the indication is an add-on indication and not a substitution indication, no such bioequivalence trials are required.

There are some manufacturing changes during the phase 3a programme for Kyinsu. The impact of the manufacturing change on semaglutide exposure in studies 4591 and 4592 has been evaluated in the population PK analysis and the results showed that the change in manufacturing process had no clinically relevant effect on semaglutide exposure. In addition, a comparability study (NN9535-4820) comparing semaglutide B and J was discussed in a follow-up scientific advice EMA/SA/0000134324, and the results of this study indicated clinical comparability and thus extrapolation of semaglutide to the to be-marketed Kyinsu based on a population pharmacokinetic analysis (data not shown).

Dose proportionality and time-dependency
Dose proportionality for Kyinsu was explored using a PopPK approach which is acceptable. No clinically relevant deviations from dose proportionality were evident for semaglutide or insulin icodec. However, there was a numerical trend of less than dose proportional increase with exposure with dose for semaglutide. The SmPC has been updated including information that the semaglutide PK is approximately dose proportional in the dose range 0.1-1 mg.

The risk of (clinically significant) time-dependency in semaglutide or insulin icodec PK is considered low which is also in line with the insulin icodec and semaglutide monotherapy products.

Immunogenicity
A trend towards higher exposure with higher ADA titers of insulin icodec was observed. The trend towards higher exposure with higher ADA titers has also been observed in previous application (EMEA/H/C/005978/0000 Awiqli). As for anti-semaglutide antibodies, the presence of ADA does not appear to affect the PK of semaglutide.

Target population
From a PK perspective, the Phase 3 studies COMBINE 1 and COMBINE 2 adequately reflects the target population. COMBINE 1 and 2 included collection of PK data with a sparse PK design which were analysed using a PopPK approach.

Overall, the PopPK model is considered to have rather low regulatory impact in the current procedure, as it is used for descriptive purposes mainly and to support SmPC statements in SmPC 5.2.

The PopPK models were developed on sufficiently large datasets for semaglutide and insulin icodec.

For insulin icodec, the exclusions were limited to rather few observations and is considered acceptable. For semaglutide, a rather large number of PK observations were excluded (1916 samples, 15.8% of the PK dataset prior to any exclusions). A main reason was data below LLOQ which is reasonable.

The covariate distributions for semaglutide and insulin icodec PopPK analyses are considered reasonable given the target population (Type 2 diabetes patients).

The parameter estimates of the final semaglutide and insulin PopPK models, and their RSEs, were reasonable. The choice of structural models were linear two- and one-compartment models for semaglutide and insulin icodec, respectively, which is acceptable.

According to the model diagnostic plots, including VPCs, the final models gave acceptable description of the observed data despite that the variability was slightly over-predicted for Studies 4359 and 4710. The studies COMBINE 1 and 2, where variability was described adequately, is a better reflection of the target population and therefore, the final models are acceptable.

The only identified clinically significant covariate was body weight. The applicant used forest plots (data not shown) to conclude if the covariates were clinically relevant, which is acceptable.

Although treatment arm (Kyinsu vs semaglutide monotherapy) was not a clinically relevant covariate, the final semaglutide model predicted higher semaglutide C_{max} for Kyinsu than semaglutide monotherapy. This agrees with the single-dose clinical pharmacology studies 4359 and 4710 where the semaglutide C_{max} was ~1.5- to 2-fold higher for Kyinsu than semaglutide monotherapy. The PopPK model was used to describe the difference in C_{max} at steady-state where the difference was less pronounced (~1.3- to 1.5-fold) compared to a single-dose.

Of note, injection site and drug product were not clinically relevant.

Special populations
No dose adjustment is required for patients with hepatic impairment based on results for the mono-components. This is considered adequate also for the fixed combination.

A PopPK approach was used to describe the other relevant special populations. Renal function, sex, ethnic factors and age were not clinically relevant covariates.

Body weight was identified as a clinically relevant PK covariate for semaglutide and insulin icodec. This is reasonable and in line with the corresponding mono-products Ozempic and Awiqli. Body weight is not described as a clinically significant covariate in SmPC section 5.2. This is acceptable since the Kyinsu dose is individualized regardless of body weight. Any need for a different dose will be implicitly handled in the clinical setting. Thus, the information is a clinically relevant covariate will not be valuable for prescribers for Kyinsu treatment in the target population (adult Type 2 diabetes patients).

Interactions
No new interaction studies have been performed for the fixed combination, data for the individual compounds are referred to. SmPC section 4.5: The information regarding interactions for insulin icodec is acceptable. The information regarding interactions for semaglutide has been updated in accordance with the interaction text in the SmPC of Ozempic and Wegovy.

Pharmacodynamics

The insulin icodec/semaglutide combination is a once-weekly fixed ratio combination product of a long-acting human insulin analogue (insulin icodec) together with a GLP-1 receptor agonist (semaglutide). Since both insulin icodec and semaglutide are efficacious when given once-weekly, both components can be mixed as a defined fixed ratio formulation to be delivered by one single injection combining the complementary therapeutic benefits of the constituent agents.

The mechanism of action and pharmacodynamic properties of both components, insulin icodec and semaglutide, have been well characterised in the development programs of the mono-components supporting their respective MAAs. The mechanism of action for semaglutide is complementary to the mechanism of action of insulin icodec with regards to the glucose lowering effect. Both components have a long duration of action and can be given as OW injections.

The primary pharmacology of insulin icodec has been well characterised within the original MAA and was not further investigated with this application.

No PD studies were performed. The pharmacodynamic properties of the mono-components, insulin icodec and semaglutide, have been addressed and well characterised within the original MAA, respectively.

The exposure-response analyses of Kyinsu was investigated for HbA1c reduction. The analyses showed that both components, Icodec and semaglutide, contribute to the glucose lowering effect.

The rationale for the chosen starting dose and titration scheme in the clinical studies was based on data from PK studies 4359 and 4710.

2.7.4. Conclusions on clinical pharmacology

The pharmacokinetics of insulin icodec and semaglutide in the new formulation has been sufficiently characterised, and bridging to clinical pharmacology data of the mono-components is acceptable. The bioanalytical method and immunogenicity method has been adequately validated.

A higher C_{max} of semaglutide (up to 2-fold following single-dose and estimated to 1.5-fold higher at steady-state) was observed following administration of Kyinsu compared to semaglutide alone.

The primary pharmacology of insulin icodec has been well characterised within the original MAA and was not further investigated with this application. No PD studies were performed. The pharmacodynamic properties of the mono-components, insulin icodec and semaglutide, have been addressed and well characterised within the original MAA, respectively.

The exposure-response analyses of Kyinsu showed that both components, Icodec and semaglutide, contribute to the glucose lowering effect.

The rationale for the chosen starting dose and titration scheme in the clinical studies was based on data from PK studies 4359 and 4710.

2.7.5. Clinical efficacy

The evaluation of efficacy is based on the results of the three clinical trials in the phase 3a COMBINE programme (**Table** 6).

Table 6. Clinical phase 3a studies

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
NN1535-4591 (COMBINE 1)	Randomised patients: IcoSema (n=646) insulin icodec (n=645) Exposed patients: IcoSema (n=644) insulin icodec (n=644)	52 weeks, multi-national, multi-centre, randomised, open-label, parallel group, treat-to-target/ dose escalation confirmatory study with 2 treatment arms	Once-weekly s.c. IcoSema (700 units/mL + 2 mg/mL)– individualised dosing Once-weekly s.c. insulin Icodec (700 units/mL) – individualised dosing	T2D patients (GLP-1 RA naïve, inadequately controlled with daily basal insulin)
NN1535-4592 (COMBINE 2)	Randomised patients: IcoSema (n=342) semaglutide (n=341)	52 weeks, multi-national, multi-centre, randomised, open-label, parallel group, treat-to-target/ dose escalation confirmatory	Once-weekly s.c. IcoSema (700 units/mL + 2 mg/mL) – individualised dosing	T2D patients (insulin naïve, inadequately controlled with a GLP-1 agonist)

	Exposed patients: IcoSema (n=341) semaglutide (n=340)	study with 2 treatment arms	Once-weekly s.c. semaglutide (1.34 mg/mL), 1 mg	
NN1535-4593 (COMBINE 3)	Randomised patients: IcoSema (n=340) insulin glargin + insulin aspart (n=339) Exposed patients: IcoSema (n=340) insulin glargin + insulin aspart (n=328)	52 weeks, multi-national, multi-centre, randomised, open-label, parallel group, treat-to-target/ dose escalation confirmatory study with 2 treatment arms	Once-weekly s.c. IcoSema (700 units/mL + 2 mg/mL) – individualised dosing Once-daily s.c. insulin glargine combined with 2-4 times daily insulin aspart (100 units/mL and 100 units/mL)– individualised dosing	T2D patients (inadequately controlled with daily basal insulin)

Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

2.7.5.1. Dose-response studies

No formal dose-response studies were performed.

Dose selection rationale for the fixed-ratio combination

The starting dose for Kyinsu was based on the observations in the PK studies 4359 and 4710. In study 4359, the subjects experienced more GI AEs with Kyinsu than with semaglutide alone. In study 4710, with a lower starting dose, the incidence of GI AEs was reduced for Kyinsu and similar to semaglutide alone there was no restriction on the maximum dose of insulin in comparator groups (i.e. for basal-bolus insulin or insulin icodec) in studies 4591 and 4593.

The dose for Kyinsu in study 4710 (40 DS corresponding to 40 U insulin icodec/0.114 mg semaglutide) was chosen as the starting dose of Kyinsu for the phase 3a studies.

In the clinical studies, titration algorithms were in place for both the Kyinsu treated groups and those treated with insulin icodec and with insulin glargine. For Kyinsu dose adjustments of ±10 DS (equivalent to 10 U insulin icodec/0.029 mg semaglutide) was applied.

A treat-to-target concept was applied in all phase 3a studies for Kyinsu and the insulin comparators, where the dose was adjusted for each individual participant according to a pre-specified titration algorithm with the aim of achieving pre-defined glycaemic targets (4.4−7.2 mmol/L). The titration was based on the last 3 fasting SMPG values prior to dose adjustment. A fixed dose/dose escalation treatment was applied for the semaglutide comparator in study 4592.

The maximum dose of Kyinsu was 350 DS, corresponding to 350 units insulin icodec and 1 mg semaglutide. At the time the phase 3a COMBINE protocols were developed, 1 mg semaglutide was the approved maximum dose for semaglutide s.c. in treatment of T2DM. Since then, 2 mg of semaglutide has also been approved, which is currently the approved maximum dose of semaglutide. There was no restriction on the maximum dose of insulin in comparator groups (i.e. for basal-bolus insulin or insulin icodec) in studies 4591 and 4593.

Titration and SMPG values

When switching from daily basal insulin (studies 4591 and 4593), transient increases in mean fasting SMPG values of 1.9-2.2 mmol/L was observed during the first 2 weeks of treatment in the Kyinsu group. Subjects with higher HbA1c baseline values (≥8.5%) and subjects switching from higher pre-study basal insulin doses (≥40 U) experienced increases in SMPG up to 3 mmol/L. There was a tendency of longer time to return to baseline in subjects with higher pre-study insulin dose. In study 4592, minor increases in fasting SMPG (≤1 mmol/L) was observed for both Kyinsu and semaglutide. Across all studies, the SMPG values had returned to baseline value after about 7-9 weeks of treatment. Patients treated with Kyinsu reached target SMPG values (<7.2 mmol/L) at week 14-18.

In study 4593, CGM data confirmed that less subjects in the Kyinsu group (30-33%) spent time in range (TIR), 3.9-10.0 mmol/L, compared to patients treated with basal-bolus insulin (47-51%) during the first 4 weeks of treatment. TIR increased over time in both treatment groups. After 8 weeks of treatment, the difference in TIR between the Kyinsu group (52%) compared to basal-bolus insulin group (55%) was less pronounced. The CGM data was aligned with the SMPG data. More subjects in the Kyinsu group (66-69%) spent time above range (>10.0 mmol/L) compared to patients treated with basal-bolus insulin (50-52%) during the first 3 weeks of treatment, with the greatest increase in time above range (TAR) after 2 weeks of treatment.

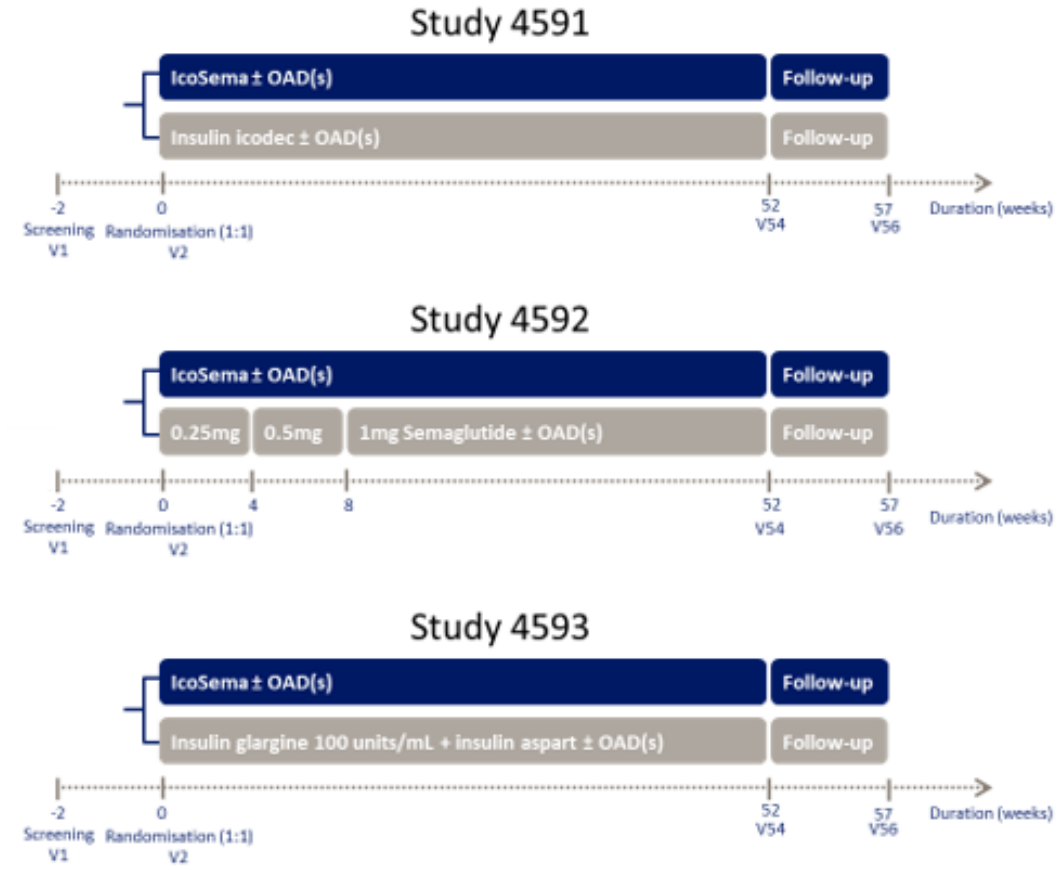
In addition, the incidence of hyperglycaemia was increased for Kyinsu compared to insulin icodec overall in study 4591 (4.2% versus 2.6%) and for Kyinsu compared to IGlar+IAsp in study 4593 (4.1% versus 1.2%) (See Safety section). Most of the hyperglycaemic events in the Kyinsu group were reported during the first 12 weeks of treatment in the studies.

Information regarding increases in fasting SMPG values during the first weeks of treatment in patients when switching from basal insulin has been adequately reflected in the SmPC.

2.7.5.2. Main study(ies)

The evaluation of efficacy is based on the results of the three phase 3a studies in the COMBINE programme: studies NN1535-4591 (COMBINE 1), NN1535-4592 (COMBINE 2) and NN1535-4593 (COMBINE 3) (**Figure 9**).

Figure 9. Overview of the phase 3a studies



Abbreviations: IcoSema: insulin icodec and semaglutide

Methods

All three phase 3a studies were multinational, multicentre, randomised (1:1), 52-week, open-label, parallel-group, confirmatory studies with 2 treatment arms. The studies compared the efficacy and safety of treatment with once-weekly Kyinsu versus an active comparator. Both treatment arms were with and without OADs. The population studied spanned participants with T2D previously on basal insulin (study 4591 and 4593) or GLP-1 Ras (study 4592).

Study 4591 (COMBINE 1) – patients inadequately controlled with daily basal insulin

Study 4591 included adult T2DM patients inadequately controlled with daily basal insulin (treated ≥ 90 days before screening) ± OAD (with stable doses ≥90 days). A total of 1,291 participants were randomised to receive Kyinsu (n=646) or insulin icodec (n=645). Of these, 61.9% were male, 63.1% were White, 32.5% were Asian, 3.4% were Black or African American. Their mean baseline characteristics were, age: 60.6 years; HbA_{1c}: 8.22%, FPG: 8.60 mmol/L, BMI: 29.9 kg/m^2, diabetes duration: 15.3 years.

Study 4592 (COMBINE 2) – patients inadequately controlled with GLP-1 RA

Study 4592 included adult insulin naïve T2DM patients inadequately controlled with GLP-1 RA (treated ≥ 90 days before screening) ± OAD (with stable doses ≥90 days). A total of 683 participants were randomised to receive Kyinsu (n=342) or semaglutide (n=341). Of these, 58.1% were male, 63.5% were White, 27.7% were Asian, 3.1% were Black or African American. Their mean baseline

characteristics were, age: 59.1 years; HbA_{1c}: 8.00%, FPG: 9.45 mmol/L, BMI: 31.11 kg/m^2, diabetes duration: 12.6 years.

Study 4593 (COMBINE 3) – patients inadequately controlled with daily basal insulin

Study 4593 included adult T2DM patients inadequately controlled with daily basal insulin (treated ≥ 90 days before screening) ± OAD (with stable doses ≥90 days). A total of 679 participants were randomised to receive Kyinsu (n=340) or basal-bolus insulin (n=339). Of these, 58.8% were male, 53.5% were White, 38.7% were Asian, 5.2% were Black or African American. Their mean baseline characteristics were, age: 59.6 years; HbA_{1c}: 8.30%, FPG: 8.68 mmol/L, BMI: 30.39 kg/m^2, diabetes duration: 14.4 years.

Study participants

Across the studies, inclusion criteria were patients diagnosed with T2DM ≥180 days before screening, HbA1c ≥7% and ≤10% and BMI ≤40 kg/m^2. Exclusion criteria was treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within 90 days before screening and anticipated initiation or change in concomitant medication (for more than 14 consecutive days) known to affect weight or glucose metabolism (table 14, table 15).

Sulfonylureas, meglitinides (glinides) and DPP-4 inhibitors were discontinued at randomisation. Risk of hypoglycaemia increases when insulin secretagogues like sulfonylureas and glinides are used in association with insulin or combination injectable antidiabetic therapy. Therefore, to minimise the risk sulfonylureas and glinides were discontinued at randomisation. Likewise, DPP-4 inhibitors were discontinued since the combined use of a GLP-1 RA and a DPP-4 inhibitor is not currently recommended.

Table 7. Inclusion criteria across the COMBINE studies

Inclusion criterion	Study 4591	Study 4592	Study 4593
Informed consent obtained before any study-related activities	x	x	x
Male or female of at least 18 years of age[a]	x	x	x
Diagnosed with type 2 diabetes mellitus ≥ 180 days before screening	x	x	x
HbA_{1c} of 7.0-10.0% (53.0-85.8 mmol/mol) (both inclusive)	x	x	x
Once or twice daily basal insulin[b] ≥ 90 days before screening with or without OADs[c]	x		x
Insulin naïve[d]		x	
Daily or weekly GLP-1 receptor agonist[e] ≥ 90 days before screening with or without OADs[c]		x	
Body mass index (BMI) ≤ 40.0 kg/m^2	x	x	x
Not currently using real time continuous or flash glucose monitoring	x	x	x

[a] Participants in Japan and Taiwan had to be ≥20 years at the time of signing informed consent.
[b] 20-80 units/day (neutral protamine hagedorn insulin, insulin degludec, insulin detemir, insulin glargine 100 units/mL, or insulin glargine 300 units/mL).
[c] Metformin, sulfonylureas, meglitinides (glinides), DPP 4 inhibitors, sodium glucose co transporter 2 inhibitors, alpha glucosidase inhibitors, thiazolidinediones, or marketed oral combination products *only including the products listed here.*
[d] Exceptions are permitted: short term insulin treatment for a maximum of 14 days before screening

and/or prior insulin treatment for gestational diabetes.
[e] Once-weekly semaglutide >1 mg was not allowed

Table 8. Inclusion criteria across the COMBINE studies

Exclusion criteria for study 4591, 4592 and 4593
Known or suspected hypersensitivity to randomised treatment or related products
Previous participation in this study. Participation is defined as signed informed consent.
Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using a highly effective contraceptive method
Participation in any interventional, clinical study within 90 days before screening
Any disorder, except for conditions associated with T2D, which in the investigator's opinion might jeopardise participant's safety or compliance with the protocol
Anticipated initiation or change in concomitant medication (for more than 14 consecutive days) known to affect weight or glucose metabolism (e.g., treatment with orlistat, thyroid hormones, or systemic corticosteroids)
Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria within 90 days before screening
Any episodes of diabetic ketoacidosis within 90 days before screening
Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma
Presence or history of pancreatitis (acute or chronic) within 180 days before screening
Any of the following: Myocardial infarction, stroke, hospitalization for unstable angina pectoris or transient ischaemic attack within 180 days before screening
Chronic heart failure classified as being in New York Heart Association Class IV at screening
Planned coronary, carotid or peripheral artery revascularisation
Renal impairment measured as estimated glomerular filtration rate value of < 30 mL/min/1.73 m^2 at screening as defined by KDIGO 2012
Impaired liver function, defined as alanine aminotransferase ≥2.5 times or bilirubin > 1.5 times upper normal limit at screening
Inadequately treated blood pressure defined as systolic ≥180 mmHg or diastolic ≥ 110 mmHg at screening
Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 90 days before 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
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 before screening
Additional exclusion criteria for study 4591 and 4593
Known hypoglycaemic unawareness as indicated by the investigator according to Clarke's questionnaire question 8
Recurrent severe hypoglycaemic episodes within the last year (12 months) as judged by the investigator

Treatments

All trial products were injected subcutaneously.

Insulin icodec/semaglutide (Kyinsu) (700 U/mL + 2 mg/mL) combines the active substances of two approved substances, insulin icodec and semaglutide. Three active comparators were included in the

COMBINE studies: Insulin icodec 700 units/mL, semaglutide 1.34 mg/mL and insulin glargine 100 units/mL (+ insulin aspart 100 units/mL).

The PDS290 pre-filled pen-injector was used for administration of Kyinsu, insulin icodec, and semaglutide while insulin glargine was administered using the SoloStar pre-filled pen-injector and insulin aspart using the pre-filled FlexPen. All trial products were injected in thigh, upper arm, or abdomen.

Starting doses

Study 4591

Insulin icodec/semaglutide (Kyinsu) and insulin icodec were injected once weekly on the same day each week, at any time of the day.

Insulin icodec/semaglutide (Kyinsu) was taken once-weekly at the same day of the week. The starting dose at randomisation was 40 dose steps (equivalent to 40 units of insulin icodec and 0.114 mg of semaglutide) and titrated to target in 10 DS increments.

Insulin icodec was taken once weekly at the same day of the week. All participants received a loading dose at randomisation, which consisted of total daily basal insulin dose before randomisation x 7 + 50% of their total daily basal insulin dose x 7. The following week, the dose was the total daily dose before randomisation x 7.

Study 4592

At randomisation eligible participants were randomised to receive Kyinsu or semaglutide.

Insulin icodec/semaglutide (Kyinsu) was taken once-weekly at the same day of the week. The starting dose at randomisation was 40 dose steps (equivalent to 40 units of insulin icodec and 0.114 mg of semaglutide) and titrated to target in 10 DS increments.

Semaglutide was taken once weekly at the same day of the week. The starting dose should be 0.25 mg.

The first dose of Kyinsu or semaglutide should be administered at least 5 days after the last dose of pre-trial weekly GLP-1 receptor agonist. The first dose of Kyinsu or semaglutide could be administered the following day after the last dose of pre-trial daily GLP-1 receptor agonist.

Study 4593

At randomisation eligible participants were randomised to receive Kyinsu or basal-bolus insulin treatment.

Insulin icodec/semaglutide (Kyinsu) was taken once-weekly at the same day of the week. The starting dose at randomisation was 40 dose steps (equivalent to 40 units of insulin icodec and 0.114 mg of semaglutide) and titrated to target in 10 DS increments.

Insulin glargine was taken once daily at the same time of the day every day. Starting dose was in accordance with local label.

Insulin aspart was taken with the main meals 2-4 times a day. The starting dose was 4 units per main meal.

Dose adjustments of trial products

Study 4591

Adjustment of Kyinsu *dose and insulin icodec dose*

The dose of Kyinsu and insulin icodec were adjusted once weekly by the investigator based on the 3 fasting SMPG values measured on 2 days prior to the dose adjustment and on the day of the contact.

Adjustment of Kyinsu and insulin icodec were done in accordance with **Table 9.**

Study 4592

Adjustment of Kyinsu *dose*

The dose of Kyinsu was adjusted once weekly by the investigator based on the 3 fasting SMPG values measured on 2 days prior to the dose adjustment and on the day of the contact.

Adjustment of Kyinsu was done in accordance with **Table 9.**

Adjustment of semaglutide dose

After 4 weeks of treatment with 0.25 mg, the dose was increased to 0.5 mg once-weekly. After at least 4 more weeks the dose was increased to 1 mg once-weekly. If adverse events occur, the escalation to 1 mg could be extended up to 26 weeks after randomisation. Dose reductions of semaglutide from 1 mg to 0.5 mg was allowed in case of safety concern or unacceptable intolerability.

Study 4593

Adjustment of Kyinsu *dose and insulin glargine dose*

The dose of Kyinsu and insulin glargine were adjusted once weekly by the investigator based on the 3 fasting SMPG values measured on 2 days prior to the dose adjustment and on the day of the contact.

Adjustment of Kyinsu and basal insulin were done in accordance with **Table 9.**

Adjustment of insulin aspart dose

During the first 8 weeks after randomisation insulin aspart should only be adjusted for safety reasons. Thereafter, the doses could be considered adjusted twice weekly at intervals of 3-4 days, either as self-titration or assisted by the investigator. Dose adjustment was based on the pre-prandial or bedtime SMPG values measured on the 3 days prior to titration in accordance with **Table 10**.

Maximum dose

The maximum allowed weekly dose of Kyinsu was 350 dose steps (DS) (equivalent to 350 units insulin icodec and 1 mg semaglutide). The maximum dose of semaglutide was 1 mg once weekly. There was no restriction on the maximum dose of insulin icodec, insulin glargine or insulin aspart.

Missed dose

Missing Kyinsu *dose guidance*

If an Kyinsu or insulin icodec dose is missed for ≤3 days after the planned dosing day, the participants should inject the planned dose. If the dose is missed for >3 days, the participants should await the next planned day of injection.

Missing semaglutide dose guidance

If a semaglutide dose is missed, it should be administered as soon as possible and within 5 days after the missed dose. If more than 5 days have passed, the missed dose should be skipped, and the next dose should be administered on the regularly scheduled day.

Table 9. Adjustment of Kyinsu, insulin icodec and insulin glargine doses

Fasting SMPG			**IcoSema**	**Insulin icodec**	**Insulin glargine**
Value to use	mmol/L	mg/dL	dose steps	Units	Units
Lowest of the SMPG values	<4.4	<80	-10	-20	-3
Mean of the SMPG values	4.4–7.2	80–130	0	0	0
	>7.2	>130	+10	+20	+3

Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

Table 10. Adjustment of insulin aspart doses

Target pre-prandial and bedtime SMPG		**Rule**	**Dose adjustment**
mmol/L	mg/dL		Units
4.4–7.2	80–130	≥1 SMPG below target	-1
		No SMPG below target 0-1 SMPG above target	0
		No SMPG below target ≥2 SMPGs above target	+1

Objectives

Primary objective

The primary objective for the three phase 3a COMBINE studies was to demonstrate the effect on glycaemic control of once-weekly Kyinsu in a specific T2D population. This included comparison of the change in HbA_{1c} from baseline to end of treatment to:

- confirm superiority versus insulin icodec in participants with T2D inadequately controlled with daily basal insulin (study 4591)
- confirm superiority versus semaglutide in participants with T2D inadequately controlled with a GLP-1 receptor agonist (study 4592)
- confirm non-inferiority versus daily insulin glargine combined with insulin aspart in participants with T2D inadequately controlled with daily basal insulin using a non-inferiority margin of 0.3% (study 4593)

The primary estimand was defined as the treatment effect between Kyinsu and comparator in change in HbA_{1c} from baseline to week 52 for all randomised participants regardless of initiation of non-randomised insulin treatment or additional antidiabetic treatments for more than 2 weeks and adherence to randomised treatment.

The primary estimand for the primary objective for study 4591, 4592 and 4593, respectively, are described in **Table 11**, **12** and **Table 13**.

Table 11. Estimand for primary objective in study 4591

Population	Patients with **T2D inadequately controlled with daily basal insulin** who would encounter the Intercurrent Event of **treatment discontinuation** if assigned under any treatment assignment. Patients with **T2D inadequately controlled with daily basal insulin** who would encounter the Intercurrent Event of **initiation of non-randomised insulin treatment or additional antidiabetic treatments lasting for more than 2 weeks** under any treatment assignment.
Treatment condition	Assignment to once weekly Kyinsu with or without OAD(s) regardless of discontinuation of randomised treatment for any reason and regardless of initiation of non-randomised insulin treatment or additional anti-diabetic treatments for more than 2 weeks and adherence to randomised treatment compared to titration of daily basal-bolus regimen (insulin glargine QD, insulin aspart ≤ QID)) with or without OAD(s), regardless of discontinuation of randomised treatment for any reason and regardless of initiation of non-randomised insulin treatment or additional anti-diabetic treatments for more than 2 weeks and adherence to randomised treatment.
Endpoint (variable)	Change in HbA1c from baseline to week 52
Population-level summary	Difference in mean changes from baseline
Intercurrent events and strategy to handle them	
Intercurrent event 1	Discontinuation of randomised treatment for any reason. Treatment policy.
Intercurrent event 2	Initiation of non-randomised insulin treatment or additional antidiabetic treatments lasting for more than 2 weeks. Treatment policy.

Table 12. Estimand for primary objective in study 4592

Population	Patients with **T2D inadequately controlled with a GLP-1 receptor agonist** who would encounter the Intercurrent Event of **treatment discontinuation** if assigned under any treatment assignment. Patients with **T2D inadequately controlled with a GLP-1 receptor agonist** who would encounter the Intercurrent Event of **initiation of non-randomised insulin treatment or additional antidiabetic treatments lasting for more than 2 weeks** under any treatment assignment.
Treatment condition	Assignment to once weekly Kyinsu with or without OAD(s) regardless of discontinuation of randomised treatment for any reason and regardless of initiation of non-randomised insulin treatment or additional anti-diabetic treatments for more than 2 weeks and adherence to randomised treatment compared to titration of daily basal-bolus regimen (insulin glargine QD, insulin aspart ≤ QID)) with or without OAD(s), regardless of discontinuation of randomised treatment for any reason and regardless of initiation of non-randomised insulin treatment or additional anti-diabetic treatments for more than 2 weeks and adherence to randomised treatment.
Endpoint (variable)	Change in HbA1c from baseline to week 52

Population-level summary	Difference in mean changes from baseline
Intercurrent events and strategy to handle them	
Intercurrent event 1	Discontinuation of randomised treatment for any reason. Treatment policy.
Intercurrent event 2	Initiation of non-randomised insulin treatment or additional antidiabetic treatments lasting for more than 2 weeks. Treatment policy.

Table 13. Estimand for primary objective in study 4593

Population	Patients with **T2D inadequately controlled with daily basal insulin** who would encounter the Intercurrent Event of **treatment discontinuation** if assigned under any treatment assignment Patients with **T2D inadequately controlled with daily basal insulin** who would encounter the Intercurrent Event of **initiation of non-randomised insulin treatment or additional antidiabetic treatments lasting for more than 2 weeks** under any treatment assignment.
Treatment condition	Assignment to once weekly Kyinsu with or without OAD(s) regardless of discontinuation of randomised treatment for any reason and regardless of initiation of non-randomised insulin treatment or additional anti-diabetic treatments for more than 2 weeks and adherence to randomised treatment compared to titration of daily basal-bolus regimen (insulin glargine QD, insulin aspart ≤ QID)) with or without OAD(s), regardless of discontinuation of randomised treatment for any reason and regardless of initiation of non-randomised insulin treatment or additional anti-diabetic treatments for more than 2 weeks and adherence to randomised treatment.
Endpoint (variable)	Change in HbA1c from baseline to week 52
Population-level summary	Difference in mean changes from baseline
Intercurrent events and strategy to handle them	
Intercurrent event 1	Discontinuation of randomised treatment for any reason. Treatment policy.
Intercurrent event 2	Initiation of non-randomised insulin treatment or additional antidiabetic treatments lasting for more than 2 weeks. Treatment policy.

Secondary objectives

Secondary objectives were to compare parameters of glycaemic control and safety of once weekly Kyinsu versus the comparator in specific T2D populations. This included to confirm superiority of once-weekly Kyinsu versus comparator in:

- change in body weight from baseline to week 52 (study 4591 and 4593)
- total weekly insulin dose from week 50 to week 52 (study 4593)

- number of clinically significant hypoglycaemic episodes (level 2) or severe hypoglycaemic episodes (level 3) from baseline to week 57 (study 4591 and 4593), data presented in Safety section.

Outcomes/endpoints

Change from baseline in HbA_{1c} was the primary endpoint in all COMBINE studies. All other endpoints ("change from baseline in fasting plasma glucose (FPG), "time spent in range", "weekly total insulin dose" and "change in body weight" were supportive secondary endpoints, except for "total weekly insulin dose" in study 4593 and "change in body weight" in study 4591 and 4593, respectively, which were confirmatory secondary endpoints. An overview of the efficacy-related endpoints across the COMBINE studies is provided in **Table 14**.

The number of level 2 or level 3 hypoglycaemic episodes were confirmatory endpoints in study 4591 and 4593 (see Safety section).

Table 14. Efficacy-related endpoints and analyses in COMBINE studies

	Study 4591	Study 4592	Study 4593
Glucose metabolism-related endpoints			
Change from baseline to week 52 in:			
HbA_{1c}	P	P	P
FPG	S	S	S
Time spent (%) week 48 to 52[a]:			
Time in target range 3.9-10.0 mmol/L (70-180 mg/dL)	S		S
Time spent < 3.0 mmol/L (54 mg/dL)	S		S
Time spent > 10.0 mmol/L (180 mg/dL)	S		S
Insulin-related endpoints			
Weekly basal insulin dose week 50 to 52	S		
Weekly insulin dose (total) week 50 to 52			C
Body weight-related endpoints			
Change from baseline to week 52 in:			
Body weight (kg)	C	S	C
Change from baseline in DTSQ score			S

[a] CGM was not used in China mainland **Abbreviations**: C = confirmatory secondary endpoint; P: primary endpoint; S = supportive secondary endpoint; y/n = yes/no

Sample size

Study 4591

The sample size was determined based on the number of subjects required to ensure sufficient marginal power (90%) for the confirmatory secondary hypothesis that Kyinsu is superior to insulin icodec in terms of number of hypoglycaemic episodes (level 2 and 3 combined).

For the primary hypothesis and confirmatory secondary hypothesis that Kyinsu is superior to insulin icodec in terms of change from baseline to week 52 in HbA1c and body weight respectively, a total of 680 participants and 200 participants were required.

The assumptions made considered the expected numbers of participants experiencing an intercurrent event and the expected impact of the intercurrent events on the effect size while assuming that the occurrence of intercurrent events were to be equally distributed between treatment arms.

Table 15. Sample size assumptions and power with 1290 randomised participants (Table 9-4, CSP)

Hypothesis	***Assumptions***	***Randomised participants***	***Marginal Power***	***Joint power***
Change in HbA1c, superiority	Treatment difference: -0.33%-point Standard deviation: 1.1% Intercurrent events: 17% Treatment difference adjusted: -0.274%-point	1290	99.4%	99.4%
Change in body weight, superiority	Treatment difference: -2.5 kg Standard deviation: 4.5 kg Intercurrent events: 17% Treatment difference adjusted: -2.075kg	1290	>99.9%	99.4%
Number of hypoglycaemic episodes (level 2 and 3 combined), superiority	Rate ratio: 0.65 Kyinsu episode rate per year: 0.8 icodec episode rate per year: 1.23 Intercurrent events: 17% Rate ratio adjusted: 0.68 Dispersion parameter: 3.6	1290	90%	89.5%

The joint power was calculated under the assumption of independence of the hypotheses by multiplying the respective marginal powers.

Study 4592

The sample size was determined in order to have at least 90% power for meeting the primary hypothesis. Assuming a HbA1c treatment difference of -0.274%-point, and a standard deviation (SD) of 1.1%-point, a total of 680 participants were required to ensure 90% power. The proportion of participants experiencing an intercurrent event was expected to be 17%.

Study 4593

Based on the considerations made 680 participants was required to ensure a marginal power of 84% for confirming non-inferiority using a non-inferiority margin of 0.3%-point.

Table 16. Sample size assumptions and power with 680 randomised participants (Table 9-4, CSP)

Hypothesis	***Assumptions***	***Randomised participants***	***Marginal Power***	***Joint power***
Change in HbA1c, non-inferiority	Treatment difference: 0%-point Standard deviation: 1.1% Intercurrent events: 17% Treatment difference adjusted: 0.051%-point Non-inferiority margin: 0.3%-point	680	83.8%	83.8%

Change in body weight, superiority	Treatment difference: -2.5 kg Standard deviation: 4.5 kg Intercurrent events: 17% Treatment difference adjusted: -2.075kg	680	>99.9%	83.8%
Number of hypoglycaemic episodes (level 2 and 3 combined), superiority	Rate ratio: 0.15 Kyinsu episode rate per year: 0.8 Basal-bolus episode rate per year: 5.33 Intercurrent events: 17% Rate ratio adjusted: 0.22 Dispersion parameter: 3.6	680	>99.9%	83.8%
Weekly insulin dose (total), superiority	Treatment difference: -315U Standard deviation: 210U Intercurrent events: 17%	680	>99.9%	83.8%

The joint power was calculated under the assumption of independence of the hypotheses by multiplying the respective marginal powers.

Randomisation and blinding (masking)

All three pivotal studies had a similar design that implied a baseline visit at week 0 (V2) at which all eligible subjects were to be allocated to treatment using a 1:1 ratio.

Randomisation was performed centrally using Randomisation and Trial Supplies Management (RTSM: study 4591 and 4592) or an interactive web response system (IWRS: study 4593) assigning a subject the next available treatment according to the randomisation schedule.

None of the studies used stratified randomisation.

All the studies 4591, 4592 and 4593 were open label justified by that blinding was considered to increase the treatment complexity and hence the burden on the participants in that a double-dummy technique had been necessary. Potential bias was to be reduced by using central randomisation and adjudication of events.

Statistical methods

Analysis set

The main efficacy analysis set was the full analysis set (**FAS**) defined to include all randomised subjects analysed according to the planned randomised treatment.

In addition, the following data points sets had been defined, similar for each study (table 22).

Table 17

Data points sets	Description
In-study	All data from randomisation until the last date of any of the following: • The last direct participant-site contact • Withdrawal for participants who withdraw their informed consent • The last participant-investigator contact as defined by the investigator for participants who are lost to follow-up (i.e. possibly an unscheduled phone visit)

	• Death for participants who die before any of the above
On-treatment	All data from the date of first dose of randomised treatment as recorded on the eCRF until the first date of any of the following: • The last follow-up visit (V56) • The last date on randomised treatment +6 weeks (corresponding to 5 weeks after the end of the dosing interval for both treatment arms) • The end-date for the in-study data points sets

The full analysis set, and the *in*-study data points set was to be used to estimate the primary estimand (all three studies) and the confirmatory secondary estimand related to body weight (4591, 4593).

The full analysis set, and the *on*-treatment data points set were to be used for the confirmatory secondary estimand related to hypoglycaemic episodes (4591, 4593) and weekly insulin dose (total) (study 4593).

The main analysis methods for primary and important secondary endpoints

Change in HbA1c from baseline to week 52 was to be analysed using an analysis of covariance (ANCOVA) model with region (Asia, Europe, North America, Other) and randomised treatment as fixed factors and baseline HbA1c as covariate. Presentation of results was to include the estimated mean treatment difference together with the two-sided 95% CI and the corresponding two-sided p-value.

Secondary endpoints defined as confirmatory (study 4591 and 4593):

Change in body weight from baseline week 0 (V2) to week 52 (V54) was to be estimated using a model similar to the primary analysis above substituting body weight for HbA1c.

The number of hypoglycaemic episodes was to be analysed using a negative binomial regression model (log link) with treatment and region as fixed factors, and the logarithm of the time period for which the episodes were considered as an offset.

The total insulin dose from week 50 to week 52 was to be analysed using an analysis of covariance (ANCOVA) model with region and randomised treatment as fixed factors and baseline HbA1c and pre-study weekly insulin dose (total) as covariates (study 4593).

Multiplicity control

In studies 4591 and 4593, and besides the primary hypothesis, additional confirmatory secondary hypotheses were to be tested. The type I error was to be controlled in the strong sense using a hierarchical (fixed sequence) testing procedure (shown below, Outcomes and estimation).

Handling of missing data

Missing HbA1c values at week 52 were to be imputed by using **multiple imputation** and assuming that subjects with missing data was to behave similarly as comparable subjects within the same treatment arm.

Missing HbA1c measurements at week 52 for participants **experiencing** intercurrent events was to be imputed from participants experiencing intercurrent events and had a measurement at week 52 in each treatment arm.

Missing HbA1c measurements at week 52 for participants **not experiencing** intercurrent events were to be imputed from available measurements at week 52 from participants not experiencing intercurrent events in each treatment arm.

Sensitivity or supplementary analysis method(s)

For the primary endpoint, a two-dimensional **tipping point analysis** was to be performed.

In addition, a **supplementary** analysis, addressing an "attributable" estimand similar to the one had been defined. This estimand was to aim at estimating the effect of randomised treatment had all participants stayed on the randomised treatment for the entire 52 weeks treatment period.

Intercurrent events that were considered adversely related to randomised treatment were to be considered attributable and assigned an unfavourable outcome based on a **composite** strategy and using data from the comparator arm. A **hypothetical** estimand strategy was to be used for the remainder intercurrent events and data missing e.g. due to participants being lost to follow-up.

Subgroup analyses

No subgroup analyses had been planned for any of the pivotal studies.

Error probabilities, adjustment for multiplicity and interim analyses

The testing of the null hypotheses was performed using a 2-sided 95% confidence interval approach.

The testing of certain secondary efficacy endpoints (see above, study 4591 and 4593 alone) occurred according to a predefined order until a non-significant result appeared, i.e., one null hypothesis was only to be tested if the previous null hypotheses had been rejected in favour of Kyinsu.

There was no interim analysis planned or performed in any of the studies 4591, 4592 or 4593.

Results

Participant flow

The COMBINE programme included a total of 2,653 participants with T2D in the full analysis set, of which 1,328 participants were randomised to Kyinsu and 1,325 participants to comparators (table x-z). Across the studies, the rate of permanent discontinuation of treatment and the rate of withdrawals from the studies for Kyinsu was 6.1%-10.1% and 4.1-5.4%, respectively (**Table 18**, **Table 19** and **Table 20**).

Table 18. Participant disposition - study 4591

	IcoSema		Ico		Total	
	N	(%)	N	(%)	N	(%)
Screened					1671	
Screen failures					347	
Withdrawn prior to randomisation					33	
Randomised	646	(100.0)	645	(100.0)	1291	(100.0)
Exposed	644	(99.7)	644	(99.8)	1288	(99.8)
Discontinuation of randomised treatment	65	(10.1)	44	(6.8)	109	(8.4)
Adverse event	34	(5.3)	13	(2.0)	47	(3.6)
Hypoglycaemic episode	0		3	(0.5)	3	(0.2)
Protocol deviation	7	(1.1)	4	(0.6)	11	(0.9)
Violation of the in- and/or exclusion criteria	7	(1.1)	4	(0.6)	11	(0.9)
Intention of becoming pregnant	0		0		0	
Participation in another clinical study	0		0		0	
Lack of efficacy	0		0		0	
Lost to follow-up	0		2	(0.3)	2	(0.2)
Pregnancy	0		0		0	
Site closure	1	(0.2)	0		1	(0.1)
Epi/pandemic	0		0		0	
Withdrawal of consent	16	(2.5)	10	(1.6)	26	(2.0)
Other	7	(1.1)	12	(1.9)	19	(1.5)
Discontinuation of randomised treatment and not withdrawn from study during the treatment period	30	(4.6)	13	(2.0)	43	(3.3)
Adverse event	22	(3.4)	4	(0.6)	26	(2.0)
Hypoglycaemic episode	0		2	(0.3)	2	(0.2)
Protocol deviation	2	(0.3)	1	(0.2)	3	(0.2)
Violation of the in- and/or exclusion criteria	2	(0.3)	1	(0.2)	3	(0.2)
Intention of becoming pregnant	0		0		0	
Participation in another clinical study	0		0		0	
Lack of efficacy	0		0		0	
Lost to follow-up	0		0		0	
Pregnancy	0		0		0	
Site closure	0		0		0	
Epi/pandemic	0		0		0	
Other	6	(0.9)	6	(0.9)	12	(0.9)
Discontinuation of randomised treatment and withdrawn from study during the treatment period	35	(5.4)	31	(4.8)	66	(5.1)
Adverse event	12	(1.9)	9	(1.4)	21	(1.6)
Hypoglycaemic episode	0		1	(0.2)	1	(0.1)
Protocol deviation	5	(0.8)	3	(0.5)	8	(0.6)
Violation of the in- and/or exclusion criteria	5	(0.8)	3	(0.5)	8	(0.6)
Intention of becoming pregnant	0		0		0	
Participation in another clinical study	0		0		0	
Lack of efficacy	0		0		0	
Lost to follow-up	0		2	(0.3)	2	(0.2)
Pregnancy	0		0		0	
Site closure	1	(0.2)	0		1	(0.1)
Epi/pandemic	0		0		0	
Withdrawal of consent	16	(2.5)	10	(1.6)	26	(2.0)
Other	1	(0.2)	6	(0.9)	7	(0.5)
Withdrawn from study	35	(5.4)	34	(5.3)	69	(5.3)
Withdrawal of consent by participant	28	(4.3)	24	(3.7)	52	(4.0)
Lost to follow-up	4	(0.6)	7	(1.1)	11	(0.9)
Death	2	(0.3)	3	(0.5)	5	(0.4)
Site closure	1	(0.2)	0		1	(0.1)
Epi/pandemic	0		0		0	

Table 19. Participant disposition - study 4592

	IcoSema		Sema 1.0 mg		Total	
	N	(%)	N	(%)	N	(%)
Screened					847	
Screen failures					153	
Withdrawn prior to randomisation					11	
Randomised	342	(100.0)	341	(100.0)	683	(100.0)
Exposed	341	(99.7)	340	(99.7)	681	(99.7)
Discontinuation of randomised treatment	21	(6.1)	13	(3.8)	34	(5.0)
Adverse event	8	(2.3)	9	(2.6)	17	(2.5)
Hypoglycaemic episode	0		0		0	
Protocol deviation	4	(1.2)	1	(0.3)	5	(0.7)
Violation of the in- and/or exclusion criteria	4	(1.2)	1	(0.3)	5	(0.7)
Intention of becoming pregnant	0		0		0	
Participation in another clinical study	0		0		0	
Lack of efficacy	0		0		0	
Lost to follow-up	0		1	(0.3)	1	(0.1)
Pregnancy	0		0		0	
Site closure	0		0		0	
Epi/pandemic	0		0		0	
Withdrawal of consent	6	(1.8)	2	(0.6)	8	(1.2)
Other	3	(0.9)	0		3	(0.4)
Discontinuation of randomised treatment and not withdrawn from study during the treatment period	9	(2.6)	7	(2.1)	16	(2.3)
Adverse event	5	(1.5)	6	(1.8)	11	(1.6)
Hypoglycaemic episode	0		0		0	
Protocol deviation	2	(0.6)	1	(0.3)	3	(0.4)
Violation of the in- and/or exclusion criteria	2	(0.6)	1	(0.3)	3	(0.4)
Intention of becoming pregnant	0		0		0	
Participation in another clinical study	0		0		0	
Lack of efficacy	0		0		0	
Lost to follow-up	0		0		0	
Pregnancy	0		0		0	
Site closure	0		0		0	
Epi/pandemic	0		0		0	
Other	2	(0.6)	0		2	(0.3)
Discontinuation of randomised treatment and withdrawn from study during the treatment period	12	(3.5)	6	(1.8)	18	(2.6)
Adverse event	3	(0.9)	3	(0.9)	6	(0.9)
Hypoglycaemic episode	0		0		0	
Protocol deviation	2	(0.6)	0		2	(0.3)
Violation of the in- and/or exclusion criteria	2	(0.6)	0		2	(0.3)
Intention of becoming pregnant	0		0		0	
Participation in another clinical study	0		0		0	
Lack of efficacy	0		0		0	
Lost to follow-up	0		1	(0.3)	1	(0.1)
Pregnancy	0		0		0	
Site closure	0		0		0	
Epi/pandemic	0		0		0	
Withdrawal of consent	6	(1.8)	2	(0.6)	8	(1.2)
Other	1	(0.3)	0		1	(0.1)
Withdrawn from study	14	(4.1)	7	(2.1)	21	(3.1)
Withdrawal of consent by participant	10	(2.9)	6	(1.8)	16	(2.3)
Lost to follow-up	2	(0.6)	1	(0.3)	3	(0.4)
Death	2	(0.6)	0		2	(0.3)
Site closure	0		0		0	
Epi/pandemic	0		0		0	

Table 20. Participant disposition - study 4593

	IcoSema		IGlar+IAsp		Total	
	N	(%)	N	(%)	N	(%)
Screened					844	
Screen failures					145	
Withdrawn prior to randomisation					20	
Randomised	340	(100.0)	339	(100.0)	679	(100.0)
Exposed	340	(100.0)	328	(96.8)	668	(98.4)
Discontinuation of randomised treatment	28	(8.2)	48	(14.2)	76	(11.2)
Adverse event	16	(4.7)	9	(2.7)	25	(3.7)
Hypoglycaemic episode	0		0		0	
Protocol deviation	1	(0.3)	2	(0.6)	3	(0.4)
Violation of the in- and/or exclusion criteria	1	(0.3)	2	(0.6)	3	(0.4)
Intention of becoming pregnant	0		0		0	
Participation in another clinical study	0		0		0	
Lack of efficacy	1	(0.3)	0		1	(0.1)
Lost to follow-up	0		4	(1.2)	4	(0.6)
Pregnancy	0		0		0	
Site closure	1	(0.3)	2	(0.6)	3	(0.4)
Epi/pandemic	0		0		0	
Withdrawal of consent	7	(2.1)	20	(5.9)	27	(4.0)
Other	2	(0.6)	11	(3.2)	13	(1.9)
Discontinuation of randomised treatment and not withdrawn from study during the treatment period	12	(3.5)	11	(3.2)	23	(3.4)
Adverse event	8	(2.4)	4	(1.2)	12	(1.8)
Hypoglycaemic episode	0		0		0	
Protocol deviation	1	(0.3)	0		1	(0.1)
Violation of the in- and/or exclusion criteria	1	(0.3)	0		1	(0.1)
Intention of becoming pregnant	0		0		0	
Participation in another clinical study	0		0		0	
Lack of efficacy	1	(0.3)	0		1	(0.1)
Lost to follow-up	0		0		0	
Pregnancy	0		0		0	
Site closure	0		0		0	
Epi/pandemic	0		0		0	
Other	2	(0.6)	7	(2.1)	9	(1.3)
Discontinuation of randomised treatment and withdrawn from study during the treatment period	16	(4.7)	37	(10.9)	53	(7.8)
Adverse event	8	(2.4)	5	(1.5)	13	(1.9)
Hypoglycaemic episode	0		0		0	
Protocol deviation	0		2	(0.6)	2	(0.3)
Violation of the in- and/or exclusion criteria	0		2	(0.6)	2	(0.3)
Intention of becoming pregnant	0		0		0	
Participation in another clinical study	0		0		0	
Lack of efficacy	0		0		0	
Lost to follow-up	0		4	(1.2)	4	(0.6)
Pregnancy	0		0		0	
Site closure	1	(0.3)	2	(0.6)	3	(0.4)
Epi/pandemic	0		0		0	
Withdrawal of consent	7	(2.1)	20	(5.9)	27	(4.0)
Other	0		4	(1.2)	4	(0.6)
Withdrawn from study	16	(4.7)	38	(11.2)	54	(8.0)
Withdrawal of consent by participant	13	(3.8)	28	(8.3)	41	(6.0)
Lost to follow-up	1	(0.3)	6	(1.8)	7	(1.0)
Death	1	(0.3)	2	(0.6)	3	(0.4)
Site closure	1	(0.3)	2	(0.6)	3	(0.4)
Epi/pandemic	0		0		0	

Intercurrent events

In study 4591, more subjects treated with Kyinsu had intercurrent events (16.7%) compared to insulin icodec (13.3%).

In study 4592, more subjects in the semaglutide group (23.5%) than in the Kyinsu group (9.4%) experienced intercurrent events.

In study 4593, more subjects in the IGlar+IAsp group had intercurrent events (18.9%) compared with the Kyinsu group (13.2%). One participant discontinued with Kyinsu due to lack of efficacy (in study 4593) (**Table 21**).

Table 21. Intercurrent events and HbA1c assessments at week 52 - full analysis set

	IcoSema		Comparator	
	N	(%)	N	(%)
4591				
Full analysis set	646		645	
Participants without intercurrent events	538	(83.3)	559	(86.7)
With week 52 assessment	535	(82.8)	554	(85.9)
Missing week 52 assessment (missing-at-random)	3	(0.5)	5	(0.8)
Participants with intercurrent events	108	(16.7)	86	(13.3)
With week 52 assessment (retrieved data)	63	(9.8)	51	(7.9)
Discontinued randomised treatment	18	(2.8)	8	(1.2)
Initiated non-randomised insulin treatment or additional antidiabetic treatments for more than 2 weeks	45	(7.0)	43	(6.7)
Without week 52 assessment	45	(7.0)	35	(5.4)
Discontinued randomised treatment	38	(5.9)	31	(4.8)
Initiated non-randomised insulin treatment or additional antidiabetic treatments for more than 2 weeks	7	(1.1)	4	(0.6)
4592				
Full analysis set	342		341	
Participants without intercurrent events	310	(90.6)	261	(76.5)
With week 52 assessment	307	(89.8)	261	(76.5)
Missing week 52 assessment (missing-at-random)	3	(0.9)	0	
Participants with intercurrent events	32	(9.4)	80	(23.5)
With week 52 assessment (retrieved data)	18	(5.3)	74	(21.7)
Discontinued randomised treatment	6	(1.8)	4	(1.2)
Initiated non-randomised insulin treatment or additional antidiabetic treatments for more than 2 weeks	12	(3.5)	70	(20.5)
Without week 52 assessment	14	(4.1)	6	(1.8)
Discontinued randomised treatment	13	(3.8)	5	(1.5)
Initiated non-randomised insulin treatment or additional antidiabetic treatments for more than 2 weeks	1	(0.3)	1	(0.3)
4593				
Full analysis set	340		339	
Participants without intercurrent events	295	(86.8)	275	(81.1)
With week 52 assessment	290	(85.3)	271	(79.9)
Missing week 52 assessment (missing-at-random)	5	(1.5)	4	(1.2)
Participants with intercurrent events	45	(13.2)	64	(18.9)
With week 52 assessment (retrieved data)	27	(7.9)	26	(7.7)
Discontinued randomised treatment	11	(3.2)	9	(2.7)
Initiated non-randomised insulin treatment or additional antidiabetic treatments for more than 2 weeks	16	(4.7)	17	(5.0)
Without week 52 assessment	18	(5.3)	38	(11.2)
Discontinued randomised treatment	16	(4.7)	38	(11.2)
Initiated non-randomised insulin treatment or additional antidiabetic treatments for more than 2 weeks	2	(0.6)	0	

Additional antidiabetic treatment, regardless of duration

Tables 20-22 include all antidiabetic treatment initiated after baseline until the last dose of randomised treatment, regardless of treatment duration. Participants who continued their pre-study treatment with insulin, DPP-4i, SU or glinides after randomisation were not included in these tables.

Tables 17-19 include initiation of non-randomised insulin or new antidiabetic treatment after baseline until the last dose of randomised treatment, which lasted more than 2 weeks. These tables also include participants who continued their pre-study treatment with insulin, DPP-4i, SU or glinides after randomisation.

In patients switching from basal insulin, additional antidiabetic treatment, regardless of duration, was initiated after baseline by 11.1% in the Kyinsu group and 7.6% in the insulin icodec group in study 4591 and by 8.2% in the Kyinsu group and 3.8% in the IGlar+IAsp group in study 4593, of which initiation of non-randomised insulin was most frequently occurring in the Kyinsu group (study 4591: 8.7% vs. 3.6% for Kyinsu vs. insulin icodec; study 4593: 6.8% vs. 0.6% for Kyinsu vs. IGlar+IAsp) (**Table 22**, **Table 24**).

Additional antidiabetic treatment, including increased doses of background medication, for more than 2 weeks, was initiated by 8.0% in the Kyinsu group and 7.3% in the insulin icodec group in study 4591 and by 5.3% in the Kyinsu group and 5.0% in the IGlar+IAsp group in study 4593. When focusing on participants prescribed an increased dose of background antidiabetic medication, the number was low across the COMBINE studies (30 participants in total; 13 (Kyinsu : 7, Ico: 6), 9 (Kyinsu : 0, sema: 9),

and 8 (Kyinsu : 3, IGlar+IAsp: 5) for study 4591, 4592, and 4593, respectively) (**Table 25**, **Table 27**).

Most additional antidiabetic treatment regardless of duration in the Kyinsu group was initiated during the first 12 week of treatment. In study 4591 and 4593, 8.7% and 6.5%, respectively, in the Kyinsu group initiated additional antidiabetic treatment week 1-12, of which 6.7% and 5.9%, respectively, in the Kyinsu group initiated non-randomised insulin (**Table 28**). During week 1-12, the median duration of treatment with additional non-randomised insulin in the Kyinsu group was 7 days in study 4581 and 4 days in study 4593. The median duration of treatment with additional OADs was 55 days in both study 4591 and 4593 (**Table 29**).

In patients switching from GLP-1 agonist (study 4592), the proportion of participants with changes to background antidiabetic treatment was lower in the Kyinsu arm (6.4%) compared to the semaglutide arm (19.9%) (**Table 23**).

Table 22. Additional anti-diabetic medications - from baseline until 1 week after last dose of randomised treatment - summary - 4591 - full analysis set

	IcoSema		Ico		Total	
	N	(%)	N	(%)	N	(%)
Number of participants	646		645		1291	
Any change	72	(11.1)	49	(7.6)	121	(9.4)
Initiation of non-randomised insulin	56	(8.7)	23	(3.6)	79	(6.1)
Basal insulin	42	(6.5)	11	(1.7)	53	(4.1)
Insulin degludec	1	(0.2)	0		1	(0.1)
Insulin degludec U100	4	(0.6)	2	(0.3)	6	(0.5)
Insulin detemir U100	3	(0.5)	3	(0.5)	6	(0.5)
Insulin glargine biosimilar 1 U300	0		1	(0.2)	1	(0.1)
Insulin glargine U100	22	(3.4)	6	(0.9)	28	(2.2)
Insulin glargine U300	9	(1.4)	1	(0.2)	10	(0.8)
Insulin human injection, isophane	4	(0.6)	0		4	(0.3)
Bolus insulin	16	(2.5)	15	(2.3)	31	(2.4)
Insulin	1	(0.2)	3	(0.5)	4	(0.3)
Insulin aspart	9	(1.4)	4	(0.6)	13	(1.0)
Insulin glulisine	0		1	(0.2)	1	(0.1)
Insulin human	2	(0.3)	2	(0.3)	4	(0.3)
Insulin lispro	4	(0.6)	6	(0.9)	10	(0.8)
Pre-mix	0		1	(0.2)	1	(0.1)
Insulin human	0		1	(0.2)	1	(0.1)
Unknown	2	(0.3)	0		2	(0.2)
Insulin	2	(0.3)	0		2	(0.2)
New anti-diabetic medication	24	(3.7)	29	(4.5)	53	(4.1)
OAD	24	(3.7)	29	(4.5)	53	(4.1)
Alpha-glucosidase inhibitor	0		3	(0.5)	3	(0.2)
DPP-4i	1	(0.2)	2	(0.3)	3	(0.2)
Metformin	3	(0.5)	2	(0.3)	5	(0.4)
SGLT2i	14	(2.2)	23	(3.6)	37	(2.9)
SU	6	(0.9)	1	(0.2)	7	(0.5)
Thiazolidinediones	3	(0.5)	4	(0.6)	7	(0.5)

Table 23. Additional anti-diabetic medications - from baseline until 1 week after last dose of randomised treatment - summary - 4592 - full analysis set

	IcoSema		Sema 1.0 mg		Total	
	N	(%)	N	(%)	N	(%)
Number of participants	342		341		683	
Any change	22	(6.4)	68	(19.9)	90	(13.2)
Initiation of non-randomised insulin	11	(3.2)	23	(6.7)	34	(5.0)
Basal insulin	4	(1.2)	18	(5.3)	22	(3.2)
Insulin degludec	1	(0.3)	9	(2.6)	10	(1.5)
Insulin glargine U100	2	(0.6)	7	(2.1)	9	(1.3)
Insulin glargine U100 + GLP-1-RA	1	(0.3)	0		1	(0.1)
Insulin glargine U300	0		1	(0.3)	1	(0.1)
Insulin human injection, isophane	0		1	(0.3)	1	(0.1)
Lixisenatide	1	(0.3)	0		1	(0.1)
Bolus insulin	6	(1.8)	9	(2.6)	15	(2.2)
Insulin aspart	2	(0.6)	6	(1.8)	8	(1.2)
Insulin human	1	(0.3)	2	(0.6)	3	(0.4)
Insulin lispro	3	(0.9)	2	(0.6)	5	(0.7)
Pre-mix	2	(0.6)	1	(0.3)	3	(0.4)
Insulin aspart;insulin aspart protamine (crystalline)	1	(0.3)	0		1	(0.1)
Insulin aspart;insulin degludec	0		1	(0.3)	1	(0.1)
Insulin human;insulin human injection, isophane	1	(0.3)	1	(0.3)	2	(0.3)
New anti-diabetic medication	12	(3.5)	57	(16.7)	69	(10.1)
OAD	12	(3.5)	55	(16.1)	67	(9.8)
Alpha-glucosidase inhibitor	1	(0.3)	4	(1.2)	5	(0.7)
DPP-4i	0		1	(0.3)	1	(0.1)
Glinides	0		1	(0.3)	1	(0.1)
Metformin	1	(0.3)	5	(1.5)	6	(0.9)
SGLT2i	7	(2.0)	18	(5.3)	25	(3.7)
SU	2	(0.6)	17	(5.0)	19	(2.8)
Thiazolidinediones	1	(0.3)	16	(4.7)	17	(2.5)
GLP-1 RA	0		2	(0.6)	2	(0.3)
Semaglutide	0		2	(0.6)	2	(0.3)

Table 24. Additional anti-diabetic medications - from baseline until 1 week after last dose of randomised treatment - summary - 4593 - full analysis set

	IcoSema		IGlar+IAsp		Total	
	N	(%)	N	(%)	N	(%)
Number of participants	340		339		679	
Any change	28	(8.2)	13	(3.8)	41	(6.0)
Initiation of non-randomised insulin	23	(6.8)	2	(0.6)	25	(3.7)
Basal insulin	13	(3.8)	1	(0.3)	14	(2.1)
Insulin degludec	1	(0.3)	0		1	(0.1)
Insulin detemir	1	(0.3)	0		1	(0.1)
Insulin glargine U100	4	(1.2)	1	(0.3)	5	(0.7)
Insulin glargine U300	1	(0.3)	0		1	(0.1)
Insulin human injection, isophane	6	(1.8)	0		6	(0.9)
Bolus insulin	14	(4.1)	1	(0.3)	15	(2.2)
Insulin aspart	11	(3.2)	1	(0.3)	12	(1.8)
Insulin glulisine	1	(0.3)	0		1	(0.1)
Insulin lispro	2	(0.6)	0		2	(0.3)
Insulin porcine	1	(0.3)	0		1	(0.1)
New anti-diabetic medication	8	(2.4)	11	(3.2)	19	(2.8)
OAD	8	(2.4)	10	(2.9)	18	(2.7)
DPP-4i	1	(0.3)	0		1	(0.1)
Metformin	3	(0.9)	6	(1.8)	9	(1.3)
SGLT2i	3	(0.9)	4	(1.2)	7	(1.0)
SU	2	(0.6)	0		2	(0.3)
Thiazolidinediones	1	(0.3)	1	(0.3)	2	(0.3)
GLP-1 RA	0		1	(0.3)	1	(0.1)
Semaglutide	0		1	(0.3)	1	(0.1)

Table 25. Changes to anti-diabetic background treatment lasting more than 2 weeks - from baseline until 1 week after last dose of randomised treatment – study 4591

	IcoSema		Ico		Total	
	N	(%)	N	(%)	N	(%)
Number of participants	646		645		1291	
Any change	71	(11.0)	67	(10.4)	138	(10.7)
Initiation of non-randomised insulin treatment or additional anti-diabetic treatment	52	(8.0)	47	(7.3)	99	(7.7)
OAD	33	(5.1)	40	(6.2)	73	(5.7)
Alpha-glucosidase inhibitor	0		3	(0.5)	3	(0.2)
DPP-4i	4	(0.6)	6	(0.9)	10	(0.8)
Metformin	7	(1.1)	7	(1.1)	14	(1.1)
SGLT2i	15	(2.3)	26	(4.0)	41	(3.2)
SU	10	(1.5)	3	(0.5)	13	(1.0)
Thiazolidinediones	4	(0.6)	4	(0.6)	8	(0.6)
Basal insulin	18	(2.8)	5	(0.8)	23	(1.8)
Insulin degludec U100	3	(0.5)	1	(0.2)	4	(0.3)
Insulin detemir U100	2	(0.3)	0		2	(0.2)
Insulin glargine biosimilar 1 U300	0		1	(0.2)	1	(0.1)
Insulin glargine U100	8	(1.2)	3	(0.5)	11	(0.9)
Insulin glargine U300	4	(0.6)	1	(0.2)	5	(0.4)
Insulin human injection, isophane	1	(0.2)	0		1	(0.1)
Bolus insulin	4	(0.6)	5	(0.8)	9	(0.7)
Insulin aspart	3	(0.5)	2	(0.3)	5	(0.4)
Insulin lispro	1	(0.2)	3	(0.5)	4	(0.3)
Pre-mix	0		1	(0.2)	1	(0.1)
Insulin human	0		1	(0.2)	1	(0.1)
Termination or decreased dose of background anti-diabetic medication	25	(3.9)	32	(5.0)	57	(4.4)
OAD	25	(3.9)	32	(5.0)	57	(4.4)
Alpha-glucosidase inhibitor	1	(0.2)	2	(0.3)	3	(0.2)
Metformin	17	(2.6)	18	(2.8)	35	(2.7)
SGLT2i	8	(1.2)	14	(2.2)	22	(1.7)
Thiazolidinediones	2	(0.3)	5	(0.8)	7	(0.5)

Table 26. Changes to anti-diabetic background treatment lasting more than 2 weeks - from baseline until 1 week after last dose of randomised treatment – study 4592

	IcoSema		Sema 1.0 mg		Total	
	N	(%)	N	(%)	N	(%)
Number of participants	342		341		683	
Any change	23	(6.7)	74	(21.7)	97	(14.2)
Initiation of non-randomised insulin treatment or additional anti-diabetic treatment	13	(3.8)	71	(20.8)	84	(12.3)
OAD	12	(3.5)	64	(18.8)	76	(11.1)
SGLT2i	5	(1.5)	18	(5.3)	23	(3.4)
SU	4	(1.2)	19	(5.6)	23	(3.4)
Alpha-glucosidase inhibitor	1	(0.3)	3	(0.9)	4	(0.6)
DPP-4i	1	(0.3)	1	(0.3)	2	(0.3)
Metformin	1	(0.3)	14	(4.1)	15	(2.2)
Thiazolidinediones	1	(0.3)	16	(4.7)	17	(2.5)
Glinides	0		1	(0.3)	1	(0.1)
GLP-1 RA	0		1	(0.3)	1	(0.1)
Semaglutide	0		1	(0.3)	1	(0.1)
Basal insulin	1	(0.3)	12	(3.5)	13	(1.9)
Insulin degludec	1	(0.3)	6	(1.8)	7	(1.0)
Insulin glargine U100	0		5	(1.5)	5	(0.7)
Insulin glargine U300	0		1	(0.3)	1	(0.1)
Bolus insulin	0		3	(0.9)	3	(0.4)
Insulin aspart	0		2	(0.6)	2	(0.3)
Insulin lispro	0		1	(0.3)	1	(0.1)
Termination or decreased dose of background anti-diabetic medication	12	(3.5)	14	(4.1)	26	(3.8)
OAD	12	(3.5)	14	(4.1)	26	(3.8)
SGLT2i	7	(2.0)	5	(1.5)	12	(1.8)
Metformin	4	(1.2)	8	(2.3)	12	(1.8)
Thiazolidinediones	1	(0.3)	1	(0.3)	2	(0.3)

Table 27. Changes to anti-diabetic background treatment lasting more than 2 weeks - from baseline until 1 week after last dose of randomised treatment – study 4593

	IcoSema		IGlar+IAsp		Total	
	N	(%)	N	(%)	N	(%)
Number of participants	340		339		679	
Any change	30	(8.8)	24	(7.1)	54	(8.0)
Initiation of non-randomised insulin treatment or additional anti-diabetic treatment	18	(5.3)	17	(5.0)	35	(5.2)
OAD	14	(4.1)	15	(4.4)	29	(4.3)
DPP-4i	3	(0.9)	2	(0.6)	5	(0.7)
Metformin	6	(1.8)	9	(2.7)	15	(2.2)
SGLT2i	3	(0.9)	6	(1.8)	9	(1.3)
SU	5	(1.5)	0		5	(0.7)
Thiazolidinediones	1	(0.3)	2	(0.6)	3	(0.4)
GLP-1 RA	0		1	(0.3)	1	(0.1)
Semaglutide	0		1	(0.3)	1	(0.1)
Basal insulin	4	(1.2)	0		4	(0.6)
Insulin degludec	1	(0.3)	0		1	(0.1)
Insulin glargine U100	2	(0.6)	0		2	(0.3)
Insulin glargine U300	1	(0.3)	0		1	(0.1)
Bolus insulin	3	(0.9)	1	(0.3)	4	(0.6)
Insulin aspart	2	(0.6)	0		2	(0.3)
Insulin lispro	1	(0.3)	0		1	(0.1)
Insulin porcine	0		1	(0.3)	1	(0.1)
Termination or decreased dose of background anti-diabetic medication	14	(4.1)	8	(2.4)	22	(3.2)
OAD	14	(4.1)	8	(2.4)	22	(3.2)
Metformin	8	(2.4)	7	(2.1)	15	(2.2)
SGLT2i	6	(1.8)	0		6	(0.9)
Thiazolidinediones	1	(0.3)	1	(0.3)	2	(0.3)

Table 28. Additional anti-diabetic medications - from baseline until 1 week after last dose of randomised treatment within initial 12 weeks - IcoSema arm- summary - study 4591 and 4593, full analysis set

	4591		4593		Total	
	N	(%)	N	(%)	N	(%)
Number of participants	646		340		986	
Any change	56	(8.7)	22	(6.5)	78	(7.9)
Initiation of non-randomised insulin	43	(6.7)	20	(5.9)	63	(6.4)
Basal insulin	34	(5.3)	12	(3.5)	46	(4.7)
Insulin degludec	1	(0.2)	0		1	(0.1)
Insulin degludec U100	4	(0.6)	0		4	(0.4)
Insulin detemir	0		1	(0.3)	1	(0.1)
Insulin detemir U100	2	(0.3)	0		2	(0.2)
Insulin glargine U100	19	(2.9)	4	(1.2)	23	(2.3)
Insulin glargine U300	7	(1.1)	1	(0.3)	8	(0.8)
Insulin human injection, isophane	2	(0.3)	6	(1.8)	8	(0.8)
Bolus insulin	11	(1.7)	12	(3.5)	23	(2.3)
Insulin	1	(0.2)	0		1	(0.1)
Insulin aspart	6	(0.9)	9	(2.6)	15	(1.5)
Insulin glulisine	0		1	(0.3)	1	(0.1)
Insulin human	2	(0.3)	0		2	(0.2)
Insulin lispro	2	(0.3)	2	(0.6)	4	(0.4)
Insulin porcine	0		1	(0.3)	1	(0.1)
New anti-diabetic medication	13	(2.0)	2	(0.6)	15	(1.5)
OAD	13	(2.0)	2	(0.6)	15	(1.5)
Metformin	3	(0.5)	2	(0.6)	5	(0.5)
SGLT2i	6	(0.9)	1	(0.3)	7	(0.7)
SU	4	(0.6)	0		4	(0.4)
Thiazolidinediones	1	(0.2)	0		1	(0.1)
Increased dose of background anti-diabetic medication	4	(0.6)	1	(0.3)	5	(0.5)
OAD	4	(0.6)	1	(0.3)	5	(0.5)
Metformin	2	(0.3)	1	(0.3)	3	(0.3)
SGLT2i	1	(0.2)	0		1	(0.1)
Thiazolidinediones	1	(0.2)	0		1	(0.1)

Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

Table 29. Additional anti-diabetic medications - from baseline until 1 week after last dose of randomised treatment within initial 12 weeks - IcoSema arm- summary - study 4591 and 4593, full analysis set

	4591	4593	Total
Number of participants	646	340	986
Initiation of non-randomised insulin			
Estimated duration of events (days)			
N (E)	43 (81)	20 (59)	63 (140)
25% percentile	4.0	1.0	3.0
Median	7.0	4.0	6.0
75% percentile	14.0	7.0	12.5
New anti-diabetic medication (Non-insulin)			
Estimated duration of events (days)			
N (E)	13 (17)	2 (3)	15 (20)
25% percentile	13.0		14.0
Median	55.0		55.0
Increased dose of background anti-diabetic medication (Non-insulin)			
Estimated duration of events (days)			
N (E)	4 (4)	1 (1)	5 (5)
25% percentile		82.0	82.0
Median		82.0	82.0
75% percentile		82.0	82.0

Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

Recruitment

Trial 4591 (COMBINE 1)

The study was initiated on 01 June 2022, and the primary completion date was 19 March 2024. Study completion was 23 April 2024.

Trial 4592 (COMBINE 2)

Study initiation date was 11 April 2022. The primary completion date was 13 December 2024, and the study completion date was 16 January 2024.

Trial 4593 (COMBINE 3)

Study initiation date was 30 November 2021. The primary completion date was 14 November 2023, and the study was completed on 14 November 2023.

Conduct of the study

Trial 4591 (COMBINE 1)

Protocol amendments

There were no substantial amendments.

Protocol deviations

In total, 612 important protocol deviations were closed before database lock (DBL); of which 558 were participants-level deviations, 4 were study-level deviations, 50 were site-level deviations and none were country-level deviations.

Serious breaches

There was one serious breach reported during the study conduct. The serious breach was related to unauthorized persons who could have had accessed pseudonymized clinical trial data in the electronic

patient interactive devices (ePID) in the migration environment. Patient safety or data integrity were not impacted.

Trial 4592 (COMBINE 2)

Protocol amendments

There were no substantial amendments.

Protocol deviations

In total, 343 important protocol deviations were closed before database lock (DBL); of which 313 were participants-level deviations, 2 were study-level deviations, 28 were site-level deviations and none were country-level deviations.

Serious breaches

There was one serious breach reported during the study conduct. The serious breach was related to unauthorized persons who could have had accessed pseudonymized clinical trial data in the electronic patient interactive devices (ePID) in the migration environment. The applicant has claimed that patient safety or data integrity were not impacted.

Trial 4593 (COMBINE 3)

Protocol amendments

There were no substantial amendments.

Protocol deviations

In total, 313 important protocol deviations were closed before database lock (DBL); of which 282 were participants-level deviations, 2 were study-level deviations, 29 were site-level deviations and none were country-level deviations.

Serious breaches

There were two serious breaches reported during the study conduct.

One serious breach was reported due to a misinterpretation of the SOP HbA1c release criteria. Laboratory service provider mistakenly reported HbA1c values for 10 participants instead of cancelling them: 8 of these 10 participants were randomised into the trial. Investigations made by the applicant concluded that there was not any significant impact on data reliability or robustness, or patient safety or rights.

Baseline data

The study populations across the studies were representative for the target population. Baseline demographic and diabetes characteristics were in general balanced between groups. It was noted that mean FPG values at baseline were slightly higher in the IGlar+IAsp group (8.94 mmol/L) compared to the Kyinsu group (8.42 mmol/L) in study 4593.

Across the studies, 27-35% of T2DM subjects were recruited from Europe. In total 176 patients ≥75 years were included in the studies. It should be noted that 15-21% of patients in the studies had a body weight <70 kg with a minimum body weight of 41-43 kg. In total 14 subjects, of which most females (n=11), had a baseline body weight of <50 kg. Eight (8) were randomised to Kyinsu and six (6) to the comparator arms. The diabetes duration among these subjects was ranging from 4.5 to 24 years. Three (3) patients were reported to have diabetes complications diagnosed at screening. Five

(5) subjects were from East Asian countries and 5 were from India. The diagnosis of T2D was determined based on the participants' medical records and the investigators' clinical judgment.

The pretrial treatments with regards to insulin (study 4591 and 4593) reflects the current treatment practice and was well balanced between groups. The T2DM groups were balanced with regards to non-insulin anti-diabetic treatment.

Table 30. **Demographics and baseline characteristics - summary – full analysis set**

	4591	4592	4593
Number of participants	1291	683	679
Sex, N (%)			
N	1291 (100.0)	683 (100.0)	679 (100.0)
Male	799 (61.9)	397 (58.1)	399 (58.8)
Female	492 (38.1)	286 (41.9)	280 (41.2)
Age (years)			
N	1291	683	679
Mean (SD)	60.6 (10.3)	59.1 (10.2)	59.6 (10.4)
Median	62.0	60.0	61.0
Min ; max	22.0 ; 87.0	23.0 ; 83.0	27.0 ; 84.0
Age group, N (%)			
N	1291 (100.0)	683 (100.0)	679 (100.0)
18<= to <65 years	784 (60.7)	455 (66.6)	440 (64.8)
65<= to <75 years	411 (31.8)	196 (28.7)	202 (29.7)
75<= to <85 years	90 (7.0)	32 (4.7)	37 (5.4)
>=85 years	6 (0.5)	0	0
Race, N (%)			
N	1291 (100.0)	683 (100.0)	679 (100.0)
White	814 (63.1)	434 (63.5)	363 (53.5)
Black/African American	44 (3.4)	21 (3.1)	35 (5.2)
Asian	420 (32.5)	189 (27.7)	263 (38.7)
Other	13 (1.0)	4 (0.6)	0
Not Applicable	0	35 (5.1)	18 (2.7)
Ethnicity, N (%)			
N	1291 (100.0)	683 (100.0)	679 (100.0)
Not Hispanic/Latino	1080 (83.7)	574 (84.0)	626 (92.2)
Hispanic/Latino	211 (16.3)	74 (10.8)	35 (5.2)
Not Applicable	0	35 (5.1)	18 (2.7)
Region, N (%)			
N	1291 (100.0)	683 (100.0)	679 (100.0)
Asia	337 (26.1)	170 (24.9)	155 (22.8)
Europe	347 (26.9)	209 (30.6)	231 (34.0)
North America	295 (22.9)	206 (30.2)	143 (21.1)
Other	312 (24.2)	98 (14.3)	150 (22.1)
Body weight (kg)			
N	1291	683	679
Mean (SD)	84.5 (17.1)	89.2 (18.0)	85.8 (17.8)
Median	82.5	87.9	83.6
Min ; max	44.7 ; 141.0	40.7 ; 155.3	42.7 ; 141.2
Body weight group, N (%)			
N	1291 (100.0)	683 (100.0)	679 (100.0)
<70 kg	270 (20.9)	105 (15.4)	126 (18.6)
70<= to <90 kg	564 (43.7)	262 (38.4)	292 (43.0)
90<= to <110 kg	351 (27.2)	228 (33.4)	194 (28.6)
>=110 kg	106 (8.2)	88 (12.9)	67 (9.9)
BMI (kg/m^2)			
N	1291	683	679
Mean (SD)	29.9 (4.7)	31.1 (4.7)	30.4 (5.0)
Median	29.3	30.9	30.0
Min ; max	17.8 ; 42.1	18.1 ; 44.2	13.8 ; 43.1
BMI group, N (%)			
N	1291 (100.0)	683 (100.0)	679 (100.0)
<25 kg/m^2	211 (16.3)	71 (10.4)	99 (14.6)
25<= to <30 kg/m^2	501 (38.8)	211 (30.9)	242 (35.6)
30<= to <35 kg/m^2	349 (27.0)	236 (34.6)	200 (29.5)
>=35 kg/m^2	230 (17.8)	165 (24.2)	138 (20.3)

Table 31. Baseline diabetes characteristics – summary – full analysis set

	4591	4592	4593
Number of participants	1291	683	679
Baseline HbA1c (%)			
N	1291	683	679
Mean (SD)	8.2 (0.8)	8.0 (0.7)	8.3 (0.8)
Median	8.1	7.9	8.2
Min ; max	6.2 ; 11.6	6.6 ; 10.5	6.0 ; 11.2
Baseline HbA1c group, N (%)			
N	1291 (100.0)	683 (100.0)	679 (100.0)
HbA1c < 7.5%	259 (20.1)	187 (27.4)	109 (16.1)
7.5% <= HbA1c < 8.0%	291 (22.5)	188 (27.5)	145 (21.4)
8.0% <= HbA1c < 8.5%	252 (19.5)	135 (19.8)	164 (24.2)
8.5% <= HbA1c < 9.0%	226 (17.5)	86 (12.6)	101 (14.9)
9.0% <= HbA1c < 9.5%	148 (11.5)	48 (7.0)	91 (13.4)
HbA1c >= 9.5%	115 (8.9)	39 (5.7)	69 (10.2)
Baseline HbA1c (mmol/mol)			
N	1291	683	679
Mean (SD)	66.3 (9.1)	64.0 (8.2)	67.2 (9.0)
Median	65.0	62.8	66.1
Min ; max	44.3 ; 103.3	48.6 ; 91.3	42.1 ; 98.9
FPG (mg/dL)			
N	1241	669	660
Mean (SD)	155.0 (52.1)	170.4 (48.4)	156.4 (50.9)
Median	149.6	160.4	149.6
Min ; max	43.2 ; 437.9	81.1 ; 394.6	52.3 ; 464.9
FPG (mmol/L)			
N	1241	669	660
Mean (SD)	8.6 (2.9)	9.5 (2.7)	8.7 (2.8)
Median	8.3	8.9	8.3
Min ; max	2.4 ; 24.3	4.5 ; 21.9	2.9 ; 25.8
Duration of diabetes (years)			
N	1291	683	679
Mean (SD)	15.3 (7.8)	12.6 (6.9)	14.4 (7.6)
Median	14.7	11.6	13.5
Min ; max	0.6 ; 55.0	0.4 ; 39.7	0.4 ; 47.5
Duration of diabetes, N (%)			
N	1291 (100.0)	683 (100.0)	679 (100.0)
<10 years	331 (25.6)	268 (39.2)	204 (30.0)
>=10 years	960 (74.4)	415 (60.8)	475 (70.0)
Renal function (eGFR, mL/min/1.73m^2)			
N	1291	683	679
Mean (SD)	85.2 (19.6)	87.8 (17.8)	86.7 (19.9)
Median	88.0	89.0	89.0
Min ; max	24.0 ; 145.0	34.0 ; 139.0	30.0 ; 145.0
Renal function (eGFR, mL/min/1.73m^2), N (%)			
N	1291 (100.0)	683 (100.0)	679 (100.0)
Normal (>=90)	573 (44.4)	326 (47.7)	321 (47.3)
Mild renal impairment (60<= to <90)	568 (44.0)	309 (45.2)	291 (42.9)
Moderate renal impairment (30<= to <60)	149 (11.5)	48 (7.0)	67 (9.9)
Severe renal impairment (<30)	1 (0.1)	0	0
Hepatic function, N (%)			
N	1291 (100.0)	683 (100.0)	679 (100.0)
Normal	1197 (92.7)	601 (88.0)	614 (90.4)
Impaired	88 (6.8)	75 (11.0)	62 (9.1)
Missing	6 (0.5)	7 (1.0)	3 (0.4)

Table 32. Diabetes complications at screening – study 4591

	IcoSema			Ico			Total		
	N	(%)	E	N	(%)	E	N	(%)	E
Number of participants	646			645			1291		
All complications	266	(41.2)	450	258	(40.0)	430	524	(40.6)	880
Diabetic neuropathy	159	(24.6)	161	153	(23.7)	155	312	(24.2)	316
Diabetic retinopathy	130	(20.1)	229	127	(19.7)	217	257	(19.9)	446
Diabetic nephropathy	60	(9.3)	60	57	(8.8)	58	117	(9.1)	118

Table 33. Diabetes complications at screening – study 4592

	IcoSema			Sema 1.0 mg			Total		
	N	(%)	E	N	(%)	E	N	(%)	E
Number of participants	342			341			683		
All complications	100	(29.2)	157	93	(27.3)	149	193	(28.3)	306
Diabetic neuropathy	59	(17.3)	59	52	(15.2)	52	111	(16.3)	111
Diabetic retinopathy	38	(11.1)	64	33	(9.7)	59	71	(10.4)	123
Diabetic nephropathy	34	(9.9)	34	38	(11.1)	38	72	(10.5)	72

Table 34. Diabetes complications at screening – study 4593

	IcoSema			IGlar+IAsp			Total		
	N	(%)	E	N	(%)	E	N	(%)	E
Number of participants	340			339			679		
All complications	120	(35.3)	178	124	(36.6)	207	244	(35.9)	385
Diabetic neuropathy	69	(20.3)	72	65	(19.2)	65	134	(19.7)	137
Diabetic nephropathy	40	(11.8)	40	50	(14.7)	50	90	(13.3)	90
Diabetic retinopathy	38	(11.2)	66	52	(15.3)	92	90	(13.3)	158

Numbers analysed

The primary efficacy analysis population included all randomised subjects (FAS, by intention to treat).

Study 4591: IcoSema 646 (100%), Ico 645 (100%)

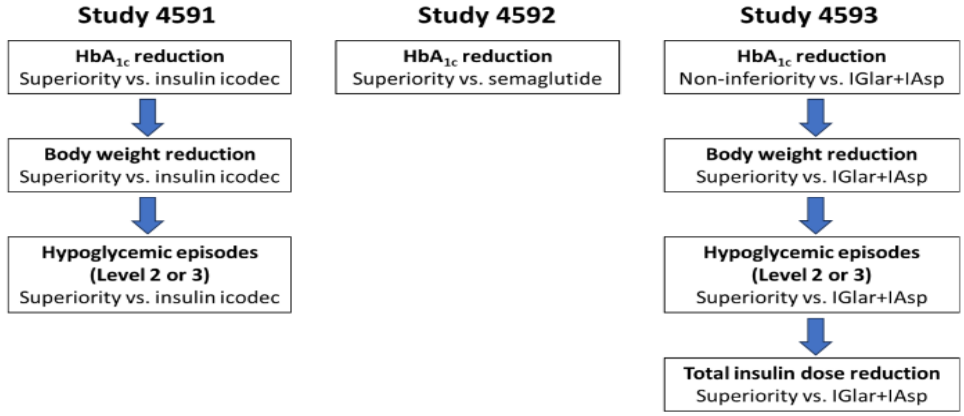
Study 4592: IcoSema 342 (100%), Sema 341 (100%)

Study 4593: IcoSema 340 (100%), IGlar+IAsp 339 (100%)

Outcomes and estimation

Prespecified hierarchical testing in the confirmatory studies

Figure 10.



Abbreviations: HbA_{1c} = glycated haemoglobin; IGlar+IAsp = Insulin glargine + insulin aspart

Primary endpoint

Change in HbA1c

The primary endpoint in all COMBINE studies was change in HbA_{1c} from baseline to week 52. The primary estimand was defined using a treatment policy approach. The primary objective was met in all studies. Kyinsu was superior in reduction of HbA_{1c} to insulin icodec (study 4591) and to semaglutide (4592) and non-inferior to basal-bolus insulin (study 4593) (**Table 35**). The change in HbA1c over time in the trials is presented in **Figure 11**, **Figure 12** and **Figure 13**.

Table 35. HbA_{1c} (%) Change from Baseline at end of trial

	IcoSema	Comparator	Estimated treatment difference [95% CI] IcoSema vs comparator
Trial 4591 (COMBINE 1)			
	IcoSema (n=646)	**Insulin icodec** (n=645)	
HbA_{1c} (%) Estimated change from baseline (week 52)	-1.55	-0.89	ETD: -0.66 [-0.76 ; -0.57][a]
Trial 4592 (COMBINE 2)			
	IcoSema (n=342)	**Semaglutide** (n=341)	
HbA_{1c} (%) Estimated change from baseline (week 52)	-1.35	-0.90	ETD: -0.44 [-0.56 ; -0.33][a]
Trial 4593 (COMBINE 3)			
	IcoSema (n=340)	**IGlar+IAsp** (n=339)	
HbA_{1c} (%) Estimated change from baseline (week 52)	-1.47	-1.40	ETD: -0.06 [-0.22 ; 0.09][b]

[a] Superiority was confirmed for IcoSema, [b] non-inferiority was confirmed for IcoSema

Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide**.**

Figure 11. HbA1c by treatment week in study 4591

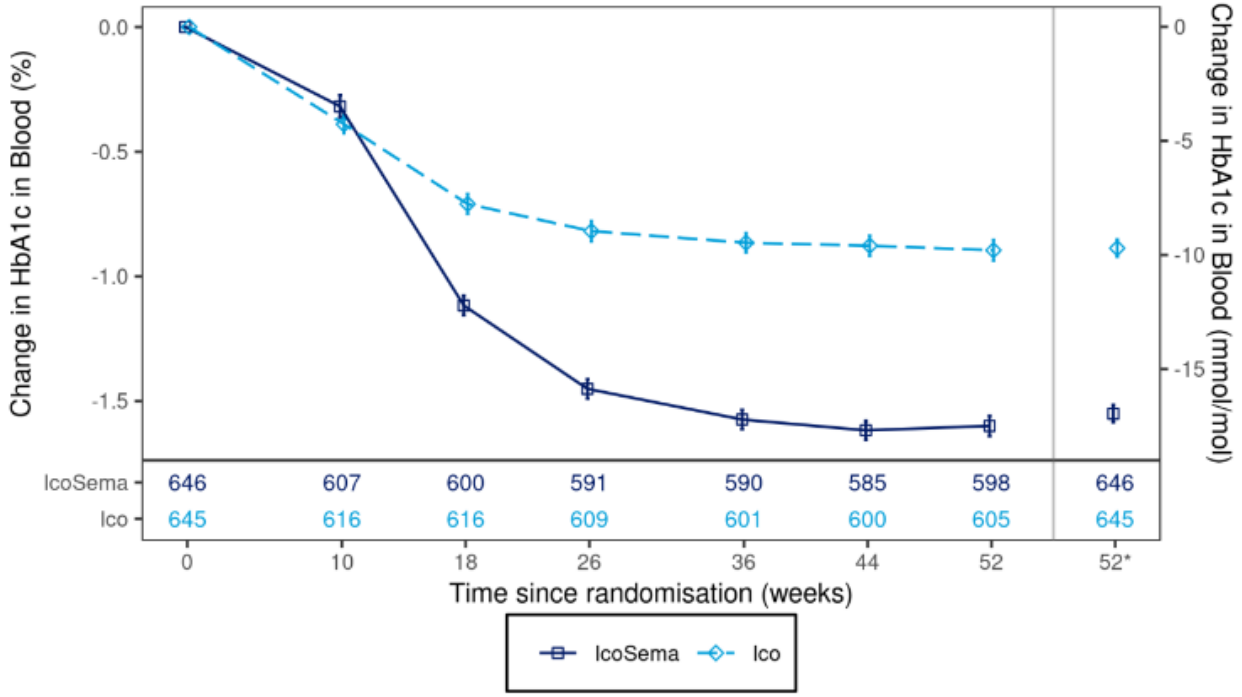


Figure 22. HbA1c by treatment week in study 4592

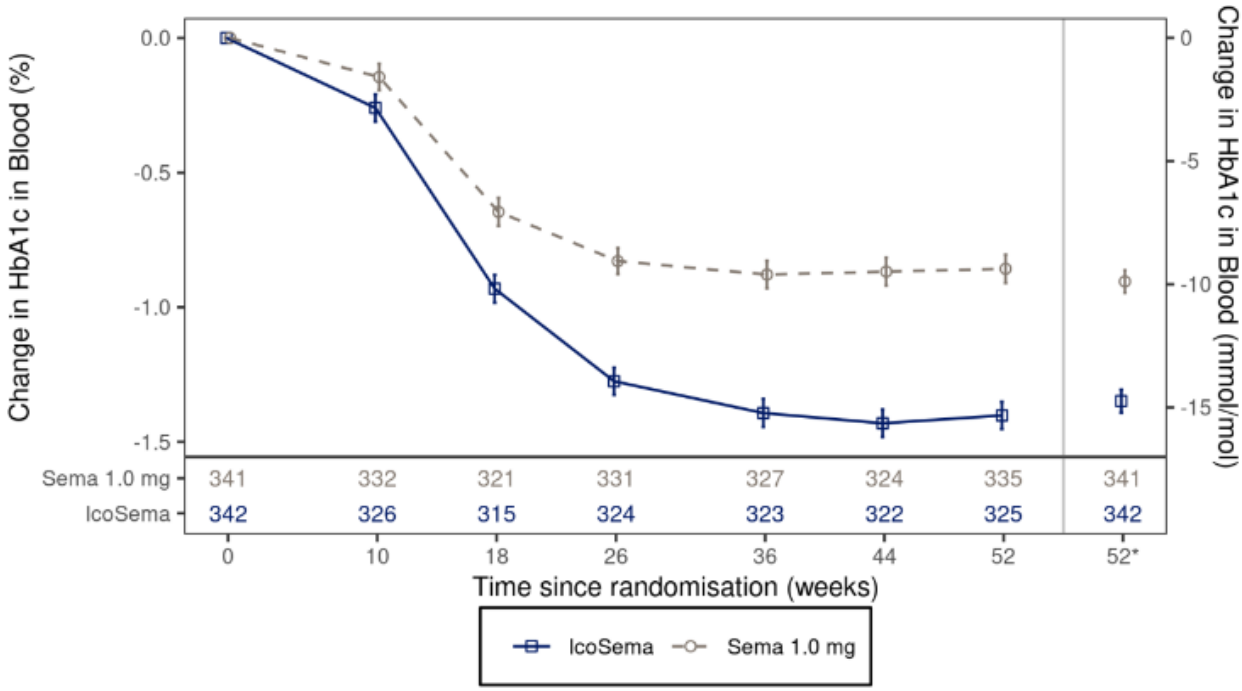
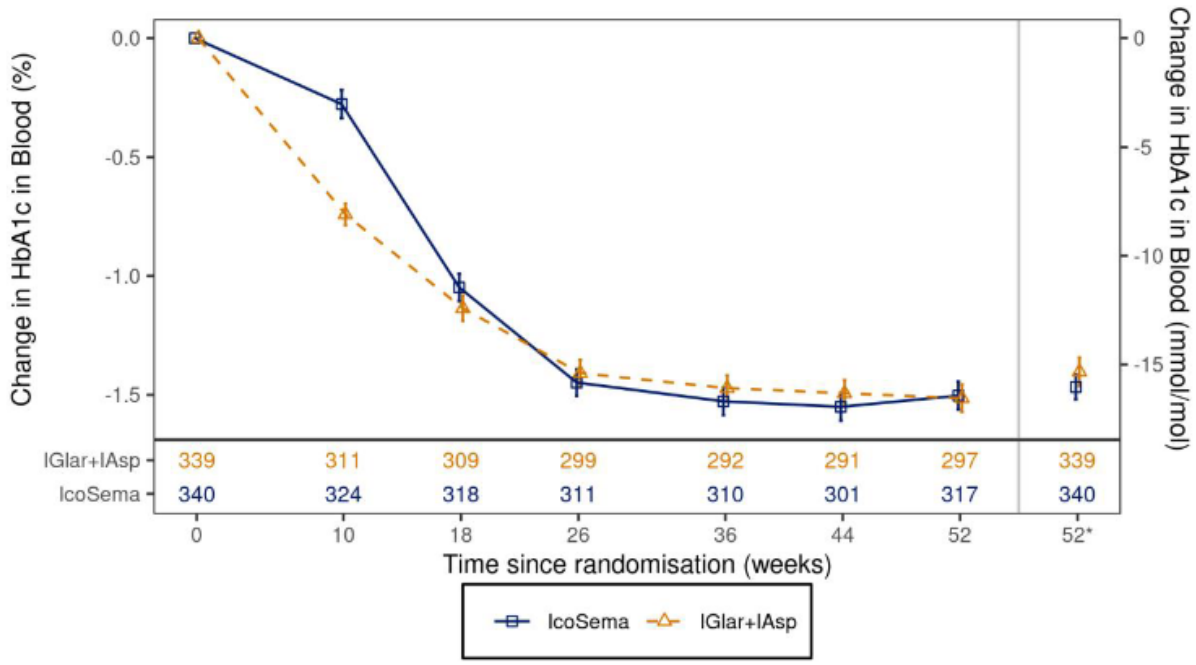


Figure 13. HbA1c by treatment week in study 4593



Secondary endpoints

Mean weekly insulin dose

Weekly insulin dose (total) for week 50 to 52 was a **confirmatory endpoint in study 4593** and a supportive endpoint in study 4591.

Across all studies, Kyinsu was started at 40 DS, then up-titrated gradually during the first half of study and plateaued afterwards. The maximum dose on the Kyinsu was 350 DS per week in all COMBINE studies, corresponding to 350 U insulin icodec and 1 mg semaglutide per week. There was no restriction on the maximum dose of insulin in comparator groups (i.e. for basal-bolus insulin or insulin icodec) in studies 4591 and 4593.

In study 4593, superiority of Kyinsu versus IGlar+IAsp was confirmed for the key secondary endpoint mean weekly *total insulin dose* from week 50 to 52 (ETD: -270 U [-303; -236]).
The mean weekly *basal insulin dose* from week 50 to 52 was numerically lower for Kyinsu compared to IGlar+IAsp (196 U versus 285 U). In study 4591, mean weekly basal insulin dose from week 50 to 52 was numerically lower for Kyinsu compared to insulin icodec (182 U versus 355 U; ETD: -172 U [-190; -155]) (**Table 36**).

Across the COMBINE studies, 108 patients (8.1%) received an Kyinsu dose ≥350 dose steps for at least 3 consecutive weeks. Body weight, BMI, HbA_{1c} and FPG were found to be slightly higher in these 108 patients (BW: 101-106 kg, BMI: 34-35 kg/m^2, HbA1c: 8.3-8.7%, FPG: 9.4-10.6 mmol/l) compared to the entire Kyinsu group (BW: 85-87 kg, BMI: 30-31 kg/m^2, HbA1c: 8.2%, FPG: 8.8-8.9 mmol/l). Of the 108 patients, 11 patients (10.2%) increased the dose of or initiated additional glucose lowering medication after receiving ≥350 dose steps for 3 consecutive weeks. During the first 10 weeks of treatment, FPG and HbA1c increased, with the most pronounced increase in patients in study 4591 (**Figure 14**, **Figure15**). Most notably, however, is that the treatment goal of HbA1c <7 was not achieved for any of the patients in either study (**Figure 14**). **Information that the maximum recommended weekly dose for Kyinsu is 350 dose steps has been adequately included in the SmPC**.

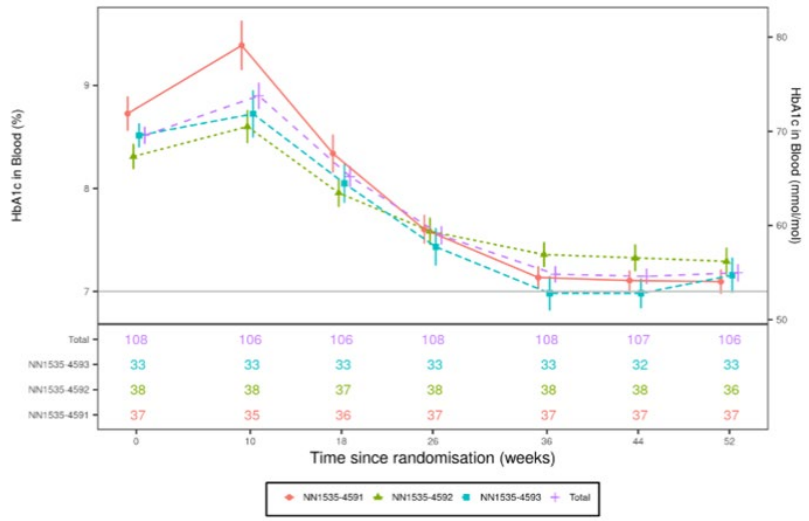
Table 36. Weekly basal insulin dose week 50 to 52

	IcoSema	Comparator	Estimated treatment difference [95% CI] IcoSema vs comparator
Trial 4591 (COMBINE 1)			
	IcoSema (n=646)	**Insulin icodec** (n=645)	
Weekly insulin dose week 50-52			
Basal (U)	182	355	ETD: -172 [-190; -155]
Basal (U/kg)	2.24	4.02	ETD: -1.78 [-1.96; -1.59]
Trial 4592 (COMBINE 2)			
	IcoSema (n=342)	**Semaglutide** (n=341)	
Weekly insulin dose week 50-52			
Basal (U)	196	-	-
Basal (U/kg)	2.22		
Trial 4593 (COMBINE 3)			
	IcoSema (n=340)	**IGlar+IAsp** (n=339)	
Weekly insulin dose week 50-52			
Basal (U)	196	285	ETD: -89.0 [-109; -68.8]
Basal (U/kg)	2.38	3.19	ETD: -0.81 [-1.02; -0.59]
Total (U)	196	466	ETD: -270 [-303; -236] •
Total (U/kg)	2.38	5.21	ETD: -2.84 [-3.19; -2.48]

• Superiority was confirmed for IcoSema, p-value 0.0001, adjusted for multiplicity

Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide**.**

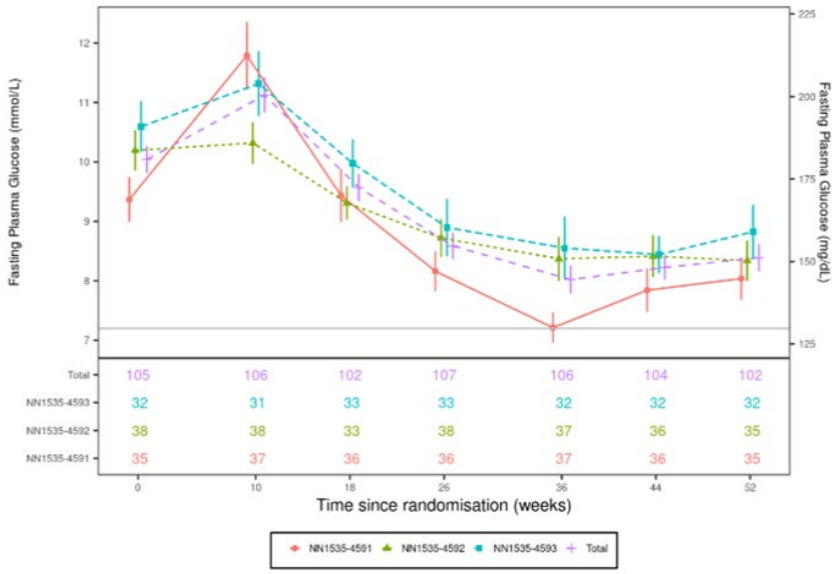
Figure 14. HbA1c- participants sustaining ≥350 dose steps for ≥3 consecutive weeks – mean plot – in-study – IcoSema arm – full analysis



HbA1c: Haemoglobin A1c
Number of participants contributing to the data points appears in the bottom panel.
Legend: Mean (symbol) and mean ± standard error to the mean (error bars).

Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

Figure 15. Fasting plasma glucose- participants sustaining ≥350 dose steps for ≥3 consecutive weeks – mean plot – in-study – IcoSema arm – full analysis



Number of participants contributing to the data points appears in the bottom panel.
Legend: Mean (symbol) and mean ± standard error to the mean (error bars).

Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

Semaglutide dose

The end dose of the semaglutide component in Kyinsu arms was calculated based on observed data, and mean dose ranged from 0.48 to 0.56 mg weekly across studies. For participants randomised to semaglutide in study 4592, at end of treatment the actual mean weekly semaglutide dose was 0.99 mg. Therefore, the full potential of semaglutide in Kyinsu may not being exploited. This was also commented on in the CHMP advice.

Change in body weight

Change in bodyweight was a **confirmatory secondary endpoint in study 4591 and 4593** and was a supportive secondary endpoint in study 4592.

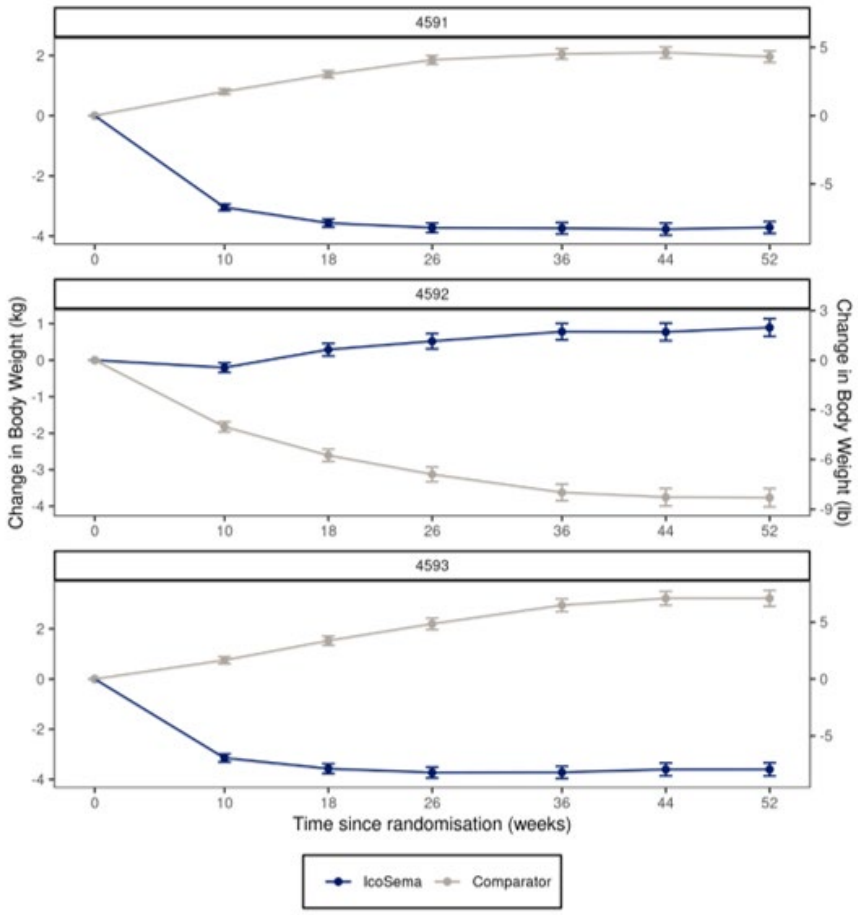
In patients previously on daily basal insulin (studies 4591 and 4593), body weight decreased in the Kyinsu group (-3.7 kg and -3.6 kg, respectively) and increased in the insulin treated groups. Superiority of Kyinsu was confirmed to insulin icodec in study 4591 (ETD -5.59 kg [-6.14; -5.04]) and to IGlar+IAsp in study 4593 (ETD: -6.72 kg [-7.58; -5.86]). In insulin naïve patients (study 4592), body weight slightly increased in the Kyinsu group (0.84 kg) whereas body weight decreased in the semaglutide group (-3.7 kg). The estimated treatment difference in change in body weight for Kyinsu compared to semaglutide was 4.54 kg [-0.12; 1.04] (**Table 37**), (**Figure 16**).

Table 37. Body weight at end of treatment – change from baseline

Study	Estimated change from baseline in body weight (kg)		Estimated treatment difference (kg) [95% CI]	P-value
	IcoSema	Comparator		
Study 4591 (IcoSema vs insulin icodec)	-3.70	1.89	-5.59 [-6.14; -5.04]	<0.0001
Study 4592 (IcoSema vs semaglutide	0.84	-3.70	4.54 [3.84; 5.23]	
Study 4593 (IcoSema vs IGlar+IAsp)	-3.56	3.16	-6.72 [-7.58; -5.86]	<0.0001

Note: Superiority was confirmed for IcoSema in studies 4591 and 4592, p <0.000, adjusted for multiplicity.
Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

Figure 16. Body weight by treatment week - change from baseline - study 4591, 4592 and 4593



Changing in fasting plasma glucose

Change in fasting plasma glucose (FPG) from baseline to week 52 was a supportive secondary endpoint in all three studies.

Mean FPG values at baseline were comparable between treatment arms in each study, except that mean FPG values at baseline were slightly higher in the IGlar+IAsp group (8.94 mmol/L) compared to the Kyinsu group (8.42 mmol/L) in study 4593 (**Table 38**).

In study 4592, the reduction in FPG from baseline to end of treatment was numerically larger for v than for semaglutide (EDT: -1.07 [-1.37; -0.76]). In study 4591, the decrease in FPG was initially greater for patients treated with insulin icodec compared to Kyinsu; however, from week 22 onwards, the reduction in FPG was slightly greater in the Kyinsu group compared to the insulin icodec group (ETD: -0.14 [-0.38; 0.10]. In study 4593, the reduction in FPG from baseline to end of treatment was more pronounced from baseline to end of treatment in the IGlar+IAsp group compared to Kyinsu (EDT: 0.02 [-0.34; 0.38]) (**Table 40**). The FPG change from baseline by treatment weeks is presented in **Figure 17**.

Table 39. **Baseline values of FPG in study 4591 and 4593**

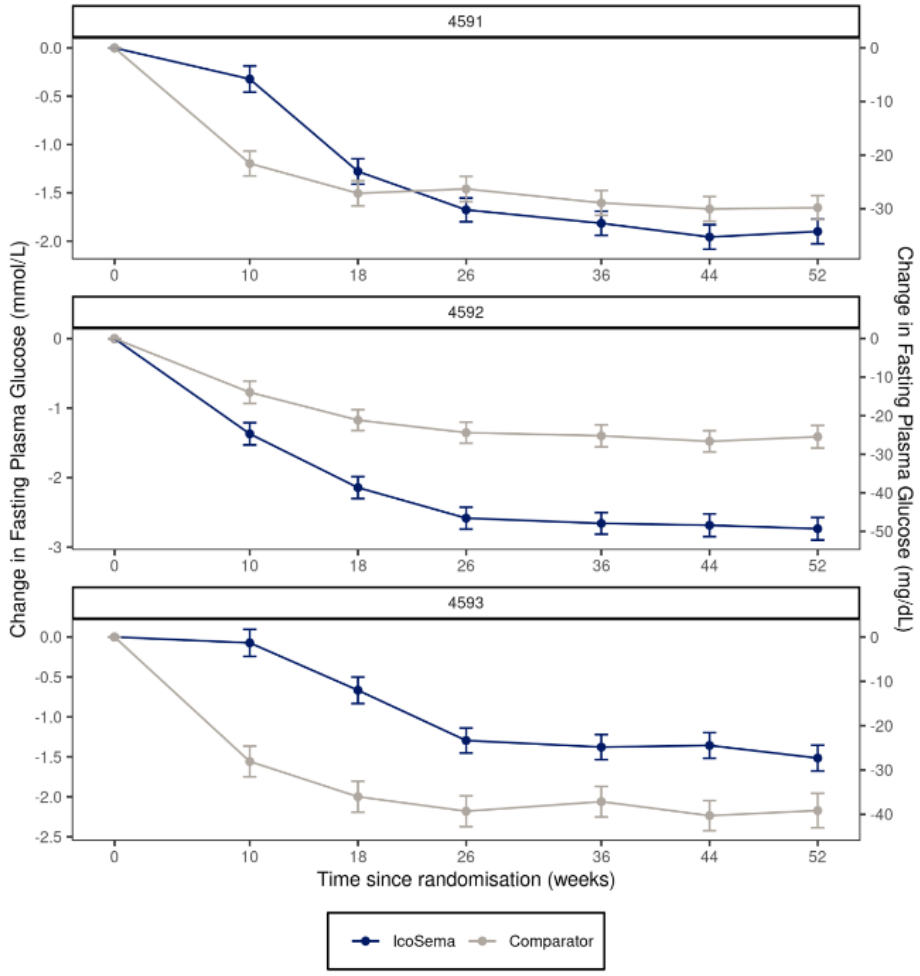
	IcoSema		Comparator	
	N	Mean (SD)	N	Mean (SD)
Fasting Plasma Glucose (mmol/L)				
4591	646	8.64 (2.83)	645	8.57 (2.95)
4592	342	9.56 (2.71)	341	9.35 (2.66)
4593	340	8.42 (2.54)	339	8.94 (3.08)

Table 40. Changes in fasting plasma glucose

	IcoSema	**Comparator**	**Estimated treatment difference [95% CI] IcoSema vs comparator**
Trial 4591 (COMBINE 1)			
	IcoSema (n=646)	**Insulin icodec** (n=645)	
FPG Estimated change from baseline (mmol/L)	-1.68	-1.54	ETD: -0.14 [-0.38; 0.10]
Trial 4592 (COMBINE 2)			
	IcoSema (n=342)	**Semaglutide** (n=341)	
FPG Estimated change from baseline (mmol/L)	-2.48	-1.41	ETD: -1.07 [-1.37; -0.76]
Trial 4593 (COMBINE 3)			
	IcoSema (n=340)	**IGlar+IAsp** (n=339)	
FPG Estimated change from baseline (mmol/L)	-1.56	-1.58	ETD: 0.02 [-0.34; 0.38]

Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

Figure 17. Fasting plasma glucose by treatment week, change from baseline -full analysis set



Time spent in glycaemic target range (CGM metrics)

"Time in range (TIR) 3.9-10.0 mmol/L", "Time above range (TAR) >10.0 mmol/L" and "Time below range (TBR) <3.0 mmol/L" were secondary supportive endpoints in study 4591 and 4593.

In the Kyinsu phase 3a programme, study 4591 and 4593 had CGM metrics endpoints for the last 4 weeks of planned treatment. In study 4593, patients were also equipped with a CGM device from week 0 to week 8 (see section 3.3.4.1). The CGM data in study 4591 and 4593 were blinded for both subjects and investigators. 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). A difference of 1%-point corresponds to 14.4 minutes more time in range.

In study 4591, subjects in the Kyinsu group compared to the insulin icodec group spent more time in glycaemic range 3.9-10.0 mmol/L (73.3% versus 61.8%) and slightly less time above range >10 mmol/L (23.3% vs 37.0%). TBR was <1% and no important differences between treatment groups. In study 4593, there were no important differences between the treatment groups in TIR or TAR. Slightly more patients treated with IGlar+IAsp spent time below range (0.5% vs 0.2%); however, TBR was <1%.

In study 4591 and 4593, data on TIR is presented in **Table 41**, data on TAR is presented in **Table 42** and data on TBR is presented in **Table 43**.

Table 41. Time spent in range (TIR) 3.9-10.0 mmol/L (70-180 mg/dL)

	IcoSema	Comparator	Estimated treatment difference [95% CI] IcoSema vs comparator
Trial 4591 (COMBINE 1)			
	IcoSema (n=646)	**Insulin icodec** (n=645)	
Time spent (%) week 48 to 52 Time in range 3.9-10.0 mmol/L	73.3	61.8	ETD: 11.5 [9.35; 13.7]
Trial 4593 (COMBINE 3)			
	IcoSema (n=340)	**IGlar+IAsp** (n=339)	
Time spent (%) week 48 to 52 Time in range 3.9-10.0 mmol/L	68.6	66.4	ETD: 2.21 [-0.86; 5.27]

Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

Table 42. Time spent above range (TAR) >10 mmol/L (180 mg/dL)

	IcoSema	Comparator	Estimated treatment ratio [95% CI] IcoSema vs comparator
Trial 4591 (COMBINE 1)			
	IcoSema (n=646)	**Insulin icodec** (n=645)	
Time spent (%) week 48 to 52 Time spent >10 mmol/L	23.3	37.0	ETR: 0.63 [0.58; 0.69]
Trial 4593 (COMBINE 3)			
	IcoSema (n=340)	**IGlar+IAsp** (n=339)	
Time spent (%) week 48 to 52 Time spent >10 mmol/L	31.5	31.4	ETR: 1.00 [0.89; 1.13]

Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

Table 43. Time spent below range (TBR) < 3.0 mmol/L (54 mg/dL)

	IcoSema	Comparator	Estimated treatment ratio [95% CI] IcoSema vs comparator
Trial 4591 (COMBINE 1)			
	IcoSema (n=646)	**Insulin icodec** (n=645)	
Time spent (%) week 48 to 52 Time spent < 3.0 mmol/L	0.26	0.31	ETR: 0.84 [0.64; 1.11]
Trial 4593 (COMBINE 3)			
	IcoSema (n=340)	**IGlar+IAsp** (n=339)	
Time spent (%) week 48 to 52 Time spent < 3.0 mmol/L	0.18	0.46	ETR: 0.40 [0.29; 0.55]

Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

Rate of hypoglycaemic events

The number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3) was a secondary confirmatory safety endpoint in study 4591 and 4593 and was a secondary supportive safety endpoint in study 4592, see Safety section.

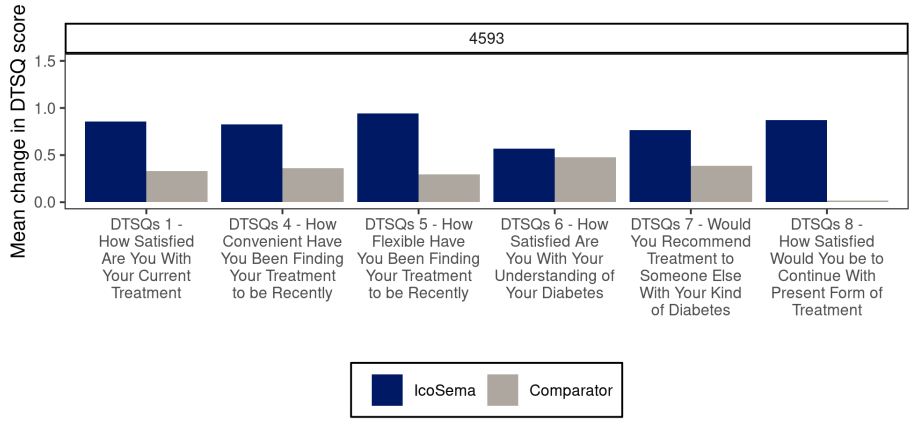
Patient reported outcomes

DTSQ

In 4593, 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.

In study 4593, the change in DTSQ total score was numerically greater for Kyinsu compared to IGlar+IAsp and estimated treatment difference was 3.00 [1.98; 4.02] (**Figure 18**).

Figure 18. DTSQ total treatment satisfaction score by question at week 52 - change from baseline – study 4593



DTSQ: Diabetes Treatment Satisfaction Questionaire

Ancillary analyses

Other efficacy analysis

Achievement of HbA_{1c} target without body weight gain and without hypoglycaemia

The odds ratio of achieving HbA_{1c} <7% without body weight gain and without either level 2 or 3 hypoglycaemia was numerically higher for Kyinsu compared to insulin icodec (study 4591) and IGlar+IAsp (study 4593), respectively. In study 4592; however, the responder rates of achieving HbA_{1c} targets without weight gain and without either level 2 or 3 hypoglycaemia was numerically lower for Kyinsu (30.2%) compared to semaglutide (40.5%) (**Table 44**).

Table 44. Achievement of HbA1c targets (<7%) after 52 weeks without body weight gain and severe (level 3) or clinically significant (level 2) hypoglycaemic episodes during the prior 12 weeks

Study	Estimated proportion of subjects (%)		Estimated odds ratio [95% CI]
	IcoSema	Comparator	
Study 4591 (IcoSema vs insulin icodec)	55.73	10.17	11.13 [8.22; 15.05]
Study 4592 (IcoSema vs semaglutide	30.23	40.54	0.64 [0.46; 0.88]
Study 4593 (IcoSema vs IGlar+IAsp)	50.07	5.95	15.86[9.75; 25.83]

Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

Waist circumference (cm)

In patients switching from daily basal insulin (studies 4591 and 4593), waist circumference decreased in the Kyinsu group and increased in the comparator groups. In participants on pre-study GLP-1 RAs (study 4592), mean waist circumference decreased in the semaglutide group whereas increased waist circumference was observed in the Kyinsu group (**Table 45**).

Table 45. Waist circumference after 52 weeks - change from baseline – full analysis set

Study	Estimated change from baseline in waist circumference (cm)		Estimated treatment difference (cm) [95% CI]
	IcoSema	Comparator	
Study 4591 (IcoSema vs insulin icodec)	-2.58	2.00	-4.58 [-5.23; -3.94]
Study 4592 (IcoSema vs semaglutide	1.08	-3.52	4.61 [3.76; 5.45]
Study 4593 (IcoSema vs IGlar+IAsp)	-3.03	1.83	-4.86 [-6.01; -3.70]

Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

Blood lipid related parameters

Lipids (HDL cholesterol, LDL cholesterol, VLDL cholesterol, triglycerides, total cholesterol, and free fatty acids were measured in the clinical studies (**Table 46**). Evaluation of lipid parameters is difficult due to the risk of increased lipids with diabetes in general and concomitant medication with lipid-modifying agents, e.g., 62-68% of the patients were treated with statins at baseline.

Table 46. Lipids after 52 weeks - relative change from baseline - statistical analysis - on-treatment – full analysis set

Analysis of blood lipids	Estimated change from baseline (mmol/L)		Estimated treatment ratio (ETR)
Study 4591			
	IcoSema	**Insulin icodec**	
Cholesterol, total	0.96	0.99	0.97 (0.95; 0.99)

HDL cholesterol	1.07	1.06	1.01 (0.99; 1.03)
LDL cholesterol	0.95	0.99	0.96 (0.92; 0.99)
VLDL cholesterol	0.83	0.88	0.94 (0.90; 0.98)
Triglycerides	0.83	0.88	0.94 (0.90; 0.98)
Free fatty acids	0.83	0.81	1.02 (0.96; 1.08)
Study 4592			
	IcoSema	**Semaglutide**	
Cholesterol, total	0.97	0.98	0.99 (0.96; 1.02)
HDL cholesterol	1.20	1.20	0.98 (0.96; 1.01)
LDL cholesterol	0.99	0.98	1.01 (0.95; 1.06)
VLDL cholesterol	0.81	0.87	0.93 (0.88; 0.99)
Triglycerides	0.82	0.88	0.93 (0.88; 0.99)
Free fatty acids	0.74	0.84	0.84 (0.78; 0.90)
Study 4593			
	IcoSema	**IGlar+IAsp**	
Cholesterol, total	0.95	0.99	0.96 (0.93; 0.99)
HDL cholesterol	1.06	1.04	1.02 (0.99; 1.04)
LDL cholesterol	0.93	1.01	0.92 (0.88; 0.97)
VLDL cholesterol	0.85	0.91	0.94 (0.88; 1.00)
Triglycerides	0.85	0.91	0.94 (0.88; 1.00)
Free fatty acids	0.82	1.00	0.82 (0.75; 0.89)

Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

Vital signs

Blood pressure and pulse rate were measured in the clinical studies (**Table 47**). In study 4592, SBP decreased more for semaglutide (-3.06 mmHg) than for Kyinsu (-0.42 mmHg). DBP increased slightly for Kyinsu (0.23 mmHg) and decreased for semaglutide (-1.06 mmHg).

Table 47. Vital signs after 52 weeks - change from baseline - statistical analysis - on-treatment – full analysis set

Analysis of blood pressure (mmHg) and pulse (bpm)	**Estimated mean change from baseline for blood pressure (mmHg) and pulse (bpm)**		**Estimated treatment difference (ETD)**
Study 4591			
	IcoSema	**Insulin icodec**	

Systolic blood pressure (mmHg)	-4.43	-1.66	-2.77 (-1.44; 0.25)
Diastolic blood pressure (mmHg)	-1.09	-0.50	-0.59 (0.99; 1.03)
Pulse (bpm)	1.59	-0.12	1.71 (0.80; 2.62)
Study 4592			
	IcoSema	**Semaglutide**	
Systolic blood pressure (mmHg)	-0.42	-3.06	2.64 (0.72; 4.55)
Diastolic blood pressure (mmHg)	0.23	-1.06	1.29 (0.16; 2.42)
Pulse (bpm)	-1.11	-0.40	-0.72 (-1.83; 0.39)
Study 4593			
	IcoSema	**IGlar+IAsp**	
Systolic blood pressure (mmHg)	-2.38	-0.46	-1.92 (-3.67; -0.18)
Diastolic blood pressure (mmHg)	-0.54	-0.17	-0.37 (-1.50; 0.76)
Pulse (bpm)	1.11	0.67	0.44 (-0.91; 1.80)

Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

Subgroup analyses (post-hoc) based on demographic, disease, or treatment factors

There were no apparent differences in subgroups based on demographic, disease, or treatment factors, except for a tendency of greater reduction of HbA1c for the subgroup of HbA_{1c} ≥8% in studies 4591 and 4592.

2.7.5.3. Summary of main efficacy results

Table 48. Summary of efficacy for study 4591 (COMBINE 1)

Title:	**A 52-week study comparing the efficacy and safety of once weekly IcoSema and once weekly insulin icodec, both treatment arms with or without oral anti-diabetic drugs, in participants with type 2 diabetes inadequately controlled with daily basal insulin. COMBINE 1.**	
Study identifier	Protocol Number – NN1535-4591 EudraCT number – 2020-005281-34	
Database lock	14 May 2024	
Design	This was an interventional, multi-national, multi-centre, randomised, 52-week, open label, parallel group, treat-to-target confirmatory study with two treatment arms. The study investigated the efficacy and safety of treatment with once weekly IcoSema compared to once weekly insulin icodec, both treatment arms with or without OADs, in participants with T2D inadequately controlled with daily basal insulin.	
	Duration of study: 59 weeks	
Objectives	***Primary objective*** To confirm superiority of once weekly IcoSema compared with once weekly insulin icodec, both treatment arms with or without OADs, in terms of glycaemic control measured by change in HbA_{1c} from baseline after 52 weeks in participants with T2D inadequately controlled with daily basal insulin. ***Secondary objectives*** To confirm superiority of once weekly IcoSema compared to once weekly insulin icodec, both treatment arms with or without OADs, in participants with T2D inadequately controlled with daily basal insulin in terms of: • Change in body weight from baseline after 52 weeks • Number of clinically significant hypoglycaemic (level 2) or severe hypoglycaemic (level 3) episodes during 52 weeks and the 5 week follow-up period To compare parameters of glycaemic control and safety of once weekly IcoSema with once weekly	
Treatments groups	IcoSema	646 participants randomised
	Insulin icodec	645 participants randomised
Endpoints and definitions	*Primary:* • Change in HbA_{1c} (%-point) from baseline week 0 (V2) to week 52 (V54)	
	Confirmatory secondary: • Change in body weight (Kg) from baseline week 0 (V2) to week 52 (V54) • Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol /L [54 mg/dL], confirmed by BG meter) or severe hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 57 (V56)	

Title:	**A 52-week study comparing the efficacy and safety of once weekly IcoSema and once weekly insulin icodec, both treatment arms with or without oral anti-diabetic drugs, in participants with type 2 diabetes inadequately controlled with daily basal insulin. COMBINE 1.**		
	Supportive secondary efficacy: • Time in range 3.9-10.0 mmol/L (70-180 mg/dL) (% of readings) from week 48 (V50) to week 52 (V54)[a] • Time spent < 3.0 mmol/L (54 mg/dL) (% of readings) from week 48 (V50) to week 52 (V54)[a] • Time spent > 10 mmol/L (180 mg/dL) (% of readings) from week 48 (V50) to week 52 (V54)[a] • Change in fasting plasma glucose (FPG) (mmol/L) from baseline week 0 (V2) to week 52 (V54) • Weekly basal insulin dose (U) from week 50 (V52) to week 52 (V54) *Supportive secondary safety:* • Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol /L [54 mg/dL], confirmed by BG meter) from baseline week 0 (V2) to week 57 (V56) • Number of severe hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 57 (V56)		
	The imputation approach for the primary estimand and secondary estimand regarding change in body weight from baseline was a multiple imputation approach based on an ANCOVA model with randomised treatment as fixed factor. The imputation approach for the secondary estimand regarding number of clinically significant hypoglycaemic episodes (level 2) or severe hypoglycaemic episodes (level 3) from baseline was done with 1) a Bayes negative binomial model with region as fixed factor and 2) imputation of the number of episodes in the missing period for participants having discontinued randomised treatment.		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis set	Full analysis set was all randomised participants. Participants were included in the analyses according to the planned randomised treatment.		
Results	**Treatment group**	**IcoSema**	**Insulin icodec**
	Number of participants	646	645
	Change in HbA_{1c} (%-point) ETD [95% CI] p value	-1.55 -0.66 [-0.76; -0.57] <0.0001[b]	-0.89
	Change in body weight (Kg) ETD [95% CI] p value	-3.70 -5.59 [-6.14; -5.04] <0.0001[b]	1.89
	Time in range 3.9-10.0 mmol/L (70-180 mg/dL) (%) ETD [95% CI] p value	72.4 10.6 [8.43; 12.8] <0.0001[c]	61.8

Title:	**A 52-week study comparing the efficacy and safety of once weekly IcoSema and once weekly insulin icodec, both treatment arms with or without oral anti-diabetic drugs, in participants with type 2 diabetes inadequately controlled with daily basal insulin. COMBINE 1.**		
	Time spent < 3.0 mmol/L (54 mg/dL) (%) ETR [95% CI] p value	0.26 0.84 [0.64; 1.11] 0.216	0.31
	Time spent > 10 mmol/L (180 mg/dL) (%) ETR [95% CI] p value	23.3 0.63 [0.58; 0.69] <0.0001[c]	37.0
	Change in fasting plasma glucose (FPG) (mmol/L) ETD [95% CI] p value	-1.67 -0.13 [-0.37; 0.11] 0.2915	-1.54
	Change in fasting plasma glucose (FPG) (mg/dL) ETD [95% CI] p value	-30.1 -2.33 [-6.65; 2.00] 0.2915	-27.8
	Change in weekly basal insulin dose (U) from week 50 (V52) to week 52 (V54) ETD [95% CI]; p value	182 -172 [-190; -155] <0.0001[c]	355

Abbreviations: IcoSema: insulin icodec and semaglutide.

Notes: a Using continuous glucose monitoring (CGM) system, Dexcom G6. b Superiority was confirmed for Kyinsu. c Statistically significant treatment difference in favour of Kyinsu.

Table 49. Summary of efficacy for study 4592 (COMBINE 2)

Title:	**A 52-week study comparing the efficacy and safety of once weekly IcoSema and once weekly semaglutide, both treatment arms with or without oral anti-diabetic drugs, in participants with type 2 diabetes inadequately controlled with a GLP-1 receptor agonist. COMBINE 2.**	
Study identifier	Protocol Number – NN1535-4592 EudraCT number – 2020-005308-21	
Database lock	7 February 2024	
Design	This was an interventional, multi-national, multi-centre, randomised, 52-week, open label, parallel group, treat-to-target/dose escalation, confirmatory study with two treatment arms. The study investigated the efficacy and safety of treatment with once weekly IcoSema compared to once weekly semaglutide, both treatment arms with or without OADs, in participants with T2D inadequately controlled with a GLP-1 receptor agonist.	
	Duration of study: 59 weeks	
Objectives	***Primary objective*** To confirm superiority of once weekly IcoSema compared with once weekly semaglutide, both treatment arms with or without OADs, in terms of glycaemic control measured by change in HbA_{1c} from baseline after 52 weeks in participants with T2D inadequately controlled a GLP-1 receptor agonist. ***Secondary objective*** To compare parameters of glycaemic control and safety of once weekly IcoSema with once weekly semaglutide, both treatment arms with or without OADs, in participants with T2D inadequately controlled with a GLP-1 receptor agonist.	
Treatments groups	IcoSema	342 randomised participants
	Semaglutide	341 randomised participants
Endpoints and definitions	*Primary:* • Change in HbA_{1c} (%-point) from baseline week 0 (V2) to week 52 (V54)	
	Supportive secondary efficacy: • Change in fasting plasma glucose (FPG) (mmol/L) from baseline week 0 (V2) to week 52 (V54) • Change in body weight (Kg) from baseline week 0 (V2) to week 52 (V54)	
	Supportive secondary safety: • Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol /L [54 mg/dL], confirmed by BG meter) or severe hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 57 (V56) • Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol /L [54 mg/dL], confirmed by BG meter) from baseline week 0 (V2) to week 57 (V56) • Number of severe hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 57 (V56)	

Title:	**A 52-week study comparing the efficacy and safety of once weekly IcoSema and once weekly semaglutide, both treatment arms with or without oral anti-diabetic drugs, in participants with type 2 diabetes inadequately controlled with a GLP-1 receptor agonist. COMBINE 2.**		
	The imputation approach for the primary estimand and supportive secondary estimands regarding change in body weight and FPG from baseline was a multiple imputation approach based on an ANCOVA model with region and randomised treatment as fixed factors. The imputation approach for the supportive secondary estimand regarding number of hypoglycaemic episodes was done with 1) a Bayes negative binomial model with region as fixed factor and 2) imputation of the number of episodes in the missing period for participants having discontinued randomised treatment.		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis set	Full analysis set was all randomised participants. Participants were included in the analyses according to the planned randomised treatment.		
Results	**Treatment group**	**IcoSema**	**Semaglutide**
	Number of participants	342	341
	Change in HbA_{1c} (%-point) ETD [95% CI] p value	-1.35 -0.44 [-0.56; -0.33] <0.0001[a]	-0.90
	Change in fasting plasma glucose (FPG) (mmol/L) ETD [95% CI] p value	-2.48 -1.05 [-1.36; -0.75] <0.0001[b]	-1.43
	Change in fasting plasma glucose (FPG) (mg/dL) ETD [95% CI] p value	-44.6 -18.9 [-24.4; -13.5] <0.0001[b]	-25.7
	Change in body weight (Kg) ETD [95% CI] p value	0.84 4.54 [3.84; 5.23] <0.0001[c]	-3.70

Abbreviations: IcoSema: insulin icodec and semaglutide.

Notes: a Superiority was confirmed for Kyinsu. b Statistically significant treatment difference in favour of Kyinsu. c Statistically significant treatment difference in favour of semaglutide

Table 2. Summary of efficacy for study 4593 (COMBINE 3)

Title:	**A 52-week study comparing the efficacy and safety of once weekly IcoSema and daily insulin glargine 100 units/mL combined with insulin aspart, both treatment arms with or without oral anti-diabetic drugs, in participants with type 2 diabetes inadequately controlled with daily basal insulin. COMBINE 3.**	
Study identifier	Protocol Number – NN1535-4593 EudraCT number – 2020-005309-18	
Database lock	8 December 2023	
Design	This was an interventional, multi-national, multi-centre, randomised, 52-week, open label, parallel group, treat-to-target confirmatory study with two treatment arms. The study investigated the efficacy and safety of treatment with once weekly IcoSema compared to daily insulin glargine combined with insulin aspart, both treatment arms with or without OADs, in participants with T2D inadequately controlled with daily basal insulin.	
	Duration of trial: 59 weeks	
Objectives	***Primary objective*** To confirm non-inferiority of once weekly IcoSema compared with daily insulin glargine combined with insulin aspart, both treatment arms with or without OADs, in terms of glycaemic control measured by change in HbA_{1c} from baseline after 52 weeks in participants with T2D inadequately controlled with daily basal insulin using a non-inferiority margin of 0.3%-point. ***Secondary objective*** To confirm superiority of once weekly IcoSema compared to daily insulin glargine combined with insulin aspart, both treatment arms with or without OADs, in participants with T2D inadequately controlled with daily basal insulin in terms of: • Change in body weight from baseline after 52 weeks • Number of clinically significant hypoglycaemic (level 2) or severe hypoglycaemic (level 3) episodes during 52 weeks and the 5 week follow-up period • Weekly insulin dose (total) from week 50 to week 52 To compare parameters of glycaemic control, patient reported outcomes and safety of once weekly IcoSema with daily insulin glargine combined with insulin aspart, both treatment arms with or without OADs, in participants with T2D inadequately controlled with daily basal insulin.	
Treatments groups	IcoSema	340 randomised participants
	Insulin glargine + insulin aspart	339 randomised participants
Endpoints and definitions	*Primary:* • Change in HbA_{1c} (%-point) from baseline week 0 (V2) to week 52 (V54)	
	Confirmatory secondary: • Change in body weight (Kg) from baseline week 0 (V2) to week 52 (V54)	

Title:	**A 52-week study comparing the efficacy and safety of once weekly IcoSema and daily insulin glargine 100 units/mL combined with insulin aspart, both treatment arms with or without oral anti-diabetic drugs, in participants with type 2 diabetes inadequately controlled with daily basal insulin. COMBINE 3.**		
	• Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol /L [54 mg/dL], confirmed by BG meter) or severe hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 57 (V56) • Weekly insulin dose (U) from week 50 (V52) to week 52 (V54)		
	Supportive secondary efficacy: • Time in range 3.9-10.0 mmol/L (70-180 mg/dL) (% of readings) from week 48 (V50) to week 52 (V54)[a] • Time spent < 3.0 mmol/L (54 mg/dL) (% of readings) from week 48 (V50) to week 52 (V54)[a] • Time spent > 10 mmol/L (180 mg/dL) (% of readings) from week 48 (V50) to week 52 (V54)[a] • Change in fasting plasma glucose (FPG) (mmol/L) from baseline week 0 (V2) to week 52 (V54) • Change in Diabetes Treatment Satisfaction Questionnaire (DTSQs) in total treatment satisfaction (score 0-36[b]) from baseline week 0 (V2) to week 52 (V54)		
	Supportive secondary safety: • Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol /L [54 mg/dL], confirmed by BG meter) from baseline week 0 (V2) to week 57 (V56) • Number of severe hypoglycaemic episodes (level 3) from baseline week 0 (V2) to week 57 (V56)		
	The imputation approach for the primary estimand and secondary estimands regarding change in body weight from baseline and weekly insulin dose was a multiple imputation approach based on an ANCOVA model with region randomised treatment as fixed factors. The imputation approach for the secondary estimand regarding number of hypoglycaemic episodes was done with 1) a Bayes negative binomial model with region as fixed factor and 2) imputation of the number of episodes in the missing period for participants having discontinued randomised treatment.		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis set	Full analysis set was all randomised participants. Participants were included in the analyses according to the planned randomised treatment.		
Results	**Treatment group**	**IcoSema**	**Insulin glargine + insulin aspart**
	Number of participants	340	339
	Change in HbA_{1c} (%-point) ETD [95% CI] p value	-1.47 -0.06 [-0.22; 0.09] <0.0001[c]	-1.40

Title:	**A 52-week study comparing the efficacy and safety of once weekly IcoSema and daily insulin glargine 100 units/mL combined with insulin aspart, both treatment arms with or without oral anti-diabetic drugs, in participants with type 2 diabetes inadequately controlled with daily basal insulin. COMBINE 3.**		
	Change in body weight (Kg) ETD [95% CI] p value	-3.56 -6.72 [-7.58; -5.86] <0.0001[d]	3.16
	Weekly insulin dose (U) from week 50 (V52) to week 52 (V54) ETD [95% CI]; p value	196 -270 [-303; -236] <0.0001[d]	466
	Time in range 3.9-10.0 mmol/L (70-180 mg/dL) (%) ETD [95% CI] p value	68.5 2.05 [-1.01; 5.11] 0.1892	66.4
	Time spent < 3.0 mmol/L (54 mg/dL) (%) ETR [95% CI] p value	0.18 0.40 [0.29; 0.55] <0.0001[e]	0.46
	Time spent > 10 mmol/L (180 mg/dL) (%) ETR [95% CI] p value	31.5 1.00 [0.89; 1.13] 0.9713	31.4
	Change in fasting plasma glucose (FPG) (mmol/L) ETD [95% CI] p value	-1.56 0.05 [-0.31; 0.41] 0.7941	-1.61
	Change in fasting plasma glucose (FPG) (mg/dL) ETD [95% CI] p value	-28.1 0.86 [-5.59; 7.30] 0.7941	-29.0
	Change in estimated DTSQ score (0-36) ETD [95% CI] p value	4.42 3.00 [1.98; 4.02] <0.0001[e]	1.42

Abbreviations: IcoSema: insulin icodec and semaglutide.

Notes: a Using continuous glucose monitoring (CGM) system, Dexcom G6. b The higher the score the greater the satisfaction with treatment. c Non-inferiority was confirmed for Kyinsu. d Superiority was confirmed for Kyinsu. e Statistically significant treatment difference in favour of Kyinsu

2.7.5.4. Clinical studies in special populations

The number of participants in each special population category are presented for two phase 1 and three phase 3 studies in **Table 51**. A total of 165 patients ≥ 75 years of age were included in the controlled Kyinsu trials, thereby fulfilling the requirements set out in ICH E7.

Table 51. Clinical studies in special populations – summary – full analysis set

	Phase 1 Studies (4359 and 4710)		Phase 3 Studies (4591, 4592 and 4593)	
	N	(%)	N	(%)
Number of participants	51		2653	
Renal impairment	12	23.50	1433	54.01
Mild	12	23.50	1168	44.03
Moderate	0		264	9.95
Severe	0		1	0.04
Hepatic impairment	5	9.80	225	8.48
Age group	51	100.00	2653	100.00
<18 years	0		0	
18<= to <65 years	51	100.00	1679	63.29
65<= to <75 years	0		809	30.49
75<= to <85 years	0		159	5.99
>=85 years	0		6	0.23

2.7.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of the fixed-ratio combination of Kyinsu in patients with T2DM has been investigated in three pivotal phase 3a randomised, parallel group, open-label 52-week studies. The studies compared the efficacy and safety of treatment with once-weekly Kyinsu (700 U/mL insulin icodec+2 mg/mL semaglutide) versus an active comparator. The population studied included participants with T2DM previously on basal insulin or GLP-1 RAs. A treat-to-target approach was applied for Kyinsu in all COMBINE studies as well for the insulin comparators.

Studies 4591 (N=1,291) and 4593 (N=679) evaluated the once weekly FRC Kyinsu in patients inadequately controlled on daily basal insulin therapy. All patients included had to be treated with basal insulin for at least 90 days. Once weekly insulin icodec (700 U/mL) was used as the comparator in study 4591 and daily insulin glargine (100 U/mL) in combination with insulin aspart (100 U/mL) was used as the comparator in study 4593.

Study 4592 (N=683) was designed to evaluate the FRC in insulin naïve patients inadequately controlled with GLP-1 RA. All patients included had to be treated with GLP for at least 90 days (excluding higher doses than 1.0 mg of once weekly semaglutide). Once weekly semaglutide (1.34 mg/mL) was used as the comparator.

The relevant regulatory guideline in this type of application is the Guideline on Clinical Development of Fixed Combination Medicinal Products (EMA/CHMP/158268/2017). The design of studies 4591 and 4592 are both similar to an 'add-on indication', as outlined in the FRC guideline. Study 4591 was designed to support the use of the FRC in patients insufficiently controlled on basal insulin by adding a GLP-1 agonist. Study 4592 was designed to support the use of the FRC in patients insufficiently controlled on GLP-1 RA therapy with addition of basal insulin. In study 4593, a fixed combined treatment of basal insulin and GLP-1 RA was compared with a basal-bolus insulin regimen. Given that

GLP-1RAs enhances the endogenous post-prandial insulin release, the possibility of adding a GLP-1 RA as an alternative to prandial bolus insulin has been discussed in current diabetes guidelines. Therefore, this study design was considered to be of interest.

The **open-label design** used is not preferred. The CHMP advice did not consider an open-label design to be appropriate, and the applicant was encouraged to mask the studies. Although differences in posology (titration schedule) of Kyinsu and the comparators, a double-blind, double-dummy design could have been feasible in studies 4591 and 4592.

The disadvantage of only **one fixed dose ratio** of semaglutide/icodec developed in the clinical programme was expressed in the CHMP advice. Adjusting the dose to the insulin icodec requirement (treat to target) may not result in the optimal dose of semaglutide for every patient. The **starting dose** of insulin icodec (40 U) for Kyinsu is lower than the starting dose of insulin icodec for the monocomponent Awiqli (70 U). The semaglutide starting dose for Kyinsu is below the lowest dose of semaglutide shown to be efficient (0.144 mg compared to 0.25 mg). The **maximum dose** of Kyinsu is 350 dose steps (corresponding to 350 U insulin icodec and 1 mg semaglutide). At the time the phase 3a COMBINE protocols were developed, 1 mg semaglutide was the approved maximum dose for semaglutide s.c. in treatment of T2DM. Since then, 2 mg of semaglutide has also been approved, which is currently the approved maximum dose of semaglutide. There was no restriction on the maximum dose of insulin icodec or daily dose of insulin glargine or insulin aspart. **Titration algorithms** were in place for both the Kyinsu treated groups and those treated with insulin icodec and with insulin glargine. For Kyinsu dose adjustments of ±10 DS (equivalent to 10 U insulin icodec/0.029 mg semaglutide) was applied. The titration was based on the last 3 fasting SMPG values prior to dose adjustment. A fixed dose/dose escalation treatment was applied for the semaglutide comparator in study 4592.

All three pivotal studies had a similar design that implied a baseline visit at week 0 (V2) at which all eligible subjects were to be allocated to treatment using a **1:1** ratio. **Randomisation** was performed centrally. None of the studies used stratified randomisation.

The **sample size calculation** performed for each study respectively is endorsed as having been thorough considering, where relevant, not only the primary endpoint but also those secondary endpoints predefined as confirmatory while also discussing the expected occurrence of intercurrent events and their potential impact on the estimates. However, regarding occurrence the same assumption were made (17%) irrespective of study and further, it had been assumed that intercurrent events were to be equally distributed between arms. The **non-inferiority** margin of 0.3%-point defined in study 4593 had been agreed by CHMP (advice procedure EMA/SA/0000050205).

The chosen **primary and secondary outcomes and endpoints** are acceptable. The **inclusion and exclusion criteria** were considered adequate to ensure that a population representative for the target population was included in the studies. Patients with severe renal impairment (eGFR <30 ml/min/1.73m^2) were excluded from the studies. Across the trials, patients were 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. DPP-4 inhibitors were to be discontinued since the combined use of a GLP-1 RA and a DPP-4 inhibitor is not currently recommended.

The primary estimand had been identically defined in all the three studies. This is considered a concern with regard to study **4593**. Two ICEs had been identified, and the predefined primary strategy was a treatment policy.

For the two superiority studies, the primary **treatment policy** estimand is agreed.

With regard to the primary non-inferiority hypothesis in study 4593 and as advised by the CHMP (EMA/SA/0000050205), the applicant should have approached the intercurrent events with a hypothetical strategy.

Intercurrent events were defined as treatment discontinuation (intercurrent event 1) or initiation of non-randomised insulin treatment or additional antidiabetic treatments lasting for more than 2 weeks (intercurrent event 2, i.e., rescue medication).

The applicant has described that the **statistical assessments** were based on pre-specified analyses for each study individually, with common statistical principles implemented across the Kyinsu clinical development programme. This is agreed and considered appropriate when based on the study similarities.

Study **4591** investigated the additional/add-on effect of semaglutide, and study **4592** the additional/add-on effect of insulin icodec. Study **4593** had a different approach and is per se not pivotal for the sought indication.

While study **4591** and **4592** had a superiority objective (expected), the primary objective of study **4593** was to show non-inferiority.

Overall, the statistical analysis plan (SAP) for study **4591** has been found adequate.

The statistical analysis plan for study **4592** lacked a multiple testing procedure but appears otherwise adequate. The lack of type I error control should have implications for the presentation of results in section 5.1 of the SmPC.

The statistical analysis plan for study **4593** is considered adequate but for the fact that comments received from the CHMP advice procedure regarding what was considered appropriate ICE strategies were not considered (primary estimand). An analysis where a hypothetical strategy was employed for both the intercurrent events was therefore requested. This analysis supports the conclusion of non-inferiority between Kyinsu and IGlar+IAsp (the outcome is presented below).

Irrespective of study, the assessment of efficacy was based on the FAS using the same definition. The inclusion in the primary analysis of all randomised subjects is supported.

In line with the primary treatment policy estimand, all data collected week 52 was to be used for the analysis, including retrieved data after any intercurrent event.

Handling of missing primary endpoint data was by the use of multiple imputation. The assumption made was that subjects with missing data behave similarly as comparable subjects within the same treatment arm: subjects experiencing intercurrent events without data week 52 behave as subjects experiencing intercurrent events with data at week 52 within the same treatment arm and similar for subjects not experiencing intercurrent events.

The CHMP (advice procedure EMA/SA/0000050205) considered this to be a reasonable option to target a treatment policy strategy if sufficient cases with the intercurrent event and measurements are available and if the assumption that conditional on the intercurrent event missingness is independent of the measurements. The applicant was informed that this assumption had to be justified. In case no or insufficient data was obtained after the intercurrent event, it was advised that reference based multiple imputation methods (as jump-to-reference) were to be employed. Two alternatives had been predefined by the applicant, however none that matched the view expressed in the advice.

To challenge the assumption made for the primary analysis of the primary endpoint in study **4591** and study **4592**, the applicant was requested to perform a sensitivity analysis in which all missing data were handled applying a jump-to-reference approach. The requested sensitivity analyses were performed and support the robustness of the superiority conclusions for the primary endpoint in both

study 4591 (Kyinsu versus insulin icodec) and 4592 (Kyinsu versus semaglutide). In addition, the applicant has confirmed that the amount of data for the imputation model described for the primary analysis was sufficient for meaningful imputation.

The only **sensitivity analysis** planned for the primary endpoint was a Tipping point analysis. The approach assuming a worse outcome in the Kyinsu arm and a better outcome in the comparator arm compared to what was imputed in the primary analysis is appreciated for challenging primary outcome robustness although does not per se challenge the assumption made regarding missing data.

Similar for all studies, a **supplementary analysis** addressing an attributable estimand referring to Darken et. al 2020 had been defined and appears to be in alignment with the supplementary analysis recommended within the CHMP advice procedure ((EMA/SA/0000050205)).

This analysis was to address an estimand aiming at estimating the effect of randomised treatment had all participants stayed on the randomised treatment for the entire 52 weeks treatment period. Here, intercurrent events that were considered adversely related to randomised treatment were to be considered attributable and were to be assigned an unfavourable outcome referring to a **composite** estimand strategy. For the nonattributable intercurrent events and data missing e.g. due to subjects being lost to follow-up, a **hypothetical strategy** was to be used.

What was to be considered attributable events had been predefined and were identical irrespective of study. In principle, almost all the reasons leading to the occurrence of an intercurrent event were to be deemed attributable. Nonattributable intercurrent events were those where the reason for its occurrence pertained to either an AE not possible or probably related to randomised treatment, pregnancy, or the subject's wish of becoming pregnant or "other". These are agreed. This approach was foremost of interest with regard to the two superiority studies. For the testing of non-inferiority, the approach may be anticonservative since, in case of an attributable intercurrent event, an unfavourable outcome was to be assigned using the estimated change from baseline from the comparator arm at week 52.

The applicant provided thorough presentations of the occurrence of intercurrent events and the availability of week 52 HbA1c assessments.

Study 4591: Overall, the number of subjects having experienced an **intercurrent event** (**ICE**) was 108/646 (**16.7%**) in the Kyinsu arm and 86/645 (**13.3%**) in the Ico arm. Among those with an ICE, many had a week 52 assessment (**retrieved data**): 63/108 (58.3%): Kyinsu and 51/86 (59.3%): Ico. Of those without having experienced an intercurrent event, very few lacked week 52 data: 3/538 (0.6%) and 5/559 (0.9%).

Hence, the total number of subjects with a **missing week 52 assessment** was (45+3)/646 (**7.4%**) in the Kyinsu arm with the higher number representing those having experienced an intercurrent event. The corresponding number in the control arm was: (5+35)/645 (**6.2%**).

Study 4592: Here, there was an obvious imbalance in the frequency of **intercurrent events**. Overall, the number of subjects having experienced an ICE was 32/342 (**9.4%**) in the Kyinsu arm, whereof 19 (5.6%) was due to treatment discontinuation, compared to a total of 80/341 (**23.5%**) intercurrent events in the semaglutide monotherapy arm whereof the majority, 20.8% (71/341), was due to initiation of non-randomised insulin treatment or additional antidiabetic treatments lasting for more than 2 weeks.

Of those with an intercurrent event in the Kyinsu arm, 18/32 (56.2%) had a week 52 assessment (**retrieved data**). The corresponding number in the Sema arm was 74/80 (**92.5%**). This implied that the total number of subjects with **missing week 52** assessment was higher in the Kyinsu arm than in the control arm: (3+14)/342 (**5.0%**) and (0+6)/341 (**1.8%**), respectively.

Study 4593: Overall, the number of subjects having experienced an **intercurrent event** was 45/340 (**13.2%**) in the Kyinsu arm and 64/339 (**18.9%**) in the IGlarg + IAsp arm whereof 27 (7.9%): Kyinsu and 47 (13.9%): control implied treatment discontinuation.

The total number of subjects with a **missing week 52 assessment** (intercurrent event or not) was 23/340 (**6.8%**): Kyinsu and 42/339 (**12.4%**): IGlarg + IAsp.

Concerning all the studies, the total lack of predefined subgroup analyses is somewhat surprising in a pivotal study. The performance of post-hoc exploratory ditto is acknowledged.

With the main focus being study 4591 and 4592, the clinical study program is considered adequate in order to support an application for a fixed combination with regards to design, study size and duration.

Efficacy data and additional analyses

The study populations across the studies were representative for the target population. **Baseline demographic and diabetes characteristics** were in general balanced between groups. It was noted that mean FPG values at baseline were slightly higher in the IGlar+IAsp group (8.94 mmol/L) compared to the Kyinsu group (8.42 mmol/L) in study 4593. Across the studies, 27-35% of T2DM subjects were recruited from Europe. In total 176 patients ≥75 years were included in the studies. The pretrial treatments with regards to insulin (study 4591 and 4593) reflects the current treatment practice and was well balanced between groups. The T2DM groups were balanced with regards to non-insulin anti-diabetic treatment.

Across the studies, 90-94% of the patients treated with Kyinsu, and 86-96% of patients treated with the comparator product completed the trials without permanent discontinuation of trial product. The lowest number of subjects completing the study without permanently discontinuing study treatment was noted in the IGlar+IAsp group (86%).

In patients previously treated with daily basal insulin (studies 4591 and 4593), fasting SMPG values increased when **initiating treatment with** Kyinsu**.** Patients with higher baseline HbA1c (≥8.5%) and higher pre-study basal insulin doses (≥40 U) experienced increases in SMPG up to 3 mmol/L. In the Kyinsu group, SMPG values returned to baseline at week 7-9 and reached glycaemic target (<7.2 mmol/L) at week 14-18. CGM data collected in study 4593 was aligned with the SMPG data. In study 4593, more subjects in the Kyinsu group (66-69%) spent time above >10.0 mmol/L compared to patients treated with basal-bolus insulin (50-52%) during the first 3 weeks of treatment. In addition, the incidence of hyperglycaemic events was increased for Kyinsu compared to insulin icodec overall in study 4591 (4.2% versus 2.6%) and for Kyinsu compared to IGlar+IAsp in study 4593 (4.1% versus 1.2%). Most of the hyperglycaemic events in the Kyinsu group were reported during the first 12 weeks of treatment in the studies. Increases in SMPG values upon insertion of Kyinsu in patients switching from daily basal insulin has been adequately reflected in the SmPC.

In **patients switching from basal insulin, additional antidiabetic treatment regardless of duration** was initiated after baseline by 11.1% in the Kyinsu group and 7.6% in the insulin icodec group in study 4591 and by 8.2% in the Kyinsu group and 3.8% in the Iglar+IAsp group in study 4593, of which initiation of non-randomised insulin was most frequently occurring in the Kyinsu group (study 4591: 8.7% vs. 3.6% for Kyinsu vs. insulin icodec; study 4593: 6.8% vs. 0.6% for Kyinsu vs. IGlar+IAsp). **Additional antidiabetic treatment for more than 2 weeks, defined as rescue medication and an intercurrent event**, was initiated by 8.0% in the Kyinsu group and 7.3% in the insulin icodec group in study 4591 and by 5.3% in the Kyinsu group and 5.0% in the IGlar+IAsp group in study 4593. Most additional antidiabetic treatment regardless of duration **in the** Kyinsu **group** was initiated in the **during the first 12 week of treatment.** In study 4591 and 4593, 8.7% and 6.5%, respectively, in the Kyinsu group initiated additional antidiabetic treatment week 1-12, of which **6.7%**

and 5.9%, respectively, in the Kyinsu **group initiated non-randomised insulin**. **During week 1-12**, the median duration of treatment with additional non-randomised insulin in the Kyinsu group was 7 days in study 4581 and 4 days in study 4593. The median duration of treatment with additional OADs was 55 days in both study 4591 and 4593. In patients switching from GLP-1 agonist (study 4592), the proportion of participants with changes to background antidiabetic treatment was lower in the Kyinsu arm (6.4%) compared to the semaglutide arm (19.9%). Guidance on adjustment of antidiabetic medication for patients switching from daily basal insulin to Kyinsu has been adequately included in section 4.2 of the SmPC.

Superiority was demonstrated for the **primary endpoint mean change in HbA1c** from baseline in patients previously treated with daily basal insulin in study 4591 (-0.66% [-0.76; -0.57]) and in insulin naïve patients previously treated with GLP-1 RA in study 4592 (-0.44% [-0.56; -0.33]). In study 4591, the outcome of the supplementary analysis of the "attributable" estimand was -0.60% (95% CI: -0.69, -0.51). In study 4592, the corresponding outcome was -0.56% (95% CI: -0.69, -0.44). In study 4593, non-inferiority was confirmed for the primary endpoint and the 95% CI using a non-inferiority margin of 0.3% (-0.06% [-0.22; 0.09]). Here, the supplementary estimand analysis outcome was -0.02% (95% CI: -0.15, 0.11). In the requested supplementary analysis employing a hypothetical strategy for both intercurrent events, the estimated treatment difference was -0.07% (95% CI: -0.20; 0.06), thus confirming the primary non-inferiority conclusion.

When the change in **HbA1c was plotted over time**, the curves separated after 10 weeks in study 4591. The efficacy of Kyinsu and insulin icodec, respectively, appears to have reached a plateau at week 24, after which the HbA1c reduction was maintained until week 52weeks. In study 4593, insulin glargine (+insulin aspart) compared to Kyinsu provided a greater mean HbA1c reduction from treatment start to week 18. At week 10, the reduction in HbA1c was -0.28% for Kyinsu and -0.74% for insulin glargine (+insulin aspart). From week 18 onwards, the HbA1c reduction was similar in both treatment groups.

Multiple testing procedure was in place for the **key secondary endpoints**. Other secondary endpoints were not corrected for multiplicity.

Change in body weight was a **confirmatory endpoint in study 4591 and 4593** and was a supportive endpoint in study 4592. In patients previously on daily basal insulin (studies 4591 and 4593), body weight decreased in the Kyinsu group (-3.7 kg and -3.6 kg, respectively) and increased in the insulin treated groups (1.89-3.16 kg). Superiority of Kyinsu was confirmed to insulin icodec in study 4591 (ETD: -5.59 kg [-6.14; -5.04]) and to IGlar+IAsp in study 4593 (ETD: -6.72 kg [-7.58; -5.86]). In insulin naïve patients (study 4592), body weight slightly increased in the Kyinsu group (0.84 kg) whereas body weight decreased in the semaglutide group (-3.7 kg). The estimated treatment difference in change in body weight for Kyinsu compared to semaglutide was 4.54 kg [-0.12; 1.04].

Weekly insulin dose (total) for week 50 to 52 was a **confirmatory endpoint in study 4593** and a supportive endpoint in study 4591. In study 4593, superiority of Kyinsu versus IGlar+IAsp was confirmed for the mean weekly total (bolus + basal) insulin dose (ETD: -270 U [-303; -236]). The mean weekly basal insulin dose from week 50 to 52 was numerically lower for Kyinsu (196 U) compared to IGlar+IAsp 285 U). In study 4591, mean weekly total basal insulin dose from week 50 to 52 was numerically lower for Kyinsu compared to insulin icodec (ETD: -172 U [-190; -155]).

In study 4592, the **reduction in fasting plasma glucose (FPG)** from baseline to end of treatment was numerically larger for Kyinsu (-2.48 mmol/L) than for semaglutide (-1.41 mmol/L); ETD: -1.07 [-1.37; -0.76]. In study 4591, the decrease in FPG was initially greater for patients treated with insulin icodec compared to Kyinsu; however, from week 22 onwards, there FPG reduction was numerically slightly greater in the Kyinsu group compared to the insulin icodec group (ETD: -0.14 [-0.38; 0.10]). In study 4593, the reduction in FPG from baseline to end of treatment was less pronounced from

baseline to end of treatment in the Kyinsu group compared to the IGlar+IAsp group (EDT: 0.02 [-0.34; 0.38]).

In studies 4591 and 4593, **time spent in glycaemic range (TIR) 3.9-10.0 mmol/L,** time spent above range (TAR) >10 mmol/L and time spent below range (TBR) <3.0 mmol/L week 48 to 52 were supportive endpoints. In study 4591, subjects in the Kyinsu group compared to the insulin icodec group spent more time in TIR (73.3% versus 61.8%) and slightly less time in TAR (23.3% vs 37.0%). TBR was <1% and no important differences between treatment groups. In study 4593, there were no important differences between the treatment groups in TIR or TAR and TBR was <1%.

The occurrence of **insulin antibodies** is discussed in the Safety section of this report.

Patient reported outcome (PRO) measures were included as a supportive endpoint in study 4593. The change in DTSQ total score was numerically greater for Kyinsu compared to IGlar+IAsp and ETD was 3.00 [1.98; 4.02].

Achievement of HbA_{1c} without wight gain and without hypoglycaemia was a predefined analysis in the studies. The responder rate of achieving HbA_{1c} <7% without weight gain and without level 2 or 3 hypoglycaemia was numerically higher for Kyinsu (55.7%) compared to insulin icodec (10.2%) in study 4591 and for Kyinsu (50.1%) compared to IGlar+IAsp (6.0%) in study 4593. In study 4592; however, the responder rate of achieving HbA_{1c} targets without weight gain and without either level 2 or level 3 hypoglycaemia was numerically lower for Kyinsu (30.2%) compared to semaglutide (40.5%).

Blood lipids and **vital signs** were measured in the studies. Evaluation of lipid parameters is difficult due to the risk of increased lipids with diabetes in general and concomitant medication with lipid-modifying agents, e.g., 62-68% of the patients were treated with statins at baseline. In study 4592, SBP decreased more for semaglutide (-3.06 mmHg) than for Kyinsu (-0.42 mmHg). DBP increased slightly for Kyinsu (0.23 mmHg) and decreased for semaglutide (-1.06 mmHg).

The semaglutide dose chosen for the FRC is below the lowest dose of semaglutide shown to be efficient (0.144 mg compared to 0.25 mg). In insulin naïve patients, the **dose of semaglutide in Kyinsu** appears to be insufficient to reduce body weight as a weight gain was observed. The insulin need limits the Kyinsu dose. The average semaglutide dose of the semaglutide component in Kyinsu ranged from 0.48 to 0.56 mg per week across studies. For participants randomised to semaglutide in study 4592, the actual mean weekly semaglutide dose was 0.99 mg. Therefore, the full potential of semaglutide in Kyinsu may not being exploited. This was also commented on in the CHMP advice.

The experience from the CV outcomes trial performed with semaglutide can be of interest for the prescriber, and it can therefore be acceptable to include the most important results in section 5.1 for Kyinsu.

2.7.7. Conclusions on the clinical efficacy

Data from pivotal studies support that the combination of insulin icodec and semaglutide provide a clinical benefit. The design of studies 4591 and 4592 are both similar to an 'add-on indication', as outlined in the FRC guideline. Study 4591 was designed to support the use of Kyinsu in patients insufficiently controlled on basal insulin by adding a GLP-1 agonist. In study 4592, the additive effect of basal insulin was supported in insulin-naïve patients who were inadequately controlled on GLP-1 RA therapy. The primary endpoint was met showing superiority for Kyinsu compared to insulin icodec (study 4591) and semaglutide (study 4592), respectively. In study 4593, Kyinsu was compared with a basal-bolus insulin regimen of insulin glargine+ insulin aspart. A non-inferiority was confirmed for the primary endpoint.

In study 4591, body weight significantly decreased in patients treated with Kyinsu (-3.70 kg) while body weight increased in patients treated with insulin icodec (1.89 kg) and the rate of level 2 or level 3 hypoglycaemic episodes was lower for Kyinsu (15.3 episodes/ 100 PY) compared to insulin icodec (84.4 episodes/100 PY). In addition, the mean weekly basal insulin dose was numerically lower for Kyinsu (182 U) compared to insulin icodec (355 U). However, in insulin naïve patients (study 4592), body weight slightly increased in the Kyinsu group (0.84 kg) whereas body weight decreased in the semaglutide group (-3.7 kg). The estimated number of level 2 and 3 hypoglycaemic episodes was low and similar for Kyinsu and semaglutide. In study 4591, the responder rate of achieving HbA_{1c} <7% without weight gain and without level 2 or 3 hypoglycaemia was numerically higher for Kyinsu (55.7%) compared to insulin icodec (10.2%). However, in study 4592, the responder rate of achieving HbA_{1c} targets without weight gain and without level 2 or level 3 hypoglycaemia was numerically lower for Kyinsu (30.2%) compared to semaglutide (40.5%).

The starting dose of insulin icodec (40 U) for Kyinsu is lower than the starting dose of insulin icodec for the monocomponent Awiqli (70 U). For Awiqli an additional single dose of 50% insulin icodec is recommended for patients switching from daily basal insulin.

In patients previously treated with daily basal insulin, fasting SMPG values increased when initiating treatment with Kyinsu; returned to baseline at week 7-9 and reached glycaemic target at week 14-18. Additional antidiabetic treatment, including non-randomised insulin, was needed in approximately 10% of the subjects in the Kyinsu arm in studies 4591 and 4593, of which most treatment was initiated during the first 12 weeks of treatment. The risk of increases in fasting SMPG values when switching from daily basal insulin to Kyinsu has been adequately reflected in section 4.4 of the SmPC. In addition, section 4.2 has been amended with further guidance on adjustment of antidiabetic medication for patients switching from daily basal insulin to Kyinsu.

Across the COMBINE studies, subjects that received an Kyinsu dose ≥350 dose steps (8.1%) did not achieve the treatment goal of HbA1c <7. Information has been included in section 4.2 that **the maximum recommended weekly dose for Kyinsu is 35O dose steps.**

The most important results from SUSTAIN 6 (Ozempic) is accepted to be included in section 5.1.

2.7.8. Clinical safety

2.7.8.1. Patient exposure

The safety evaluation provided in this summary is primarily focused on the phase 3a pool (studies 4591, 4592 and 4593; Table 6 in the Efficacy part), supplemented with individual studies as applicable for an overall safety evaluation**.** In the phase 3a pool, a total 1325 adult subjects with T2D (1369.43 PYE) were exposed to Kyinsu (Table 43). Of these, an exposure >=6 months was reached by 1244 participants and 1207 were exposed to Kyinsu ≥12 months. See Table 44. Thus, the minimum number of subjects that have been exposed to a least 6 and 12 months is within the requirement for safety evaluation as stated in ICH E1. The experience of patients using the FRC beyond 12 months is limited and long-term data relays on experience from the developing program for both mono-components (i.e., 78 weeks for insulin icodec from the extension phase of ONWARDS 1 [insulin naïve T2DM]) and post-marketing experience of semaglutide.

In addition to the phase 3 trials, 50 subjects with T2D have been exposed to Kyinsu in the phase 1 studies 4359 and 4710.

In the phase 3 pool, more males (60%) than females (40%) were included, and the median age was 61 years (22.0-87.0). The baseline characteristics and demography were overall generally well

balanced across treatment groups for the pooled data (and individual trials). See **Table 30 i**n efficacy section.

In the phase 3a pool, median durations of diabetes were similar in the two treatment groups (~13 years) both with wide ranges (0.4 years to ~ 55 years). Other, baseline diabetes characteristics were well-balanced across the Kyinsu and comparator groups in the phase 3a pool. This also applied to the individual trials. See **Table 31** efficacy section.

In the phase 3a pool, diabetic neuropathy was reported by 21.3%, diabetic retinopathy by 16% and diabetic nephropathy by 10.6% of the participants at screening or baseline. The frequencies were similar for the two treatment groups. See Table 52, for individual trials see **Table 32**, **Table 33** and **Table 34** in the efficacy section.

Table 32. Exposure by pool and study – summary – safety analysis set

	IcoSema		Comparator		Total	
	N	(PYE)	N	(PYE)	N	(PYE)
Phase 3a pool	1325	(1369.43)	1312	(1376.35)	2637	(2745.78)
4591	644	(660.95)	644	(677.11)	1288	(1338.05)
4592	341	(359.20)	340	(364.74)	681	(723.94)
4593	340	(349.28)	328	(334.51)	668	(683.79)

N: Number of participants; PYE: Patient years of exposure (1 PYE = 365.25 days)
Comparator: Insulin icodec (4591), semaglutide 1.0 mg (4592) and insulin glargine + insulin aspart (4593).
Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

Table 43. Exposure by month - summary - safety analysis set - phase 3a pool

	IcoSema		Comparator		Total	
	N	(%)	N	(%)	N	(%)
Number of participants	1325		1312		2637	
Duration of exposure						
>= 1 month	1318	(99.5)	1305	(99.5)	2623	(99.5)
>= 2 months	1296	(97.8)	1295	(98.7)	2591	(98.3)
>= 3 months	1278	(96.5)	1283	(97.8)	2561	(97.1)
>= 4 months	1264	(95.4)	1278	(97.4)	2542	(96.4)
>= 5 months	1252	(94.5)	1269	(96.7)	2521	(95.6)
>= 6 months	1244	(93.9)	1260	(96.0)	2504	(95.0)
>= 7 months	1239	(93.5)	1255	(95.7)	2494	(94.6)
>= 8 months	1235	(93.2)	1248	(95.1)	2483	(94.2)
>= 9 months	1232	(93.0)	1237	(94.3)	2469	(93.6)
>= 10 months	1224	(92.4)	1231	(93.8)	2455	(93.1)
>= 11 months	1219	(92.0)	1227	(93.5)	2446	(92.8)
>= 12 months	1207	(91.1)	1213	(92.5)	2420	(91.8)

N: Number of participants; %: Percentage of participants
1 month = 30.5 days. Comparator: Insulin icodec (4591), semaglutide 1.0 mg (4592) and insulin glargine + insulin aspart (4593). Phase 3a pool: 4591, 4592 and 4593.

Abbreviations**: IcoSema=fixed dose regiment insulin icodec/semaglutide.**

Table 54. Diabetes complications before or at screening safety analysis set – phase 3a pool

	IcoSema			Comparator			Total		
	N	(%)	E	N	(%)	E	N	(%)	E
Number of participants	1325			1312			2637		
All complications	491	(37.1)	801	474	(36.1)	787	965	(36.6)	1588
Diabetic neuropathy	289	(21.8)	294	272	(20.7)	276	561	(21.3)	570
Diabetic retinopathy	209	(15.8)	371	212	(16.2)	367	421	(16.0)	738
Diabetic nephropathy	136	(10.3)	136	143	(10.9)	144	279	(10.6)	280

N: Number of participants; %: Percentage of participants; E: Number of events
Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

2.7.8.2. Adverse events

Overview of adverse events

A summary of AEs reported in phase 3a studies – on-treatment – safety analysis set is presented in Table 55.

The proportion of subjects reporting any AE in the Kyinsu group was stable across the phase 3a studies (~78-79%). Compared to the Kyinsu groups, slightly lower proportions of the participants reported any AE in the comparator groups (68%-74%). In study 4592 (Kyinsu vs semaglutide) SAEs were markedly more often reported in the Kyinsu group compared to the semaglutide group (see section 2.7.8.3) and in study 4591 (Kyinsu vs insulin icodec) the proportion of participants with AEs leading to withdrawal of trial product were higher compared to the insulin icodec group. See section 3.3.7.9 below.

Table 55. Summary of AEs reported in phase 3a studies – on-treatment – safety analysis set

AEs		**Study 4591**		**Study 4592**		**Study 4593**	
		IcoSema	**Insulin icodec**	**IcoSema**	**Semaglutide**	**IcoSema**	**Basal-bolus insulin**
Total AEs	% (R)	77.8 (417.58)	73.3 (283.71)	79.2 (319.32)	74.1 (324.89)	77.6 (352.44)	67.7 (258.59)
SAEs	% (R)	9.2 (11.80)	10.7 (16.84)	11.1 (13.08)	6.2 (9.32)	12.6 (20.90)	9.1 (15.55)
Severe AEs	% (R)	5.0 (6.96)	4.8 (7.68)	4.1 (4.45)	3.2 (3.84)	6.2 (11.45)	3.4 (6.28)
AEs leading to withdrawal of trial product	% (R)	5.0 (7.56)	1.9 (2.07)	2.3 (2.23)	2.6 (4.66)	4.4 (7.44)	2.4 (2.99)

Abbreviations: AE = adverse event; % = percentage of participants with one or more events; R = rate (number of adverse events per 100 PYE), PYE = patient years of exposure (1 PYE = 365.25 days), SAEs = serious adverse events. IcoSema=fixed dose regiment insulin icodec/semaglutide.

Common adverse events

The most frequent (>=5%) adverse events by preferred term (PT) for the phase 3a pool and the individual studies is presented in Figure 19.

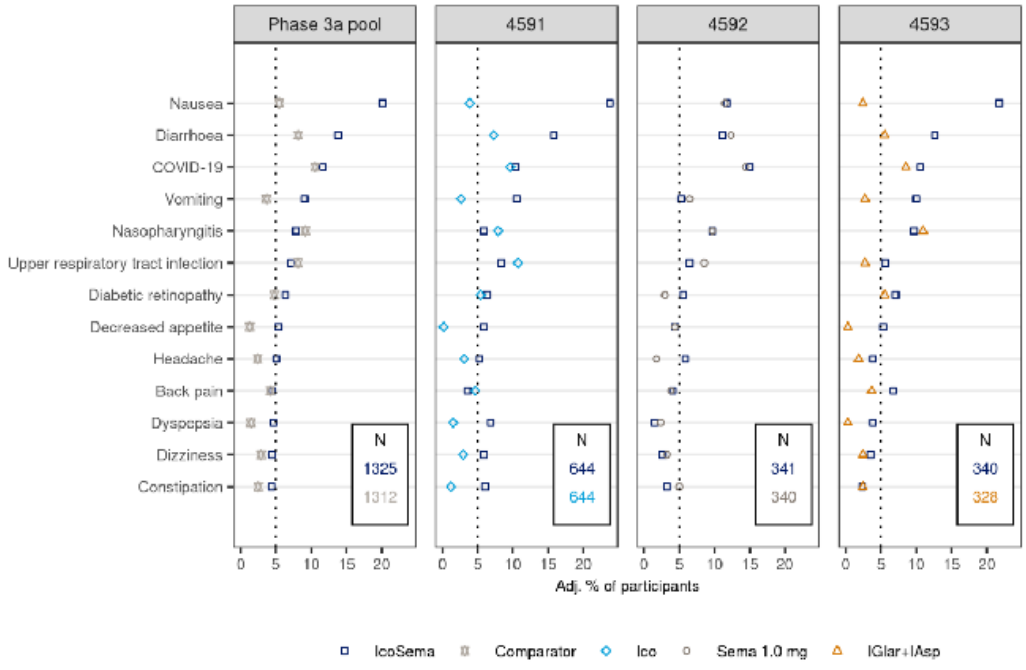
Hypoglycaemic episodes were reported separately and not presented in the context of common AEs. See section 2.7.8.3.

Overall, there were no new or unexpected common adverse events, not known for any of the two mono-components, in any of the treatment groups. In the phase 3a pool, the most frequently reported PTs reported by a proportion of ≥5% of the participants in the Kyinsu group (compared to the proportions of participants in the comparator group) were the *nausea* (20.1% vs 5.5%), *diarrhoea* (13.8% vs 8.1%), *Covid 19* (11.6% vs 10.6%), *vomiting* (9.1% vs 3.7%), *nasopharyngitis* (7.8% vs 9.2%), *upper respiratory tract infection* (7.2% vs 8.1%), *diabetic retinopathy* (6.4% vs 4.8%), *decreased appetite* (5.4% vs 1.3%) and *headache* (5.1% vs 2.4%). Other PTs reported by ≥5% of participants within any of the three individual studies were *dyspepsia* (6.8% vs 1.6%; study 4591), back-pain (6.8% vs 3.7%; study 4593), *dizziness* (4.5% vs 2.9%) and *constipation* (4.4% vs 1.4%). Besides Covid-19, the most common AEs for Kyinsu were GI events including *nausea* (20.1% vs 5.5% for the comparator group), *diarrhoea* (13.8% vs 8.1% for the comparator group) and *vomiting* (9.1% vs 3.7 for the comparator group). Other frequently (>= 5%) reported events of clinical importance for Kyinsu were *decreased appetite, headache* (5.4% vs 1.3% for comparator)*, dizziness* (4.5% vs 2.9% for comparator)*,* and *diabetes retinopathy* (6.3% vs 4.8% for comparator). All these PTs are known for either insulin icodec or semaglutide and labelled in the Kyinsu SmPC section 4.8.

In the Phase 3a pool, the PT *nephrolithiasis*" was reported by 1.0% of the participants (n=13 including 4 SAEs) for Kyinsu compared to 0.2% (n=3, no SAE) for comparators. Several of the *nephrolithiasis* cases in the Kyinsu group (including 3 of the 4 SAEs) are confounded by diseases in the medical history. None of the nephrolithiasis events reported in the Kyinsu group could be attributed to fluid depletion due to GIAEs prior to the nephrolithiasis event. Furthermore, there is known biological rational for these even and no indications of a risk for "*nephrolithiasis*" based on data from the clinical trials for any of the mono-products. The risk is therefore not considered needed to be reflected in the SmPC.

Kyinsu is a FRC of two known substances (insulin icodec and semaglutide). Thus, the ADRs for each of the mono-components will constitute the basis for events defined as ADRs also for Kyinsu.

Figure 19. Adverse events by preferred term and study - most frequent [>=5%] - dot plot - on-treatment



2.7.8.3. Serious adverse event/deaths/other significant events

Serious adverse events

Overall, in the phase 3a pool SAEs were balanced between the Kyinsu and comparator group (10.6% vs 9.1% and 14,44 vs 14.57 events per 100 PYE). The most reported SAE SOCs for Kyinsu were Injury, poisoning and procedural (1.7% vs 1.4% for the comparator) and Nervous system disorders (1.6% vs 1.1% for the comparator). See Table 54.

The SAE PTs were distributed on multiple SOCs and PTs with no apparent clustering for any treatment group (besides nephrolithiasis, see above). The most common SAE PTs in the Kyinsu group were reported by 5 (0.4%) or 4 (0.3%) participants (i.e., acute myocardial infarction, femoral neck fractures, cerebrovascular accident, intervertebral disc protrusion and nephrolithiasis). See Table 54.

For the individual studies an imbalance regarding SAEs between treatment groups is noted in study 4592 and 4593 (see Table 53). In study 4592 the difference mainly concerns events within the SOCs Injury, poisoning and procedural complications (driven by different lower limb fractures), Infections and infestations and Nervous system disorders. In study 4593 the difference concerns several SOCs including Cardiac disorders, Eye disorders, Gastrointestinal disorders and Metabolism and nutrition disorders. No obvious patterns of clinical relevance are noted.

Table 56. SAEs (PTs ≥0.3% in either group) – on-treatment – safety analysis set - phase 3a pool

SOC* and PT	IcoSema		Comparator	
	N (Adj. %)	***Adj. R***	***N (Adj. %)***	***Adj. R***
Cardiac disorders	19 (1.4)	1.75	28 (2.1)	2.24
Acute myocardial infarction	5 (0.4)	0.36	6 (0.5)	0.44
Coronary artery stenosis	1 (0.1)	0.07	4 (0.3)	0.29
Coronary artery disease	2 (0.1)	0.15	5 (0.4)	0.36
Injury, poisoning and procedural complication	22 (1.7)	2.19	18 (1.4)	1.91
Femoral neck fracture	4 (0.3)	0.36	1 (0.1)	0.07
Nervous system disorders	21 (1.6)	1.90	15 (1.1)	1.41
Cerebrovascular accident	4 (0.3)	0.29	2 (0.2)	0.15
Infection and infestation	19 (1.4)	1.53	23 (1.8)	1.98
Pneumonia	2 (0.2)	0.14	6 (0.5)	0.44
Musculoskeletal and connective tissue disorders	12 (0.9)	0.95	7 (0.5)	0.51
Intervertebral disc protrusion	4 (0.3)	0.29	0	0
Renal and urinary disorders	9 (0.7)	0.80	5 (0.4)	0.36
Nephrolithiasis	4 (0.3)	0.29	0	0

*The SOCs row presents the total numbers of events within these SOCs, i.e. total: N, adj %, and adj R N: Number of participants with one or more events; %: Percentage of participants with one or more events; E: Number of events; Adj.: Adjusted percentages and rates were calculated using the Cochran- Mantel-Haenszel method to account for differences between studies; R: Rate (number of adverse events per 100 PYE); PYE: Patient years of exposure (1 PYE = 365.25 days) Phase 3a pool: 4591, 4592 and 4593. Comparator: Insulin icodec (4591), semaglutide 1.0 mg (4592) and insulin glargine + insulin aspart (4593). MedDRA version 26.1. Note: The presented PTs are selected by applying the criteria on adjusted proportions after rounding to one decimal.

Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

Deaths

Adverse events with fatal outcome were balanced between the two treatment groups (Kyinsu: 5 AEs in 5 participants; comparator: 7 AEs in 5 participants). The majority of deaths were related to EAC confirmed cardiovascular events (4/5 for Kyinsu and 2/5 for the comparator). The remaining causes of deaths were either non-cardiovascular or undetermined. All events were judged by the investigator as unlikely related to the trial product.

Adverse events of special interest

Hypoglycaemic episodes

Plasma glucose (PG) was instructed to be recorded in the (e)diary when a hypoglycaemic episode was suspected. The subjects were recommended to measure PG every 15 minutes until the PG value was ≥3.9 mmol/L (70 mg/dL) and/or symptoms had been resolved. Repeated PG measurements and/or symptoms were by default considered as one hypoglycaemic episode until a succeeding PG value is ≥ 3.9 mmol/L (70 mg/dL) and/or symptoms had been resolved and were reported as only one hypoglycaemic episode. In case of several low PG values within the hypoglycaemic episode, the lowest value was the one that was reported as the PG value for the hypoglycaemic episode, but the start time of the episode remained as the time for the first low PG value and/or symptom.

The classification of hypoglycaemia is presented in Table 57.

Table 57. 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

Notes: The Novo Nordisk terms are adapted from IHSG, ADA, ISPAD, type 1 diabetes outcomes program and ATTD. Severe hypoglycaemia as defined by Seaquist and ISPAD.

A summary of hypoglycaemic episodes by study and classification is presented in **Table 58.**

Severe hypoglycaemic episodes: The overall proportions of participants reporting severe hypoglycaemic episodes was low for the Kyinsu groups (0-1.2%) the comparator groups (0-6-1.2%) Across the three phase 3a studies. See **Table 58.**

Severe (level 3) or clinically significant (level 2) hypoglycaemia:

In the pre-basal insulin treated populations (study 4591 and 4593), the proportions of participants and rates of severe (level 3) or clinically significant (level 2) hypoglycaemia were markedly lower for Kyinsu than the comparators i.e., insulin icodec (7.1% vs 20.8% and 13.77 vs 62.62 events per 100 PYE) and IGlar+IAsp (10.0% and 21.47 vs 58.5% and 222.72 events per 100 PYE). See **Table 58.**

The proportion and rate of severe (level 3) or clinically significant (level 2) hypoglycaemia in the comparator arm in 4591 i.e., insulin icodec, mimics the active treatment arm in the previously basal insulin treated population in the development program for Awiqli i.e., ONWARDS 2.

In the insulin naïve, pre-GLP-1RA treated population (study 4592) the proportions and rates of severe (level 3) or clinically significant (level 2) hypoglycaemia were similar for Kyinsu and semaglutide (3.5% vs 3.8% and 4.18 vs 3.56 events per 100 PYE). See **Table 58.**

Hypoglycaemic alert value (level 1 hypoglycaemia): In study 4591 and 4593 (previously basal insulin treated), hypoglycaemic alert value (level 1 hypoglycaemia) followed the pattern for severe and clinically significant hypoglycaemic episodes and were reported markedly less frequently and with lower rates in Kyinsu groups the compared to the control groups (i.e., insulin icodec respectively IGlar+IAsp). See **Table 58**.

In study 4592 (insulin naïve, pre-GLP-1RA treated), hypoglycaemic alert values were reported by a notable higher proportion of the participant and with a higher rate in the Kyinsu group compared to the semaglutide group (19.9% vs 6.2% and rate 59.58 vs 14.26 per 100 PYE). This might reflect the overall lower B-glucose effect in this population although, not reaching the category 2 hypoglycaemic episodes level.

Table 58. Hypoglycaemic episodes by study and classification - summary - on-treatment - safety analysis set individual studies in the phase 3a pool.

	IcoSema				Comparator			
	N	(%)	E	R	N	(%)	E	R
4591								
Number of participants	644				644			
Hypoglycaemia alert value (level 1)	255	(39.6)	1247	188.67	497	(77.2)	6013	888.04
Clinically significant hypoglycaemia (level 2)	45	(7.0)	90	13.62	133	(20.7)	419	61.88
Severe hypoglycaemia (level 3)	1	(0.2)	1	0.15	4	(0.6)	5	0.74
Severe (level 3) or clinically	46	(7.1)	91	13.77	134	(20.8)	424	62.62
4592								
Number of participants	341				340			
Hypoglycaemia alert value (level 1)	68	(19.9)	214	59.58	21	(6.2)	52	14.26
Clinically significant hypoglycaemia (level 2)	12	(3.5)	15	4.18	13	(3.8)	13	3.56
Severe hypoglycaemia (level 3)	0				0			
Severe (level 3) or clinically significant hypoglycaemia (level 2)	12	(3.5)	15	4.18	13	(3.8)	13	3.56
4593								
Number of participants	340				328			
Hypoglycaemia alert value (level 1)	122	(35.9)	723	206.99	303	(92.4)	5324	1591.60
Clinically significant hypoglycaemia (level 2)	32	(9.4)	71	20.33	190	(57.9)	740	221.22
Severe hypoglycaemia (level 3)	4	(1.2)	4	1.15	4	(1.2)	5	1.49
Severe (level 3) or clinically significant (level 2) hypoglycaemia	34	(10.0)	75	21.47	192	(58.5)	745	222.72

N: Number of participants with one or more episodes; %: Percentage of participants with one or more episode; E: Number of episodes; R: Rate (number of episodes per 100 PYE); PYE: Patient years of exposure (1 PYE = 365.25 days).
Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

Rate of hypoglycaemic events (secondary confirmatory safety endpoint in study 4591 and 4593)

The number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3) was a secondary confirmatory safety endpoint in study 4591 and 4593 and was a secondary supportive safety endpoint in study 4592 (**Table 59**).

A statistically significant difference in favour of Kyinsu was observed in the rate of level 2 or level 3 hypoglycaemic episodes between Kyinsu and insulin icodec in study 4591 (ETR ratio: 0.22 [0.14; 0.36]) and between Kyinsu and IGlar+IAsp in study 4593 (ETR ratio: 0.12 [0.08; 0.17]). In study 4592, the estimated number of level 2 and 3 hypoglycaemic episodes was low and similar for Kyinsu and semaglutide. See further Safety section in this report regarding hypoglycaemic events.

Table 59. Hypoglycaemic episodes of clinically significant hypoglycaemic episodes (level 2) or severe hypoglycaemic episodes (level 3) by study

Study	Estimated rate of level 2 or level 3 hypoglycaemic episodes (Episodes per 100 patient-years of exposure)		Estimated treatment rate ratio (Episodes per 100 patient-years of exposure) [95% CI]	P-value
	IcoSema	Comparator		
Study 4591 (IcoSema vs insulin icodec)	15.3	68.4	0.22 [0.14; 0.36]	<0.0001
Study 4592 (IcoSema vs semaglutide	3.99	3.34	1.20 [0.53; 2.69]	
Study 4593 (IcoSema vs IGlar+IAsp)	25.7	218	0.12 [0.08; 0.17]	<0.0001

Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

Nocturnal hypoglycaemia: Severe nocturnal hypoglycaemic episodes were similar rare in both treatment groups across the three phase 3a trials (Kyinsu: 0-0.3%; comparator: 0-0.6%). The proportions of nocturnal severe or clinically significant hypoglycaemic episodes were lower for Kyinsu compared to insulin icodec (1.4% vs 5.9%; study 4591) and IGlar+IAsp (3.5% vs 18.6%; study 4593) and the same compared to semaglutide (0.6%; study 4592).

Recurrence of severe or clinically significant hypoglycaemic episodes: In the previous basal insulin populations, only a few subjects reported > 5 severe (level 3) or clinically significant hypoglycaemia (level 2) episodes in the Kyinsu group (n=3; 0.5% [study 4591] respectively n=4; 1.2% [study 4593]). The proportions were lower compared to insulin icodec (n=24; 3.7% [study 4591]) and IGlar+IAsp (n=40; 12.2% [study 4593]).

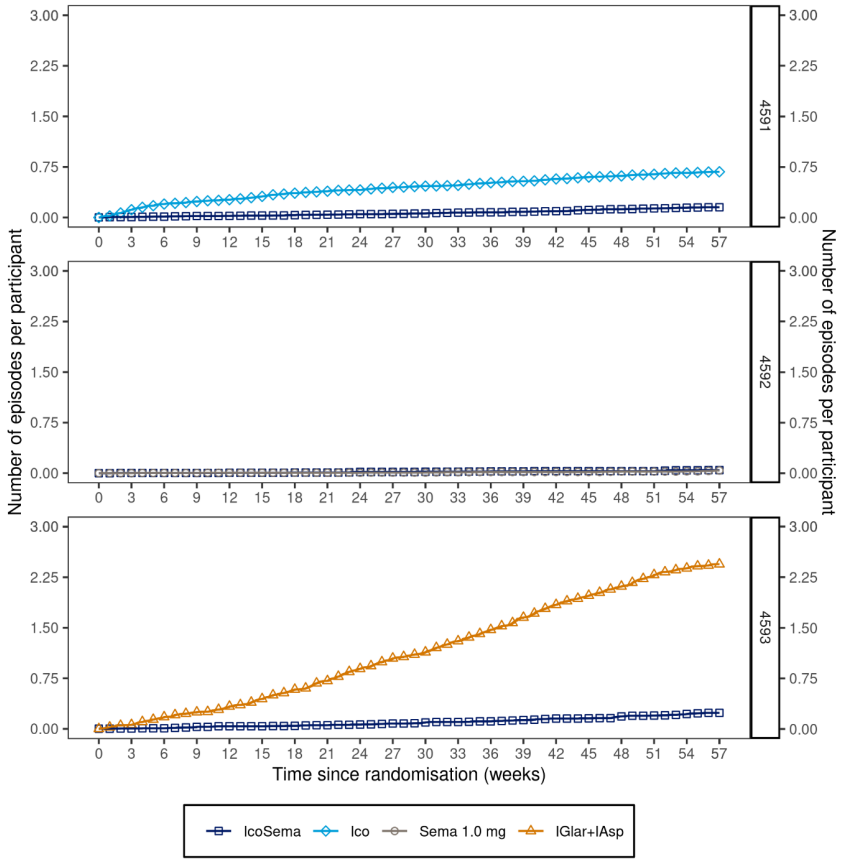
No subjects in the previous GLP-1RA population (study 4591) reported more than 5 severe (level 3) or clinically significant hypoglycaemia (level 2) episodes in any of the two treatment groups.

Occurrence of severe or clinically significant hypoglycaemic episode over the course of study: Across the studies in the phase 3a pool, the occurrence of severe or clinically significant hypoglycaemic episode appeared stable over time (up to week 57). See Figure 20. In all three studies these events were more common at day 2-3 without any large difference compared to days later in the week.

The median duration of clinically significant (level 2) hypoglycaemic episodes was slightly lower for Kyinsu (8 - 18 minutes) compared to the comparator (23-27 minutes) across all studies in the phase 3a pool. The severe (level 3) hypoglycaemic episodes were too few for a meaningful assessment.

SmPC/RMP: The risk for hypoglycaemia is considered to be adequately addressed through the information provided in the SmPC, namely in sections 4.4 and 4.8. The package leaflet contains a summary of the risk factors for hypoglycaemia, its symptoms and guidance on how to act in case of low blood sugar. To improve readability for patients the information is placed at the end of the package leaflet. Hypoglycaemia is a known and well-characterised risk associated with all insulins and should be monitored via routine pharmacovigilance, namely through signal detection and adverse reaction reporting.

Figure 20. Severe (level 3) or clinically significant hypoglycaemia (level 2) by study - on-treatment - mean cumulative function - safety analysis set



BG: Blood glucose
Safety analysis set. Severe hypoglycaemia (level 3): Hypoglycaemia with severe cognitive impairment requiring external assistance for recovery. Clinically significant hypoglycaemia (level 2): Plasma glucose value of < 3.0 mmol/L (54 mg/dL) confirmed by BG meter.

Hyperglycaemia including diabetic ketoacidosis

There were no pre-specified criteria around SMPG threshold, duration or other factors that had to be fulfilled for an event of hyperglycaemia to be reported as an AE in the phase 3a studies. Instead, the AEs were based on the medical and scientific judgement of the investigator. This should be taken into consideration when evaluating hyperglycaemia as AEs.

In the Phase 3a safety pool, the proportion of participants and rates of the overall predefined MedDRA search hyperglycaemic events incl. diabetic ketoacidosis were slightly higher for the Kyinsu group (4.1%) than for the comparator group (3.4%). A larger difference was noted for the isolated PT hyperglycaemia (Kyinsu: 3.5% vs comparator 1.5%). See Table 60.

In study 4591 and 4593 (pre-basal insulin treated populations), the PT hyperglycaemia was reported in by a higher proportion of participants for Kyinsu than for insulin icodec (3.3% vs 1.2%) respectively IGlar+IAsp (3.8% vs 0.6%). In study 4592 (pre-GLP1RA treated) the proportion of subjects with events of hyperglycaemias was only slightly higher for Kyinsu than for semaglutide (3.5% vs 2.9%).

In total 32 of the 57 (56%) events in the Kyinsu group were classified as mild, 23 (40%) as moderate and 2 (3.5%) as severe. Most of the hyperglycaemic events occurred within the first 12 weeks. See Figure 21. This reflects the (efficacy) findings that the mean fasting pre-breakfast SMPG for Kyinsu peaked at week 2 and then declined to baseline around week 10. See also efficacy part.

DKA AEs were rare without any difference between the two treatment groups. See Table 60.

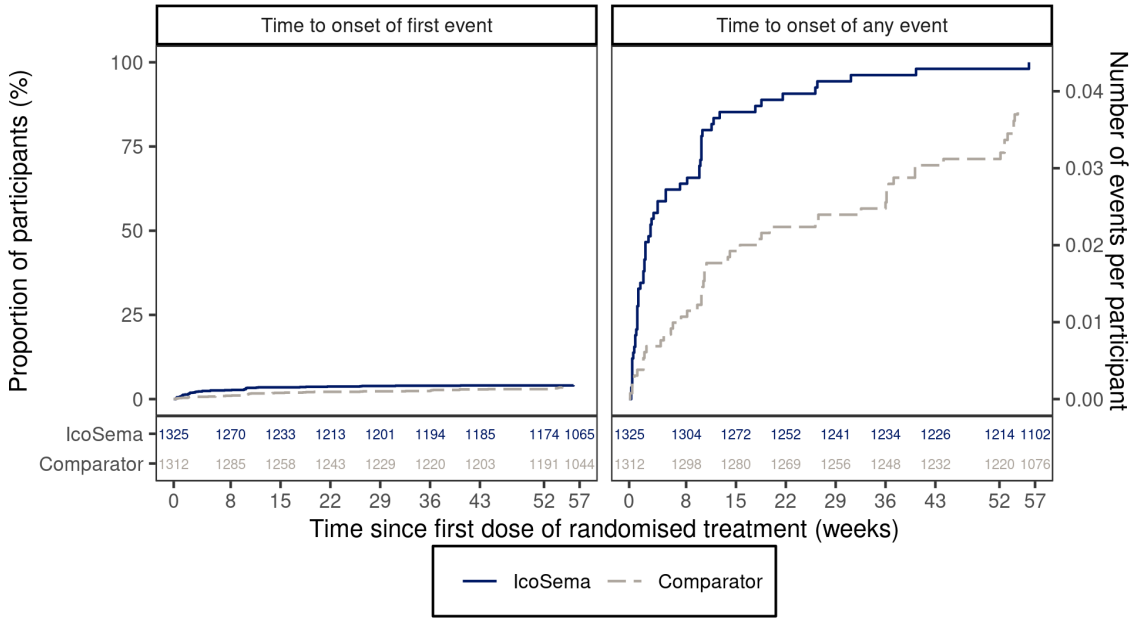
SmPC/RMP: Type 2 diabetes mellitus is characterised by chronic hyperglycaemia. The risk for hyperglycaemia is considered to be appropriately addressed through the information in SmPC, namely in section 4.4. The package leaflet contains a summary of the risk factors for hyperglycaemia, its symptoms and guidance on how to act in case of high blood sugar. To improve readability for patients the information is placed at the end of the package leaflet. This risk should be monitored via routine pharmacovigilance, namely through signal detection and adverse reaction reporting.

Table 60. Hyperglycaemia incl. diabetic ketoacidosis (predefined MedDRA search) by SOC and PT - summary - on-treatment - safety analysis set – phase 3a pool and individual studies

	IcoSema				Comparator			
	N	(%)	E	R	N	(%)	E	R
Phase 3a pool								
Number of participants	1325				1312			
PYE (years)	1369.43				1376.35			
Events	54	(4.1)	57	4.16	45	(3.4)	48	3.44
Metabolism and nutrition disorders	54	(4.1)	57	4.16	37	(2.8)	40	2.87
Hyperglycaemia	46	(3.5)	49	3.58	20	(1.5)	21	1.51
Diabetes mellitus	5	(0.4)	5	0.37	7	(0.5)	8	0.57
Diabetic ketosis	1	(0.1)	1	0.07	0			
Type 2 diabetes mellitus	1	(0.1)	1	0.07	3	(0.2)	3	0.21
Diabetic ketoacidosis	1	(0.1)	1	0.07	1	(0.1)	1	0.07
Diabetes mellitus inadequate control	0				5	(0.4)	5	0.36
Type 1 diabetes mellitus	0				1	(0.1)	1	0.08
Ketoacidosis	0				1	(0.1)	1	0.07
Investigations	0				8	(0.6)	8	0.57
Glycosylated haemoglobin increased	0				6	(0.5)	6	0.43
Blood glucose increased	0				2	(0.2)	2	0.14

Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

Figure 31. Hyperglycaemia incl. diabetic ketoacidosis (predefined MedDRA search) - proportion of participants with at least one event and mean number of events over time - on-treatment - safety analysis set - phase 3a pool



Safety analysis set. Numbers shown in the lower panel represent the number of participants at risk. Left panel: Kaplan-Meier estimate. Right panel: Mean cumulative function estimate. Phase 3a pool: 4591, 4592 and 4593. Comparator: Insulin icodec (4591), semaglutide 1.0 mg (4592) and insulin glargine + insulin aspart (4593).

Gastrointestinal adverse events (GIAE)

Gastrointestinal adverse reactions are well known for GLP-1RA.

In the phase 3a pool, gastrointestinal adverse events (GIAE) were more frequently reported and with higher rate in the Kyinsu group compared to the comparator group (42.1% vs 23.8% and 125.79 vs 45.99 events per 100 PYE). See *Table 61*. On a study level, the proportion of participants reporting GIAE events during use of Kyinsu group was lower in the pre-GLP-RA treated population (31.4%; [study 4591]) compared to the GLP-RA naïve in study 4591 and 4592 (47.0% [study 4591] respectively 43.5% [study 4593]).

In the GLP-1RA naïve (pre-basal insulin treated) populations (study 4591 and 4593), GIAE were reported in markedly higher proportions and rates during user of with Kyinsu compared to insulin icodec (47.0% vs 21.0% and 156.29 vs 33.23 per 100 PYE) respectively IGlar+IAsp (43.5% vs 18.3% and 126.83 vs 27.20 per 100 PYE).

In the pre-GLP-1 RA treated (insulin naïve) population (study 4592), there was a small difference regarding the proportions and rates of overall GI events between Kyinsu and semaglutide (31.4% vs 34.2% and 67.09 vs 88.56 events per 100 patient years).The slightly lower proportions and rates of GIAE in the Kyinsu group might reflect the lower dose of semaglutide (0.5 mg) in the Kyinsu arm compared to the comparator treated with 1.0 mg semaglutide.

In the phase 3a pool, the overall most frequently reported GIAE PTs in the Kyinsu group were *nausea* (20.1%), *diarrhoea* (13.8%) and *vomiting* (9.1%). Table 62. Most of the GI disorders events in both treatment groups were reported as mild (Kyinsu: 73% and comparator: 80%) or moderate (Kyinsu: 26% and comparator: 19%). Approximately 1% of the GI events were in both treatment groups reported as severe and 1% as serious. See Table 61.

GIAE mainly occurred during the initial 8 weeks with a median duration varying between 2 days (vomiting) to 4 days (diarrhoea) in both treatment groups. See Figure 22.

GIAEs were the major reason for withdrawal (2.7%), interruption (1.7) and decrease (4.2%) of study drug.

SmPC: The SmPC section 4.4 (warning for subjects with impaired renal function) and 4.8 is considered well reflecting the risk for GI-events.

Table 61. Gastrointestinal disorders (predefined MedDRA search) by severity - summary - on-treatment - safety analysis set - phase 3a pool

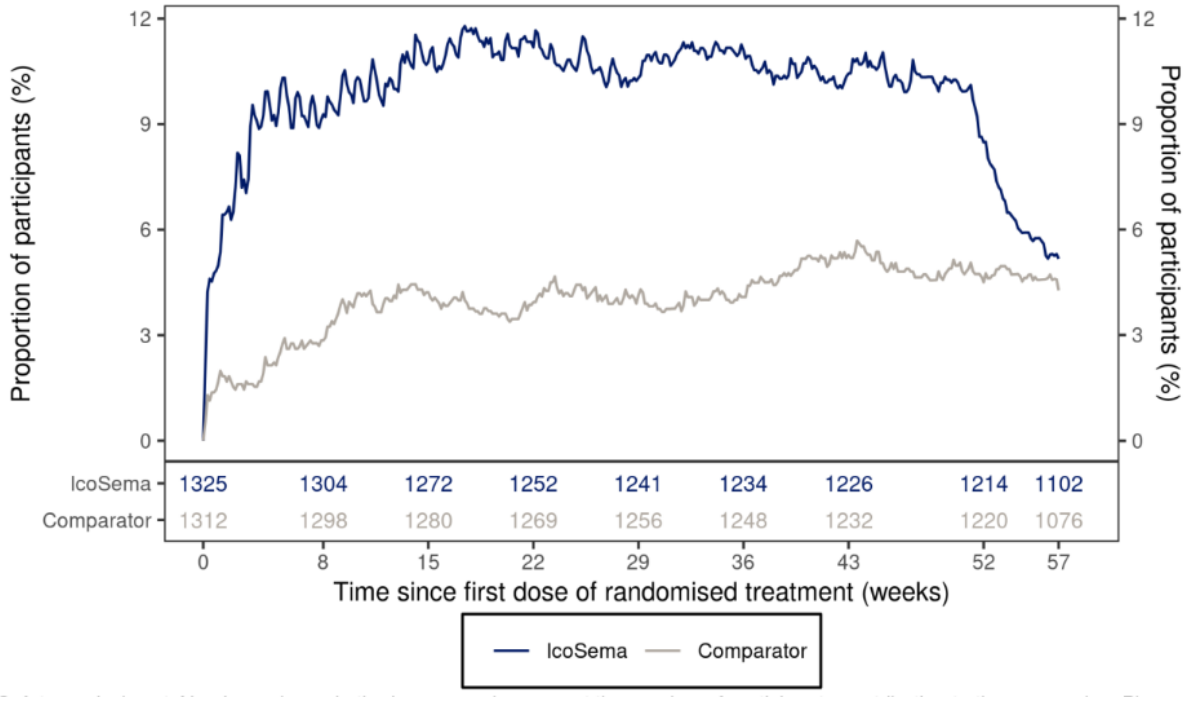
	IcoSema				Comparator			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Number of participants	1325				1312			
PYE (years)	1369.43				1376.35			
Events	558	(42.1)	1717	125.79	312	(23.8)	639	45.99
Serious								
Yes	15	(1.1)	16	1.17	12	(0.9)	17	1.23
No	554	(41.8)	1701	124.62	306	(23.3)	622	44.77
Missing	0				0			
Severity								
Severe	13	(1.0)	19	1.40	4	(0.3)	4	0.29
Moderate	192	(14.5)	451	33.00	70	(5.3)	121	8.73
Mild	469	(35.4)	1247	91.40	276	(21.0)	514	36.97
Missing	0				0			
Action taken to IcoSema/Comparator								
Drug withdrawn	33	(2.5)	50	3.67	5	(0.4)	11	0.80
Drug interrupted	23	(1.7)	34	2.49	10	(0.8)	17	1.21
Dose reduced	56	(4.2)	93	6.82	12	(0.9)	20	1.42
Dose increased	36	(2.7)	66	4.85	14	(1.1)	21	1.53
Dose not changed	505	(38.1)	1451	106.29	287	(21.9)	545	39.22
Unknown	0				0			
NA	17	(1.3)	23	1.68	23	(1.8)	25	1.82
Missing	0				0			

Table 52. Gastrointestinal disorders (predefined MedDRA search) by preferred term (≥1% participants treated with Kyinsu) - summary - on-treatment - safety analysis set - phase 3a pool

	IcoSema				Comparator			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Number of participants	1325				1312			
PYE (years)	1369.43				1376.35			
Events	558	(42.1)	1717	125.79	312	(23.8)	639	45.99
Gastrointestinal disorders	558	(42.1)	1717	125.79	312	(23.8)	639	45.99
Nausea	267	(20.1)	564	41.34	72	(5.5)	112	8.01
Diarrhoea	183	(13.8)	309	22.63	107	(8.1)	168	12.08
Vomiting	120	(9.1)	234	17.12	48	(3.7)	81	5.82
Dyspepsia	62	(4.7)	83	6.10	19	(1.4)	20	1.44
Constipation	58	(4.4)	77	5.65	33	(2.5)	43	3.10
Abdominal pain	42	(3.2)	50	3.65	25	(1.9)	27	1.96
Abdominal pain upper	36	(2.7)	47	3.44	19	(1.5)	21	1.53
Gastrooesophageal reflux disease	35	(2.6)	37	2.72	15	(1.1)	17	1.22
Abdominal discomfort	30	(2.3)	58	4.25	9	(0.7)	9	0.65
Abdominal distension	26	(2.0)	32	2.35	10	(0.8)	10	0.73
Flatulence	22	(1.7)	26	1.90	7	(0.5)	8	0.57
Eructation	17	(1.3)	27	1.98	3	(0.2)	3	0.21
Toothache	14	(1.1)	17	1.24	9	(0.7)	9	0.66
Gastritis	13	(1.0)	16	1.17	11	(0.8)	13	0.94

N: Number of participants with one or more events; %: Percentage of participants with one or more events; E: Number of events; Adj.: Adjusted percentages and rates were calculated using the Cochran-Mantel-Haenszel method to account for differences between studies; R: Rate (number of adverse events per 100 PYE); PYE: Patient years of exposure (1 PYE = 365.25 days)
Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

Figure 22 Gastrointestinal disorders (predefined MedDRA search) - proportion of participants with events by study day - prevalence plots - on-treatment - safety analysis set - phase 3a pool



Safety analysis set. Numbers shown in the lower panel represent the number of participants contributing to the summaries. Phase 3a pool: 4591, 4592 and 4593. Comparator: Insulin icodec (4591), semaglutide 1.0 mg (4592) and insulin glargine + insulin aspart (4593).

Diabetic retinopathy

Background

The semaglutide s.c. (Ozempic) for T2D CVOT (SUSTAIN 6) showed a significant higher risk of diabetic retinopathy complications (i.e., need for retinal photocoagulation, vitreous haemorrhage, need for treatment with intravitreal agents and onset of diabetes-related blindness) compared to placebo (3.0% vs 1.8%; and a HR of 1.76 [1.11; 2.78] 95% CI for time to first event). The increased risk was primarily in patients with retinopathy at baseline treated with semaglutide concomitant with insulin. In patients without retinopathy and no concomitant insulin use, there was no effect of semaglutide on the development of retinopathy complications.

Based on the results from SUSATAIN 6, the risk for diabetes retinopathy complication was included in the RMP for semaglutide as an important identified risk with an ongoing dedicated ophthalmic category 3 PASS (FOCUS) in place. The FOCUS study using standardised and validated ophthalmic assessments assesses the short- and long-term effect of semaglutide s.c. on diabetic retinopathy development and progression and will provide mechanistic insights. The study includes participants concomitantly treated with insulin and semaglutide.

Phase 3a safety pool

In the Kyinsu phase 3a studies participants with uncontrolled and potentially unstable diabetic retinopathy or maculopathy were to be excluded.

A slightly higher proportion of subjects reported AEs related to diabetic retinopathy (predefined MedDRA search) in the Kyinsu group than in the comparator group (9.2% vs 8.1%). The difference in proportion of participants reporting the PT *diabetic retinopathy* was larger in the Kyinsu group than in the comparator group (6.4% vs 4.8%). See Table 61.

Table 63. Diabetic retinopathy (predefined MedDRA search) by SOC and PT reported by ≥2 subjects in the Kyinsu group - summary - from first dose to end of study - safety analysis set - phase 3a pool

	IcoSema				Comparator			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Number of participants	1325				1312			
PYO (years)	1407.72				1398.25			
Events	123	(9.3)	157	11.16	106	(8.1)	149	10.68
Eye disorders	122	(9.2)	156	11.09	106	(8.1)	149	10.68
Diabetic retinopathy	85	(6.4)	93	6.61	63	(4.8)	73	5.25
Macular oedema	13	(1.0)	14	0.99	9	(0.7)	10	0.72
Non-proliferative retinopathy	4	(0.3)	4	0.28	1	(0.1)	1	0.07
Diabetic retinal oedema	4	(0.3)	4	0.28	8	(0.6)	8	0.57
Arteriosclerotic retinopathy	3	(0.2)	3	0.21	2	(0.2)	2	0.14
Retinal haemorrhage	3	(0.2)	3	0.21	5	(0.4)	6	0.43
Retinal vein occlusion	3	(0.2)	3	0.21	2	(0.2)	2	0.14
Vitreous detachment	3	(0.2)	3	0.21	1	(0.1)	1	0.07
Retinal exudates	2	(0.2)	2	0.14	0			
Vitreous haemorrhage	2	(0.2)	2	0.14	2	(0.2)	3	0.22
Dry age-related macular degeneration	2	(0.2)	2	0.14	1	(0.1)	1	0.07
Visual impairment	2	(0.2)	3	0.21	0			
Macular degeneration	2	(0.2)	2	0.14	1	(0.1)	1	0.07
Maculopathy	2	(0.2)	3	0.21	3	(0.2)	3	0.22
Retinal aneurysm	2	(0.2)	2	0.14	2	(0.2)	4	0.28
Retinopathy	2	(0.2)	2	0.14	5	(0.4)	5	0.35

Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

Among subjects **without diabetic retinopathy** or related conditions in medical history at baseline (~75% of the subjects), a slightly higher proportion in the Kyinsu group reported diabetes retinopathy (PT) at the scheduled week 52 eye examination compared to the comparator (5.2% vs 3.9%). Most of the diabetic retinopathy events in this subgroup were mild (Kyinsu 82% and comparator 91%). A slightly higher proportion of the events in the Kyinsu group were reported as moderate (or severe compared to the comparator group (18% [10/55 events] vs 9.3% [4/43 events]). See Table 64**.** The result in this population is not in line with previous results for semaglutide (in SUSTAIN 6, see above) and needs to be further evaluated.

Among subjects **with diabetic retinopathy** (or related conditions) at baseline (~25% of the subjects) this difference in subjects that reported diabetes retinopathy (PT) was larger (Kyinsu: 10.2% comparator: 7.6%). In the Kyinsu group 2.9% in the Kyinsu group received treatment with intravitreal agents compared to 1.8% in the comparator group. However, no subject in the Kyinsu group reported any event related to treatment by retinal photocoagulation, vitreous haemorrhage or onset of diabetes-related blindness. In the comparator group, these events were reported by none (treatment by retinal photocoagulation), 0.6% (vitreous haemorrhage) respectively none (diabetes-related blindness). Overall, the data presented do not indicate an increased risk for diabetes retinopathy complications in subjects with diabetes retinopathy at baseline between the two treatment groups. See Table 65.

Table 64. Adverse events of diabetic retinopathy (PT) by severity - summary - from first dose to end of study - participants without medical history of diabetic retinopathy (predefined MedDRA search) before first dose - safety analysis set

Phase 3a pool/study 4591/4592/4593	**IcoSema**			**Comparator in phase 3a pool/Insulin icodec/ Semaglutide/Basal-bolus insulin**		
	N (%)	E	R	N (%)	E	R
Number of participants						
Phase 3a pool	1004			983		
Study 4591	454			460		
Study 4592	277			280		
Study 4593	273			243		
Observation time (Participant years of observation)						
Phase 3a pool	1066.29			1048.63		
Study 4591	479.84			488.73		
Study 4592	298.17			304.93		
Study 4593	288.28			254.97		
AE with the PT diabetic retinopathy						
Phase 3a pool*	52 (5.2%)	55	5.17	38 (3.9%)	43	4.10
Study 4591	27 (5.9%)	30	6.25	20 (4.3%)	24	4.91
Study 4592	11 (4.0%)	11	3.69	9 (3.2%)	9	2.95
Study 4593	14 (5.1%)	14	4.86	9 (3.7%)	10	3.92
Severity (**Mild**)						
Phase 3a pool*	43 (4.3%)	45	4.23	35 (3.6%)	39	3.71
Study 4591	21 (4.6%)	23	4.79	18 (3.9%)	22	4.50
Study 4592	11 (4.0%)	11	3.69	9 (3.2%)	9	2.95
Study 4593	11 (4.0%)	11	3.82	8 (3.3%)	8	3.14
Severity (**Moderate**)						
Phase 3a pool*	8 (0.8%)	8	0.76	3 (0.3%)	4	0.39
Study 4591	6 (1.3%)	6	1.25	2 (0.4%)	2	0.41
Study 4592	0			0		
Study 4593	2 (0.7)	2	0.69	1 (0.4)	2	0.78
Severity (**Severe**)						
Phase 3a pool*	2 (0.2%)	2	0.19	0		
Study 4591	1 (0.2%)	1	0.21	0		
Study 4592	0			0		
Study 4593	1 (0.4%)	1	0.35	0		
PT diabetic retinopathy categorised as proliferative during the study						
Phase 3a pool*/study 4591/4592/4593	0			0		

Abbreviations: N = number of participants; % = Percentage of participants with one or more events; E = number of events; R: Rate (number of events per 100 PYO); PYO: Patient years of observation (1 PYO = 365.25 days) *For phase 3a pool, % and R reflect adjusted percentages and rates that were calculated using the Cochran-Mantel-Haenszel method to account for differences between studies. IcoSema=fixed dose regiment insulin icodec/semaglutide.

Table 65. Complications related to diabetic retinopathy - summary - from first dose to end of study - participants with medical history of diabetic retinopathy (predefined MedDRA search) before first dose - safety summary set

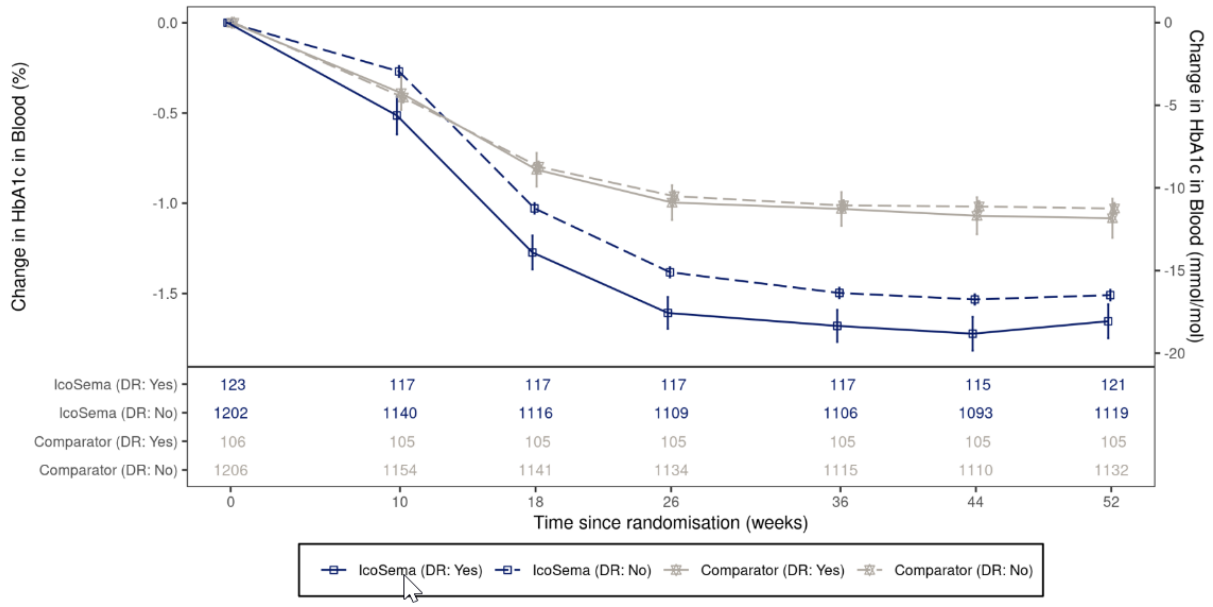
Phase 3a pool/study 4591/4592/4593	IcoSema			Comparator in phase 3a pool/Insulin icodec/ Semaglutide/Basal-bolus insulin		
	N (%)	E	R	N (%)	E	R
Number of participants						
Phase 3a pool	321			329		
Study 4591	190			184		
Study 4592	64			60		
Study 4593	67			85		
Observation time						
Phase 3a pool	341.42			349.62		
Study 4591	201.14			197.91		
Study 4592	68.71			65.84		
Study 4593	71.58			85.87		
Treatment by retinal photocoagulation						
Phase 3a pool*/study 4591/4592/4593	0			0		
Vitreous haemorrhage						
Phase 3a pool*	0			2 (0.6%)	3	0.83
Study 4591	0			0		
Study 4592	0			1 (1.7%)	1	1.52
Study 4593	0			1 (1.2%)	2	2.33
Treatment with intravitreal agents						
Phase 3a pool*	9 (2.9%)	17	5.16	6 (1.8%)	9	2.49
Study 4591	4 (2.1%)	8	3.98	2 (1.1%)	2	1.01
Study 4592	1 (1.6%)	1	1.46	1 (1.7%)	1	1.52
Study 4593	4 (6.0%)	8	11.18	3 (3.5%)	6	6.99
Onset of diabetes-related blindness						
Phase 3a pool*/study 4591/4592/4593	0			0		
Vitrectomy needed						
Phase 3a pool*/study 4591/4592/4593	0			0		

Abbreviations: N = number of participants; % = Percentage of participants with one or more events; E = number of events; R: Rate (number of events per 100 PYO); PYO: Patient years of observation (1 PYO = 365.25 days)

*For phase 3a pool, % and R reflect adjusted percentages and rates that were calculated using the Cochran-Mantel Haenszel method to account for differences between studies

Figure 23. Change in HbA1c - mean plot - in-study - by participants with events of diabetic retinopathy (predefined MedDRA search) from first dose to end of study - safety analysis set

- phase 3a pool



DR: Diabetic retinopathy; HbA1c: Haemoglobin A1c
Safety analysis set. Number of participants contributing to the data points appears in the bottom panel. Observed data including data obtained after premature treatment discontinuation.
Legend: Mean (symbol) and mean ± standard error to the mean (error bars). Comparator: Insulin icodec (4591), semaglutide 1.0 mg (4592) and insulin glargine + insulin aspart (4593).
Phase 3a pool: 4591, 4592 and 4593.

Longer diabetes durations and rapid improvements in glycaemic control (HbA1c) are risk factors for development and/or worsening of diabetes retinopathy. Correspondingly, longer diabetes durations and larger HbA1c (%) reduction from baseline to week 26, were (in both treatment groups) noted for subjects that reported any AEs related to diabetic retinopathy events during the trials. See Table 66 and Figure 23. However, an isolated effect for semaglutide could not be excluded.

Table 66. Diabetic retinopathy (predefined MedDRA search) - risk factors in participants with events vs without events - summary - from first dose to end of study - safety analysis set - phase 3a poo

	Participants **with** events		Participants **without** events	
	IcoSema	Comparator	IcoSema	Comparator
Number of participants	123	106	1202	1206
History of diabetic retinopathy, N (%)				
N	123 (100.0)	106 (100.0)	1202 (100.0)	1206 (100.0)
No	76 (61.8)	60 (56.6)	928 (77.2)	923 (76.5)
Yes	47 (38.2)	46 (43.4)	274 (22.8)	283 (23.5)
Duration of diabetes (years)				
N	123	106	1202	1206
Mean (SD)	15.7 (7.9)	15.2 (7.6)	14.2 (7.5)	14.4 (7.7)
Median	14.8	14.6	13.4	13.6
Min ; Max	1.6 ; 45.4	2.7 ; 40.8	0.4 ; 52.6	0.4 ; 55.0
Baseline HbA1c (%)				
N	123	106	1202	1206
Mean (SD)	8.2 (0.8)	8.3 (0.8)	8.2 (0.8)	8.2 (0.8)
Median	8.2	8.1	8.1	8.0
Min ; Max	6.7 ; 10.3	6.9 ; 10.0	6.4 ; 11.6	6.0 ; 11.2
Baseline HbA1c (mmol/mol)				
N	123	106	1202	1206
Mean (SD)	66.5 (8.6)	67.1 (8.8)	66.1 (8.9)	65.7 (9.0)
Median	66.1	65.0	65.0	63.9
Min ; Max	49.7 ; 89.1	51.9 ; 85.8	46.5 ; 103.3	42.1 ; 98.9
HbA1c (%) reduction from baseline to week 26, N (%)				
N	117	105	1109	1134
Mean (SD)	-1.6 (0.9)	-1.0 (1.0)	-1.4 (0.9)	-1.0 (1.0)
Median	-1.5	-1.0	-1.3	-0.9
Min ; Max	-4.4 ; 0.3	-4.3 ; 1.8	-4.5 ; 1.8	-4.3 ; 3.1

N: Number of participants with one or more events; %: Percentage of participants with one or more Events History of diabetic retinopathy is based on a predefined MedDRA search of medical history.
Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

SmPC: The risk for development of DR in subjects without DR at baseline should is reflected in the SmPC section 4.4 and 4.8.

RMP: "*Diabetic retinopathy complications*" is, as for semaglutide, proposed to be included as an important identified risk in the RMP for Kyinsu. The category 3 PASS ongoing for semaglutide (NN9535-4352: "*Long-term effects of semaglutide on diabetic retinopathy in participants with T2D*" [FOCUS]) also included as an additional PV activity for Kyinsu. A limited number of patients without diabetic retinopathy or with only microaneurysms at baseline will also be included in the FOCUS study. Thus, results from this study will possibly give some indication, whether there is risk (or not) for development of diabetes retinopathy in subjects without diabetes retinopathy at baseline co-treated with insulin and semaglutide. In the meantime, cases without diabetes retinopathy that reports diabetes retinopathy after treatment with Kyinsu had started, will be followed in the Kyinsu PSURs.

Cardiovascular disorders

EAC confirmed cardiovascular events

In the phase 3a pool, the overall proportion of subjects reporting any EAC confirmed cardiovascular event was low in both treatment groups (Kyinsu: 1.8%; comparator: 1.5%). Taken together, the

available data does not support that there is a relevant difference between Kyinsu and the comparators regarding EAC-confirmed cardiovascular events.

SmPC: Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of congestive heart failure. This is as for insulin icodec, and other insulins reflected in SmPC section 4.4.

Pulse rate

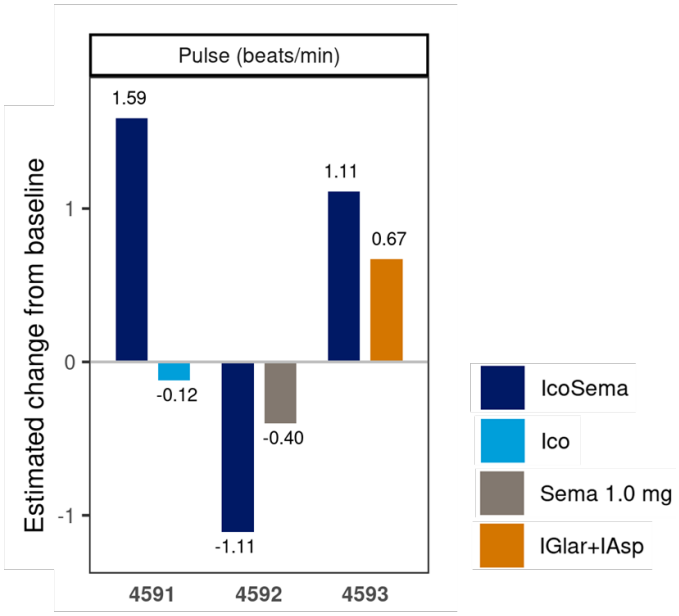
Increased pulse rate is a known side effect of GLP-1 RA.

Overall, in the phase 3a pool, a higher proportion of participants and rate of adverse events related to increased heartrate were reported for Kyinsu than for comparators (1.3% vs 0.5% and 1.28 vs 0.43 events per 100 PYE).

In the previously basal insulin treated with insulin icodec (study 4591) and IGlar+IAsp (study 4593) as comparators) the estimated mean (SE) changes in pulse were higher for the Kyinsu groups compared to insulin icodec (1.59 [0.33] vs -0.12 [0.33] bpm) respectively IGlar+IAsp (1.11 [0.48] vs 0.67 [0.50] bpm). In the pre-GLP1-RA treated population (study 4592) the mean change in pulse rate was instead lower in the Kyinsu group compared to semaglutide (-1.11 [0.40] vs -0.40 [0.4] bpm). See Figure 24.

SmPC: As for other semaglutide products, the risk for increased heart rate is reflected in the SmPC section 4.8.

Figure 24. Pulse rate (beats per minute) – change from baseline – on-treatment



	4591	4592	4593
Baseline value	74-75 bpm	78 bpm	76-77 bpm
P-value	0.0002	0.2042	0.5222

Note: Baseline values are based on the safety analysis set and the statistical analyses are based on the full analysis set. **Abbreviations:** bpm = beats per minute; IGlar+IAsp = insulin glargine + insulin aspart; Ico = insulin icodec; Sema = semaglutide

Acute renal failure

The gastrointestinal side-effects for semaglutide could potentially lead to dehydration and acute renal failure, especially in patients with impaired renal function. In the phase 3a pool the number of acute renal failure cases were similar low in the two treatment groups (0.5%; n=6 in Kyinsu group and 7 in comparator group). In the Kyinsu group two of the six cases with acute kidney failure event occurred in combination with GI side-effects. Most of the events (11/13) were mild or moderate in severity. In total 5 SAEs (3 in Kyinsu group and 2 in comparator group) with PT of acute kidney injury were reported.

SmPC: The risk for dehydration due to GI-side effects leading to deterioration of renal function is considered sufficient reflected in SmPC section 4.4 (aligned with the text in the Ozempic PI).

Hepatic disorders

In the phase 3a pool, events of hepatic disorders captured by predefined MedDRA search were reported in comparable proportion of participants and with comparable event rates in the Kyinsu and comparator groups (1.6% and 2.1% participants; 1.61 and 2.10 events per 100 PYE, respectively). All events were mild or moderate in severity and majority of the AEs were judged by the investigator as unlikely related to the trial product. Overall, the reported hepatic disorders AEs revealed no safety concerns.

Acute pancreatitis

Pancreatitis is a known risk for GLP-1RA and reflected in the SmPC for the authorised semaglutide products.

In the phase 3a studies, cases with a history of pancreatitis 6 months before screening were not included.

In the overall (phase 3a) Kyinsu group, three events of acute pancreatitis were reported in two cases compared to none in the comparator group. Overall, the reported events of acute pancreatitis revealed no new safety concerns.

SmPC: The risk for acute pancreatitis is sufficiently reflected in the SmPC section 4.4 and 4.8.

Increased lipase and amylase are known effects of semaglutide and labelled in SmPC section 4.8 for Kyinsu.

Gallbladder related disorders

Cholelithiasis is a known risk for semaglutide (i.e., GLP-1RA class effect).

In the Phase 3a pool, cholelithiasis and related events were reported by similar proportions of participants and rates for Kyinsu as for the comparators (0.8% vs 0.9% and 0.88 vs 0.94 events per 100 PYE). This frequency is slightly lower compared to those noted in the development program for Ozempic (from the EPAR: gallbladder-related AEs were reported more frequently with semaglutide [0.5 mg: 1.3%; 1.0 mg: 1.7%]).

Overall, the reported events of Gallbladder related disorders revealed no new safety concerns.

SmPC: The risk is considered sufficiently reflected in the SmPC section 4.8.

Neoplasms

In the phase 3a pool, the most reported neoplastic PTs in the Kyinsu group were large intestine polyp (Kyinsu: 0.6% vs comparator: 5%), renal cyst (Kyinsu: 0.5% vs comparator: 0.2%), and gastric polyps (Kyinsu: 0.5% vs comparator: 0.1%). Overall, duration of the studies in the phase 3a are too short to provide any useful information about neoplasms.

RMP: Medullary thyroid cancer and pancreatic cancer are important potential risks for semaglutide. As for semaglutide these risks are also included in the summary of safety concerns in the RMP for Kyinsu. The risks are followed by PASS, study MTC-22341 (Medullary Thyroid Carcinoma Surveillance Study: a case-series registry) respectively study NN9535-4447 (Epidemiological assessment of the risk for pancreatic cancer associated with the use of semaglutide in patients with T2D).

Hypersensitivity

Approximately 4% of the participants in the Kyinsu group and 5% in the comparator group reported any hypersensitivity event. In both treatment groups, the most reported hypersensitivity PTs were rash, eczema and urticaria. Most of the hypersensitivity events were reported as mild (91% in the Kyinsu group). The only SAE (anaphylactic reaction) reported in the Kyinsu group is considered not related to study treatment (wasp sting).

Additional immunological analyses were performed in 7 of the 11 the participants with systemic hypersensitivity reactions. Although, presence of anti-insulin icodec antibodies were positive in 4 of these the anti-IgE antibodies (insulin icodec and semaglutide) were negative. Overall, the number of systemic hypersensitivity reactions reported by investigator were low and no further conclusions of the results could be performed.

SmPC: The risk for hypersensitivity including anaphylactic reactions is considered sufficiently described in SmPC section 4.3, 4.4 and 4.8.

Injection site reaction

A similar proportion of subjects reported injection site reactions in the Kyinsu and comparator group (0.8%). Two subjects reporting in total 9/19 events are an explanation for the higher event rate in the Kyinsu group compared to the comparator group (1.37 vs 0.87 events per 100 PYE).

SmPC: Handling of (i.e. rotation of injection sites to avoid and reduce the risk of developing lipodystrophy and cutaneous amyloidosis) and the risk for injection site reactions is considered sufficiently reflected in the SmPC section 4.2, 4.4 and 4.8.

Lipodystrophy and cutaneous amyloidosis

In the Phase 3a pool, one case reported lipohypertrophy (PT) and one case reported cutaneous amyloidosis (PT) are reported in the Kyinsu group.

SmPC: The risk for Lipodystrophy and cutaneous amyloidosis is in line with the outcome and PRAC Recommendation for the signal procedure EPITT no: 19499 () concerning cutaneous amyloidosis for all insulin containing products reflected in SmPC section 4.2, 4.4 and 4.8.

Medication errors

In the phase 3a, medication errors (MEs) were reported by ~2% of the participants in the Kyinsu group. Most of the ME cases concerns incorrect dose administration, overdose and underdose. There was no pattern for the timing of the medication errors in the Kyinsu group. Approximately, 1/3 of the ME were in in both treatment groups (n=8/29 for Kyinsu and n= 28/75 for the comparator) were reported during the first 30 days (defined as "switched" period). The main adverse reaction resulting

from these events was Level 1 hypoglycaemic episodes. All ME cases were non-serious and mild or moderate in severity.

SmPC: The risk for/avoidance of ME are reflected in the SmPC section 4.2 and 4.4.

RMP: Medication error during switch from other injectable diabetes therapy is included as an important potential risk in the RMP. An educational material to further minimise the risk of medications errors during switch from other injectable diabetes treatments or due to mix-up is planned.

Usability test

The applicant claims that user tasks for the Kyinsu PDS290 pen is identical as for the insulin icodec PDS290 pen-injector. Therefore, results regarding handling and knowledge for the insulin icodec injector-pen (study UT253) could also support these parameters of the Kyinsu PDS290 pen-injector. Study UT253 was assessed within the insulin icodec MAA and revealed no new safety concerns.

The differentiation human factory test with the Kyinsu PDS290 pen-injector (UT290) was performed in 75 participants.

In neither of the studies any information presented how well the participants in the two tests reflected the sought indication. The population with diabetes includes subjects with e.g., impaired vision, colour blindness and impaired fine motor skills which might affect the usability of the pen.

2.7.8.4. Laboratory findings

Measured haematology parameters: Erythrocytes, haematocrit, haemoglobin, leukocytes, thrombocytes, basophils, eosinophils, lymphocytes, neutrophils and monocytes.

Measured biochemistry parameters: Albumin, ALP, ALT, AST, creatinine, potassium, sodium, gamma glutamyl transferase (GGT) and total bilirubin.

Taken together, the available laboratory data for the phase 3a studies do not support that there is a relevant difference between Kyinsu and the comparators regarding measured haematology or biochemistry parameters.

For lipids: see section 3.1.3.4. in efficacy part of the overview.

For pancreatic enzymes: see the section "Acute pancreatitis" (AESI) section 2.7.8.3 above.

2.7.8.5. Safety in special populations

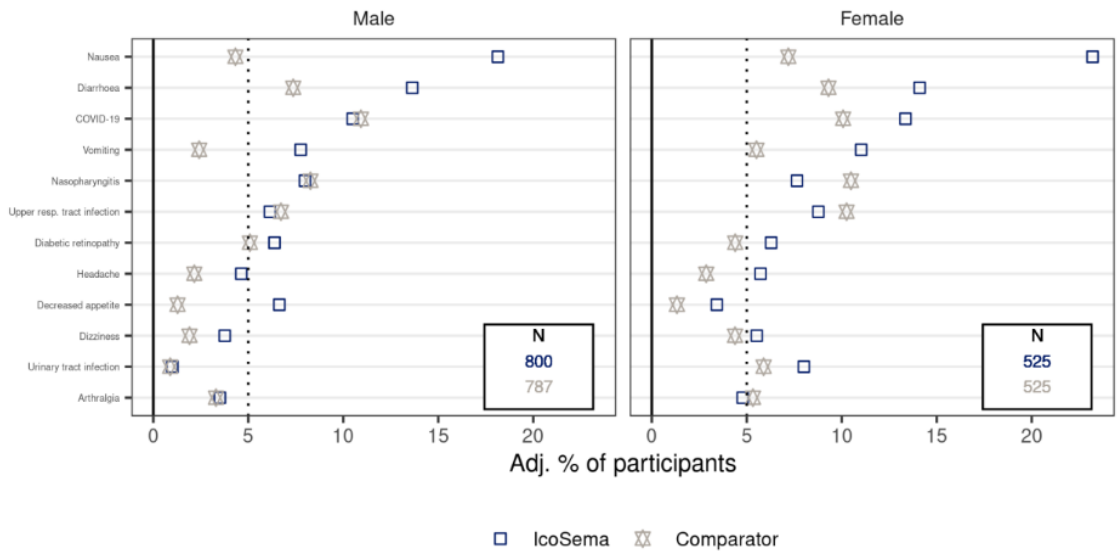
Gender

The most frequent (≥5%) AEs by sex and PT in the phase 3a pool is presented in Figure 25.

In the phase 3a pool, 800 (60.4%) males and 525 (39.6%) females were treated with Kyinsu.

Besides a slightly higher proportion of females compared to males reporting *nausea* (23.1% vs 18.1%) and *vomiting* (11.0% vs 7.8%), no pronounced differences in AEs by SOC or by SOC and PT, were observed in males compared to females.

Figure 25. Adverse events by sex and PT - most frequent [>=5%] - dot plot - on-treatment - safety analysis set - phase 3a pool.



Age

The number of participants in the overall elderly population (≥ 65 years) is sufficient (n=523 for Kyinsu) and in line with the ICH E7 guideline. In total, 79 subjects treated with Kyinsu were ≥75 years.

In the phase 3a pool, a higher proportion of participants in the Kyinsu group reported SAEs in the ≥75 years population (18.0%; 14/79) compared to the two younger populations (≥65-< 75 years: 12.3%; 55/444 and 18-<65 years: 8.9%; 71/802) but a lower proportion compared to the corresponding age-group (i.e., ≥75 years) in the comparator group (22.3%; 19/85).

In the ≥75 years population, most of the SAEs in the Kyinsu group were reported within the SOC Cardiac disorders (n=3) and in the comparator group within the SOC Injury, poisoning and procedural procedurals (n=7). No specific SAE pattern considered as ADRs for the elderly were noted. The safety pattern in elderly do not raise any specific safety concerns.

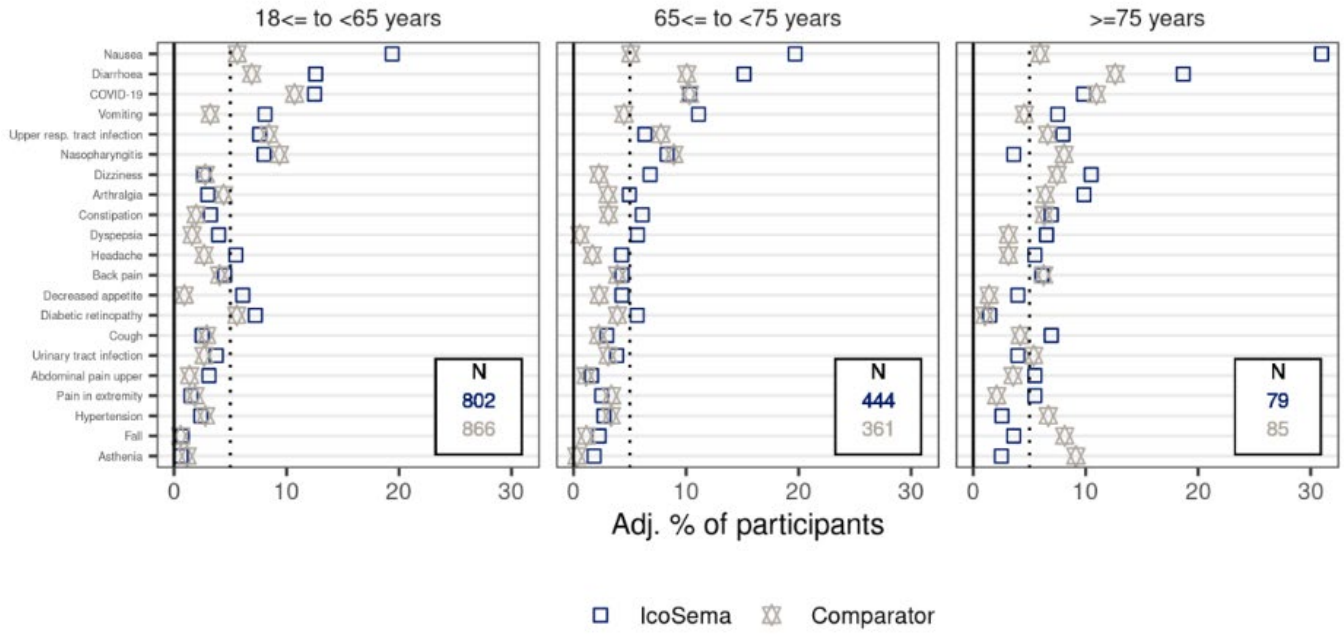
Events with fatal outcome were few and reported by similar proportions among elderly in the two treatment groups (n= 4 for Kyinsu respectively n=3 for the comparator in the age group ≥ 65 years). The causes of deaths in the ages ≥ 65 years were according to EAC information related to CV-events in 3 cases and undetermined in one case. For the corresponding comparator group also a pulmonary event respectively trauma was causes of deaths.

Withdrawals due to AEs were more common for Kyinsu in the ≥75 years (11.9%) compared to the younger populations (≥65-< 75 years: 6.1% and 18-<65 years: 2.4%). A corresponding pattern was also noticed for the comparator although, the proportions were higher for Kyinsu in all three treatment groups.

The most frequent (≥5%) AEs by age group and PT in the phase 3a pool is presented in Figure 26.

As often noticed in the elderly population there are some differences in AE profile compared to the younger population. This was also noted for the phase 3a pool, e.g. *nausea* and *diarrhea*. Most of the differences in the AE PTs were also noted for the comparator. See Figure 29. Based on the presented and available data no new safety concern is revealed for use of Kyinsu in elderly compared to the younger populations.

Figure 26. Adverse events by age group and preferred term - most frequent [>=5%] - dot plot - on-treatment - safety analysis set - phase 3a pool



Hepatic impairment

Hepatic impairment was defined as total bilirubin (TBL) >ULN and/or AST>ULN at baseline.

The criteria used differs compared to the applications for the monocomponents.

In the phase 3a pool, 106 subjects in the Kyinsu group (8%) fulfilled any of these criteria. With the response the applicant clarifies that, one patient had both total bilirubin (TBL) >ULN and AST>ULN, 6 patients (6%) had an isolated increase in total bilirubin and the remaining 99 cases (93%) had an isolated AST increase ≥ 2.5 ULN. None of the participants with hepatic impairment at baseline had a medical history of Gilberts syndrome.

Impaired liver function, defined as alanine aminotransferase ≥2.5 times or bilirubin > 1.5 times upper normal limit at screening was an exclusion criterion in the phase 3a studies.

With the used classification, the subgroup of participants with impaired hepatic function consisted of 106 participants in Kyinsu group and 117 participants in comparator group.

The most frequent (≥5%) AEs by baseline hepatic function and PT in phase 3a pool is presented in Figure 27.

No pronounced clinically significant difference in SAEs, severity and action taken to study drug or in AEs by SOC, and by SOC and PT were observed in patients classified as with hepatic impairment vs without hepatic impairment at baseline in the Kyinsu group.

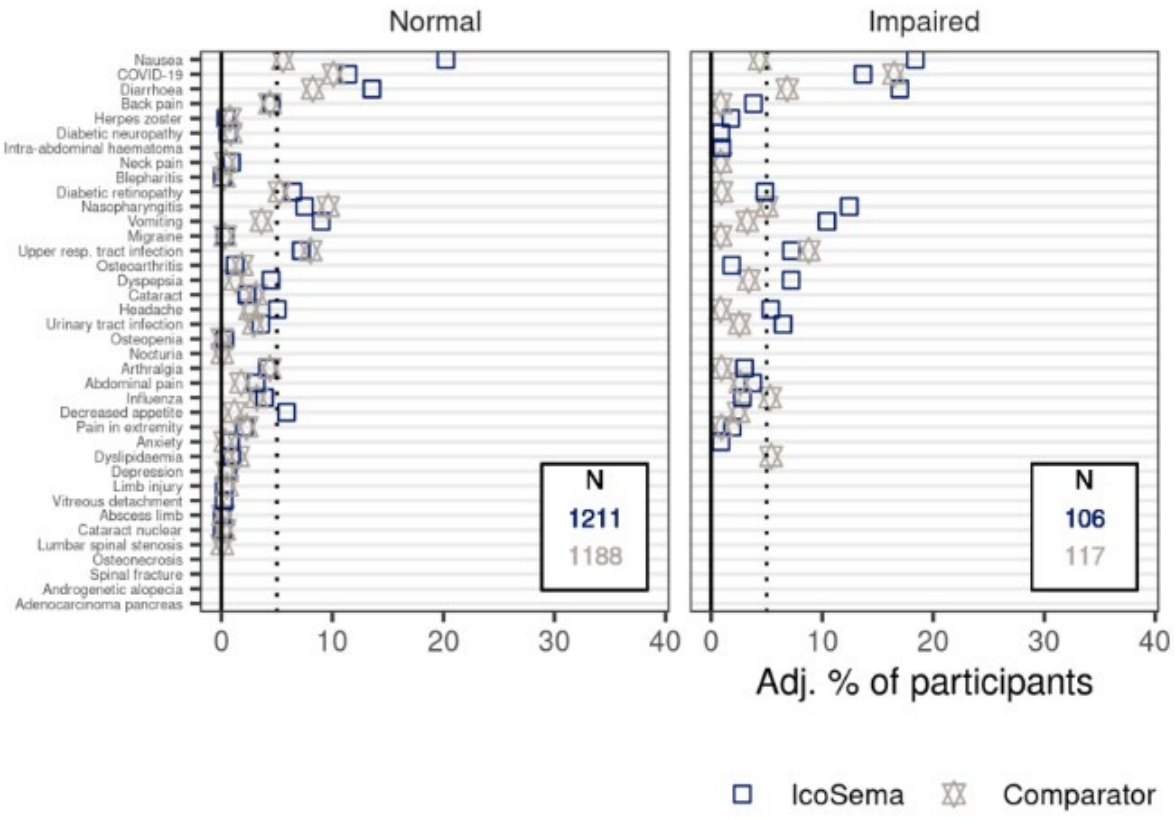
No results regarding potential differences of hypoglycaemic events have been presented.

None of the monocomponents have demonstrated any safety issue in subjects with hepatic impairment and the FDC not is expected to enhance any risk in related to hepatic impairment.

SmPC: The SmPC section 4.2 is aligned with the text for semaglutide (Ozempic) and insulin icodec (Awiqli).

RMP: Use of Kyinsu in patients with severe hepatic impairment (as for semaglutide) included in the Kyinsu RMP as a topic of missing information.

Figure 27. Adverse events by baseline hepatic function and preferred term - most frequent [>=5%] – dot plot - on-treatment - safety analysis set - phase 3a pool



Renal impairment

Use of semaglutide in various degrees of renal impairment was evaluated in the phase 1 PK study NN9535-3616.

In the phase 3a pool, Kyinsu was exposed to 604 subjects with normal (eGFR >= 90) liver function, 588 with mild renal impairment (eGFR ≥60 to 90) and 133 with moderate or severe (eGFR < 60) renal impairment.

The most common (≥5%) AEs by baseline renal function (eGFR ml/min/1.73m2) and PT in the phase 3a pool is presented in Figure 28. No pronounced treatment difference of clinical significance in AEs by SOC, and by SOC and PT were observed across baseline renal function groups.

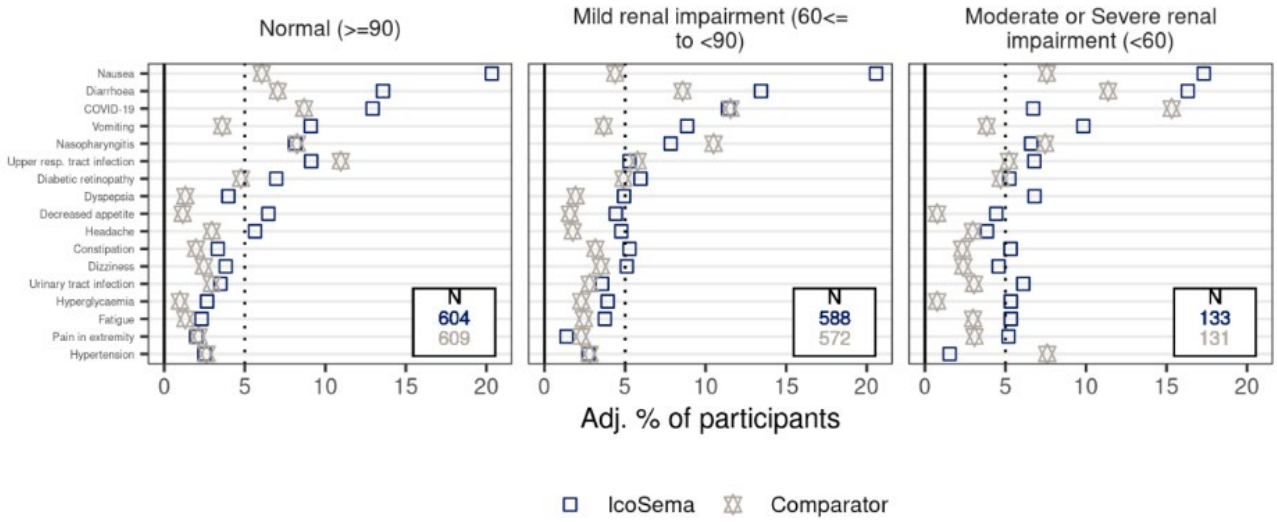
The proportion of participants with and rate of SAE were higher for those in the Kyinsu group with moderate or severe renal impairment at baseline (20.9% and 38.84 events per 100 PYE) compared to Kyinsu participants with mild (9.9% and 11.64 events per 100 PYE) or normal renal function (8.8% and 11.74 events per 100 PYE) at baseline.

No specific pattern was noted for the SAEs reported by subjects with moderate/severe renal impairment in the Kyinsu group. The most commonly reported SOCs in this group were Nervous system disorders, Cardiovascular disorders and Infections. No PT was reported by more than one subjects except three cases that reported acute kidney injury.

Among subjects with mild or moderate/severe renal impairment, there were nine (9) SAEs considered as related to study treatment in the Kyinsu groups. These SAEs included already known ADRs for Kyinsu, such as hypoglyceamia, metabolic acidosis and vomiting. The remaining non-related PTs were distributed over several SOCs without any specific pattern.

SmPC: The SmPC section 4.2 is aligned with the text for the mono-components, semaglutide (Ozempic) and insulin icodec (Awiqli).

Figure 28. Adverse events by baseline renal function (eGFR ml/min/1.73m2) and preferred term – most frequent [>=5%] - dot plot - on-treatment - safety analysis set - phase 3a pool



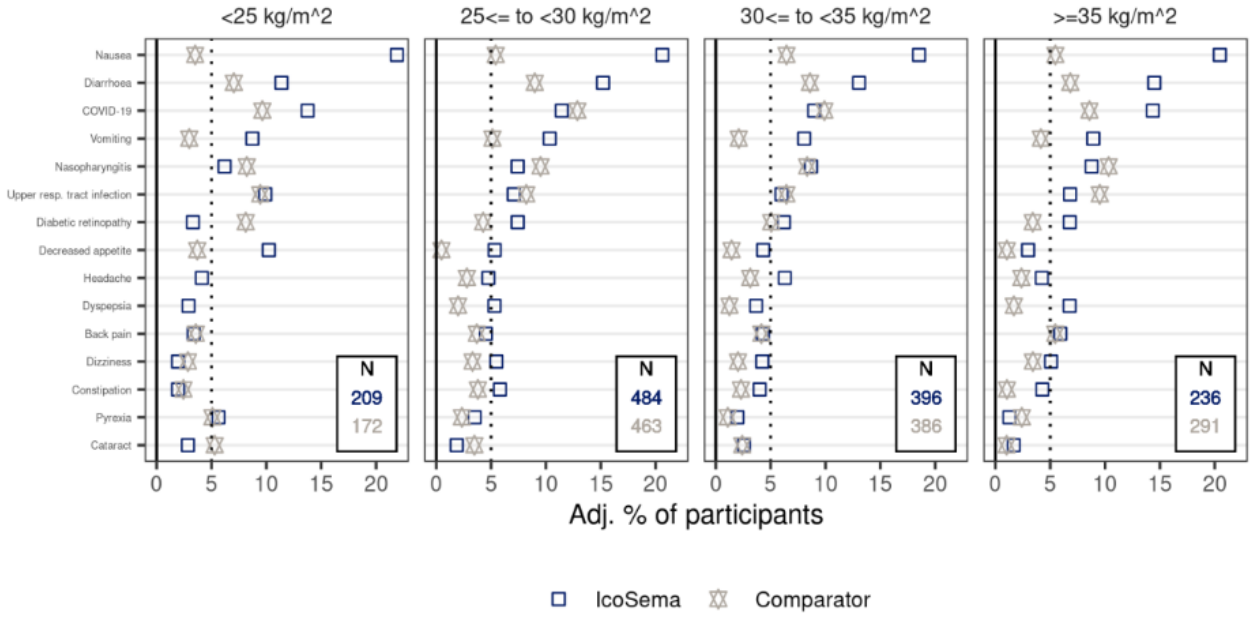
Baseline BMI

In the phase 3a pool, Kyinsu was exposed to 209 subjects with a BMI < 25 kg/m2, 484 with a BMI ≥25 to <30, 396 with a BMI ≥30 to <35 and 236 subjects with a BMI ≥ 35 kg/m2.

The most frequent AEs by baseline BMI and PT in the phase 3a pool is presented in Figure 29.

No pronounced clinically significant difference in SAEs, severity and action taken to study drug or in AEs by SOC, and by SOC and PT were observed in patients between the four different BMI groups in the Kyinsu group.

Figure 29. Adverse events by baseline BMI and PT - most frequent [>=5%] - dot plot - on-treatment - safety analysis set - phase 3a pool



Use in pregnancy and lactation

Semaglutide should not be used during pregnancy due to non-clinical reproductive toxicity findings. This is reflected in the SmPC section 4.6.

SmPC: Section 4.6 is aligned with the text for the mono-components, semaglutide (Ozempic) and insulin icodec (Awiqli).

RMP: In line with the summary of safety concerns for the two mono-components, the applicant has proposed to include use of Kyinsu during pregnancy and breastfeeding as a topic of missing information in the RMP.

Other special populations

No pronounced treatment clinically significant difference in SAEs, severity and action taken to study drug or in AEs by SOC, and by SOC and PT were observed in the subpopulations "*Race*", "*Ethnicity*", "*Region*", "*Baseline HbA1c*", '*Pre-study baseline insulin*" and "*Pre-study baseline dose*". Potential minor differences were also noted for the corresponding comparator subgroup. Furthermore, several of the sub-groups in these special populations were too small to evaluate meaningful differences and conclusions.

2.7.8.6. Immunological events

Antidrug antibody evaluations have been performed for the individual mono-components in their respective MAA, EMEA/H/C/005978/0000 for insulin icodec and EMEA/H/C/004174/0000 for semaglutide.

For Kyinsu immunogenicity was assessed throughout the clinical pharmacology study 4359 and in two of the phase 3a studies, 4591 (Kyinsu vs insulin icodec) respectively 4592 (Kyinsu vs semaglutide).

Due to different methods used for analysis of anti-drug antibodies the immunogenicity data are separately presented for participants from China regions respectively rest of the world, named below as "without China mainland". As the number of participants in the China mainland region are low these

data have been interpreted with caution and the Rapporteurs focus has been on the population "without China mainland" (n=593 respectively n=310 is study 4591 and 4592).

Anti-insulin icodec antibodies

In **study 4591** (previously basal insulin treated) approximately 20%, in the "without China mainland" group, were positive for insulin icodec antibodies at baseline. During the study 72.5% of the subjects in the Kyinsu group and 78.5% in the insulin icodec group were antibody positive at any time after baseline.

A similar proportion of the insulin icodec antibodies negative participant at baseline developed insulin icodec antibodies during treatment with Kyinsu (52.0%) as with insulin icodec (54.4%). The proportion of subjects with treatment boosted antibodies (i.e., positive at baseline and experienced a titre increase by at least two 2-fold at any time during the study) were also similar between the two treatment groups (Kyinsu: 14.6% and Insulin icodec: 15.7%). Table 67.

The immunogenicity results in study 4591 are overall comparable to insulin icodec in the previously basal insulin treated T2D population in the development program for insulin icodec (ONWARDS 2).

In **study 4592** (insulin naïve/GLP-1RA treated at baseline) almost all (99%) participants from the region "without China mainland" were antibody negative at start of treatment and 64% developed insulin icodec antibodies during treatment with Kyinsu. This is a slightly lower proportion compared to the results for insulin icodec in the insulin naïve population for insulin icodec in ONWARDS 3 (77%).

The insulin icodec titre peak appears to occur earlier for Kyinsu (around week 6-8) compared to insulin icodec (around week 10). In study 4591, a slower decline in mean antibody titres in the insulin icodec arm was noted which most probably could be explained by one subject with a steep increase of antibody titre from week 6 to the end of study (week 57).

Titre levels of insulin icodec antibodies (by quartiles) and antibody status (positivity/negativity) did not appear to be associated with efficacy parameters during the 52 weeks study durations**.** No firm conclusions could be drawn regarding correlation between change in antibody titres from baseline and efficacy parameters (due to a limited number of included cases). However, reassuringly the 26 weeks ADA findings in the development program for insulin icodec did not indicate any correlation between change in insulin icodec antibodies and efficacy parameters (EMEA/H/C/005978/0000).

Insulin icodec antibody status (positivity/negativity) did not either appear to be associated with an increased risk for injection site reactions or hypersensitivity. Neither did higher titres of insulin icodec antibodies appear to be associated with an increased risk for hypoglycaemic episodes.

Table 67. Development of treatment-induced and treatment-boosted anti-insulin icodec antibodies

	Number of participants (N)	Treatment-induced N (%)	Treatment-boosted N (%)
Study 4591 without China mainland			
IcoSema	593	307 (52.0%)	86 (14.6%)
Insulin icodec	596	323 (54.4%)	93 (15.7%)
Study 4591 China mainland			
IcoSema	51	27 (52.9%)	7 (13.7%)
Insulin icodec	48	18 (37.5%)	7 (14.6%)
Study 4592 without China mainland			
IcoSema	310	197 (64.0%)	3 (1.0%)
Study 4592 China mainland			
IcoSema	31	12 (40.0%)	0

N: Number of participants; %: Percentage of participants with any positive post baseline result among participants with any post baseline blood sample draw for antibody assessment.

Treatment-induced antibodies are defined as cases in which participants were negative at baseline and positive at any time after treatment initiation. Treatment-boosted antibodies are defined as cases in which participants were positive at baseline and experienced a titre increase by at least two 2-fold at any time during the study.

Anti-semaglutide antibodies

In study 4591, a total of 8 (1.4%) participants in the Kyinsu treatment arm tested positive for anti-semaglutide antibodies at any time during study 4591 ("without China mainland"). During the study, the percentage of participants testing positive for anti-semaglutide antibodies was between 0.2% and 0.7%.

The number of cases with anti-semaglutide antibodies were too low to allow proper assessments of associations with efficacy and safety parameters.

In the MAA for s.c. semaglutide (Ozempic; EMEA/H/C/004174/0000) it was concluded that the proportion of subjects that tested positive for anti-semaglutide antibodies varied between 1.0-2.2.% across the included trials. No effects on semaglutide exposure, HbA1c or semaglutide safety profile were identified and no association with immunogenicity related AEs were evident.

SmPC: The risk for anti-drug antibodies is reflected in SmPC section 4.4, 5.1 and 5.2.

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

No clinical studies on potential drug interactions with Kyinsu have been performed. However, interactions with other medicinal products have been assessed for the use of the mono-components insulin icodec and semaglutide.

SmPC section 4.5 for Kyinsu is based on the corresponding text/interactions for each of the two mono-components.

2.7.8.8. Discontinuation due to adverse events

Adverse events leading to drug withdrawal of randomised treatment

PTs reported for AEs leading to drug withdrawn of randomised treatment in the phase 3a pool is presented in Table 68.

Overall, in the phase 3a pool, there was a larger proportion of participants in the Kyinsu group than in the comparator group that withdrawn study drug due to adverse events (4.2% [55/1325] vs 2.2% [29/1312] participants, event rates: 6.16 vs 2.97 events per 100 PYE, respectively). The difference between the two treatment groups was larger in study 4591 with insulin icodec as comparator (5.0% vs 1.9%) whereas no difference of clinical importance was noted in study 4592 with semaglutide as comparator (2.3% vs 2.6%). The reason for withdrawals for Kyinsu was mainly GI-side effects and hyperglycaemia. Table 68. SAEs leading to withdrawals were reported by 6 participants (0.5%) with Kyinsu and 7 participants (0.5%) with the comparator. In both treatment groups, without any difference in proportions or rates, most of these events were reported within the SOC *Neoplasms benign, malignant and unspecified.*

SmPC: All of the AEs leading to withdrawal of study drug and reported by at least 2 subjects in the Kyinsu group are labelled for either of two monocomponents (semaglutide respectively insulin icodec). An exception is headache and hyperglycaemia. Headache is proposed to be labelled for Kyinsu. Hyperglycaemia is considered as lack of efficacy and therefore not qualifying as an ADR to be included in the SmPC section 4.8.

Table 68. PTs reported for AEs leading to drug withdrawn of randomised treatment (>1 participant) - on-treatment – safety analysis set - phase 3a pool.

PT	IcoSema			Comparator		
	N (Adj. %)	***E***	***Adj. R***	***N (Adj. %)***	***E***	***Adj. R***
Nausea	21 (1.6)	22	1.62	2 (0.2)	2	0.15
Diarrhoea	10 (0.8)	10	0.73	5 (0.4)	5	0.37
Vomiting	6 (0.5)	6	0.44	3 (0.2)	3	0.22
Abdominal pain	3 (0.2)	3	0.22	0	0	0
Hyperglycaemia	7 (0.5)	7	0.51	5 (0.4)	5	0.36
Headache	2 (0.2)	2	0.15	0	0	0
Rash	2 (0.2)	2	0.15	0	0	0
Fatigue	4 (0.3)	4	0.29	0	0	0
Weight increased	0	0	0	3 (0.2)	3	0.22
Wright decreased	0	0	0	2 (0.2)	2	0.14

Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

Adverse events leading to interruption of randomised treatment

The overall pattern for AEs leading to interruption of randomised treatment was similar as the pattern for AEs leading to withdrawal of treatment.

In the phase 3a pool, the proportion of participants with AEs leading to interruption of trial product and the corresponding rate of events were slightly higher for Kyinsu compared to the comparator (3.1% vs 2.3% and 5.34 vs 4.40 events per 100 PYE). The difference was larger and driven by the difference in frequencies in studies using insulin icodec (3.1% vs 1.7%) respective IGlar+IAsp (4.1% vs 3.4%) as comparators. In total in the phase 3a pool, 20 SAEs led to interruption of trial product in the Kyinsu group and 28 in the comparator groups in the phase 3a pool.

The AEs leading to interruption of Kyinsu were mainly the known GI-side effects and headache. Dizziness was also a reason for interruption of randomised treatment.

SmPC: All the indicated PTs are ADRs known and labelled for semaglutide or insulin icodec and proposed to be included in the SmPC section 4.8 also for Kyinsu.

Adverse events leading to dose reduction of randomised treatment

Across all phase 3a trials, the proportion of subjects with adverse events leading to dose reduction of randomised treatment was larger in the Kyinsu group than the in the comparator group (4.5% vs 1.4%). There was one SAE leading to dose reduction of Kyinsu and 3 SAEs in the comparator group.

Most of the ADRs leading to dose reduction were in both treatment groups GI-events (nausea, vomiting and diarrhea). In the Kyinsu group the median time of dose reduction was 45 days for events of nausea, 28.5 days for vomiting and 40.5 days for diarrhea. Reassuringly, the metabolic control remained although the dose was reduced. In total 63% (69/110) of the dose reduction events in the Kyinsu group the dose was increased again. No reoccurrence of the event occurred in ~50% of these cases.

SmPC: The text in the SmPC section 4.8 regarding this issue is considered sufficient.

2.7.9. Discussion on clinical safety

Exposure: The proposed safety population for the overall evaluation of Kyinsu is considered appropriate and accepted for the intended population. In the safety phase 3a pool, 1325 adult subjects with T2D (1369.43 PYE) have been exposed to Kyinsu in the three 52 weeks phase 3a trials The minimum number of subjects that have been exposed to Kyinsu at least 12 months (n=1207 subjects) is within the requirement for safety evaluation as stated in ICH E1.The collection of safety data has carefully been described and is considered suitably reliable. Notable is that all three trials in the phase 3a pool had open-label designs which is a limitation for evaluation of safety due to the risk for un-intended bias. The experience of patients using the FDC beyond 12 months is limited and long-term data relays on experience from the developing program for both mono-components (i.e., 78 weeks for insulin icodec from the extension phase of ONWARDS 1 [insulin naïve T2DM]) and post-marketing experience of semaglutide.

Common adverse events: The proportion of participants reporting any AE in the Kyinsu group was similar across the phase 3a studies (~78-79%). In the phase 3a pool, there were overall no new or unexpected common adverse events, not known for any of the two mono-components. Besides *Covid-19,* the most common AEs for Kyinsu was *nausea, diarrhoea* and *vomiting*. Other frequently (>= 5%) reported events of clinical importance for Kyinsu were *decreased appetite*, *headache*, *dizziness* and *diabetes retinopathy*. Besides *Covid-19,* all these PTs are known for either insulin icodec or semaglutide and proposed to be labelled in the Kyinsu SmPC section 4.8.

In study 4591 and 4593 the major differences in frequencies between Kyinsu and insulin icodec respectively IGlar+IAsp were *GI events* (see AESI below) and *decreased appetite* (5.9% vs 0.2% in study 4591 and 5.3% vs 0.3% in study 4593). In study 4592, a difference was noted for events of *headache* (5.9% vs 1.8%) and *diabetes retinopathy* (5.6% vs 2.9%). For diabetes retinopathy see AESI below.

Serious and fatal adverse events: Overall, in the phase 3a pool, SAEs were balanced between the two groups (Kyinsu: 10.6% and comparator: 9.1%). The SAE PTs were in general distributed on multiple SOCs and PTs with no apparent clustering for any treatment group (besides "nephrolithiasis", see

above). Fatal events were also balanced between the two treatment groups (0.4% in each treatment group). The majority of the fatal cases were related to EAC confirmed cardiovascular events.

Adverse events of special interest (AESI):

Hypoglycemia: Severe (category 3) hypoglycaemic episodes were reported by similar low proportions of participants and rates for Kyinsu (0-1.2%) and comparator groups 0.6-1.2% across the trials in the Phase 3a pool.

In study 4591 and 4593, severe (level 3) or clinically significant (level 2) hypoglycaemia, were reported by lower proportions and rates in the Kyinsu groups compared to the insulin icodec group in study 4591 (7.1% vs 20.8% and 13.77 vs 62.62 per 100 PYE) and compared to IGlar+IAsp in study 4593 (10.0% vs 58.5% and 21.47 vs 222.72 events per 100 PYE). Requirement of lower insulin doses in the Kyinsu groups compared to the insulin icodec respectively IGlar+IAsp might at least partly explain the lower frequencies of hypoglycaemic episodes for Kyinsu. In study 4592, the proportion and rates of severe (level 3) or clinically significant (level 2) hypoglycaemia was similar for Kyinsu and semaglutide (3.5% vs 3.8% and 4.18 vs 3.56 events per 100 PYE). However, hypoglycaemic alert values (category 1 events) were reported by a higher proportion of the participant and with a higher rate in the Kyinsu group compared to the semaglutide group (19.9% vs 6.2% and rate 59.58 vs 14.26 per 100 PYE). This might reflect the overall lower B-glucose effect in this population although, not reaching the category 2 hypoglycaemic episodes level.

The rate of clinically significant (level 2) or severe (level 3) hypoglycaemic episodes was a secondary confirmatory safety endpoint in study 4591 and 4593 and was a secondary supportive safety endpoint in study 4592. A statistically significant difference in favour of Kyinsu was observed in the rate of level 2 or level 3 hypoglycaemic episodes between Kyinsu and insulin icodec in study 4591 (ETR: 0.22 [0.14; 0.36]) and between Kyinsu and IGlar+IAsp in study 4593 (ETR: 0.12 [0.08; 0.17]).

Reassuringly most of the participants (~99%) in both Kyinsu and comparator groups had none or maximum 5 severe (level 3) or clinically significant (level 2) hypoglycaemic episodes and the occurrence of these episodes appears stable over time (up to week 57) for Kyinsu. In all three studies these events were more common at day 2-3 without any large difference compared to days later in the week.

The rate of clinically significant (level 2) or severe (level 3) hypoglycaemic episodes was a secondary confirmatory safety endpoint in study 4591 and 4593 and was a secondary supportive safety endpoint in study 4592. A statistically significant difference in favour of Kyinsu was observed in the rate of level 2 or level 3 hypoglycaemic episodes between Kyinsu and insulin icodec in study 4591 (ETR ratio: 0.22 [0.14; 0.36]) and between Kyinsu and IGlar+IAsp in study 4593 (ETR ratio: 0.12 [0.08; 0.17]). In study 4592, the estimated number of level 2 and 3 hypoglycaemic episodes was low and similar for Kyinsu and semaglutide. See further in Safety section in this report regarding hypoglycaemic events.

Hyperglycaemia: In study 4591 and 4593, the PT hyperglycaemia was reported in a higher proportion of participants for Kyinsu (3.3% respectively 3.8%) than for insulin icodec (1.2%) respectively IGlar+ IAsp (0.6%). In study 4592 the proportion of subjects with events of hyperglycaemias was only slightly higher for Kyinsu (3.5%) than for semaglutide (2.9%). Most of the hyperglycaemic events occurred within the first 12 weeks. This pattern might reflect the (efficacy) findings that the mean fasting pre-breakfast SMPG for Kyinsu peaked at week 2 and then declined to baseline around week 10. See also efficacy part. In total 32 of the 57 (56%) events in the Kyinsu group were classified as mild, 23 (40%) as moderate and 2 (3.5%) as severe. DKA AEs were rare without any difference between the two treatment groups.

Gastrointestinal adverse events (GIAE)*:* The overall most frequently reported GIAE PTs in the Kyinsu group in the phase 3a pool, were *nausea* (20.1%), *diarrhoea* (13.8%) and *vomiting* (9.1%). Most of

the GI disorders events in both treatment groups were reported as mild (Kyinsu: 73% and comparator: 80%) or moderate (Kyinsu: 26% and comparator: 19%). The proportion of subjects that reported GIAE increased during the initial 8 weeks of treatment and the median duration of the three most common GIAE varied from 2 days (vomiting) to 4 days (diarrhoea) in both treatment groups. Normally for semaglutide (monotherapy) a development of tolerance for GI-events leads to a reduced prevalence over time which is not noted for Kyinsu in study 4591 and 4593 (GLP1-RA naïve). In these studies, the proportion of participants with GI events was stable ≥10% over time.

Although, most of the events were mild, GI events are the major reason for withdrawn, interruption and decrease of study drug.

In study 4591 and 4593, the proportion of participants with GIAE was, as expected, higher for Kyinsu compared to insulin icodec (47.0% vs 21%) and IGlar+IAsp (43.5% vs 18.3%). Whereas In study 4592, the proportion and rate of overall GI events for Kyinsu was slightly lower compared to semaglutide (31.4% vs 34.2% and 67.09 vs 88.56 events per 100 PYE). This difference might well reflect the lower dose of semaglutide (0.5 mg) in the Kyinsu arm compared to the comparator treated with 1.0 mg semaglutide.

Overall, the SmPC section 4.4 (warning for subjects with impaired renal function) and 4.8 is considered sufficiently reflect the risk for GI events.

Cardiovascular disorders: Overall, no clinically significant differences regarding EAC-confirmed cardiovascular events between Kyinsu and the comparators were noted. Increased pulse rate is a known side effect of GLP-1 RA (reflected in SmPC section 4.8). In the phase 3a pool, a higher proportion of participants and rate of adverse events related to increased heartrate were reported for Kyinsu than for comparators (1.3% vs 0.5% and 1.28 vs 0.43 events per 100 PYE).

Diabetic retinopathy: An increased risk for diabetes retinopathy complications primarily in patients with retinopathy at baseline treated with s.c. semaglutide concomitant with insulin was identified in the T2D CVOT SUSTAIN 6. Thus, there is a potential risk that use of Kyinsu could increase the risk for diabetic retinopathy complications, mainly in patients with retinopathy at baseline, compared to semaglutide or insulin treatment alone. In the phase 3a Kyinsu studies participants with uncontrolled and potentially unstable diabetic retinopathy or maculopathy were to be excluded.

In the phase 3a pool a higher proportion of subjects reported AEs related to diabetic retinopathy (predefined MedDRA search) respectively the PT "diabetic retinopathy" in the Kyinsu group than in the comparator group (9.2% vs 8.1%) respectively (6.4% vs 4.8%).

Among subjects without diabetic retinopathy or related conditions in medical history at baseline (~75% of the subjects), the difference in the PT diabetes retinopathy was 5.2% vs 3.9%. Most of these events were mild (Kyinsu 82% and comparator 91%). A slightly higher proportion of the events in the Kyinsu group were reported as moderate or severe compared to the comparator group (18% vs 9.3%).

Among subjects with diabetic retinopathy (or related conditions) at baseline (~25% of the subjects) diabetes retinopathy (PT) was reported by 10.2% for Kyinsu and 7.6% for comparator. Data presented do not indicate an increased risk for diabetes retinopathy complications in subjects with diabetes retinopathy at baseline between the two treatment groups. Longer diabetes durations and rapid improvements in glycaemic control (HbA1c) are risk factors for development and/or worsening of diabetes retinopathy. Correspondingly, longer diabetes durations and larger HbA1c (%) reduction from baseline to week 26, were (in both treatment groups) noted for subjects that reported any AEs related to diabetic retinopathy events during the trials. However, an isolated effect for semaglutide could not be excluded. The risk for diabetes retinopathy complications, both in subjects with and without diabetes retinopathy at start of treatment with Kyinsu, is now reflected in SmPC section 4.4 and 4.8. The topic diabetes retinopathy complications are categorised as an important identified risk and is

followed in the ongoing category 3 PASS (FOCUS study). In the meantime, cases without diabetes retinopathy that report diabetes retinopathy after treatment with Kyinsu had started, will be followed in the Kyinsu PSURs.

Acute pancreatitis*:* Pancreatitis is a known risk for GLP-1RA, and the risk is (as for semaglutide mono-component products) reflected in the proposed SmPC (section 4.4 and 4.8) for Kyinsu. Overall, 0.2% in the Kyinsu group vs none in the comparator groups reported events of acute pancreatitis. No new safety concerns are revealed by the presented data. Increased lipase and amylase are known effects of semaglutide. However, pancreatic enzymes were not included as protocol-required safety laboratory assessments for the phase 3 studies but are proposed to be labelled in SmPC section 4.8 for Kyinsu based on previous results for semaglutide.

Gallbladder related disorders: Cholelithiasis is a known risk for semaglutide (i.e., GLP-1RA class effect). Cholelithiasis and related events were reported by similar proportions of participants and rates for Kyinsu as for the comparators (0.8% vs 0.9%). Overall, the reported events of Gallbladder related disorders revealed no new safety concerns. The risk is considered sufficiently reflected in the SmPC section 4.8.

Lipodystrophy and cutaneous amyloidosis: In the phase 3a pool, one event (PT) of "Lipodystrophy acquired" and one event (PT) of "Cutaneous amyloidosis" are reported for Kyinsu. These ADRs are known for and also reflected in the SmPC for insulin products in general.

Immunogenicity*:* Positivity for insulin icodec antibodies any time after baseline (up to week 52) was reported with similar high frequencies for Kyinsu (~70%) as for insulin icodec as mono-component (78.5%). The immunogenicity results are similar as noted for insulin icodec in the previously basal insulin treated T2D subjects in the development program for insulin icodec (ONWARDS 2) assessed in procedure EMEA/H/C/005978/0000.

Titre levels of insulin icodec antibodies (by quartiles) and antibody status (positivity/negativity) did not appear to be associated with efficacy parameters during the 52 weeks study durations**.** No firm conclusions could be drawn regarding correlation between change in antibody titres from baseline and efficacy parameters (due to a limited number of included cases). The 26 weeks ADA findings in the development program for insulin icodec did not indicate any correlation between change in insulin icodec antibodies and efficacy parameters (EMEA/H/C/005978/0000).

Insulin icodec antibody status (positivity/negativity) did not appear to be associated with an increased risk for the injection site reactions or hypersensitivity. Neither did higher titres of insulin icodec antibodies appear to be associated with an increased risk for hypoglycaemic episodes.

Anti-semaglutide antibody formation was low (1.4%). The number of cases were too low to allow proper assessments of associations with efficacy and safety parameters.

Medication errors: In the phase 3a, medication errors (MEs) were reported by ~2% of the participants in the Kyinsu group. Most of the ME cases concerns incorrect dose administration, overdose and underdose. Approximately, 1/3 of the ME were in in both treatment groups were reported during the first 30 days (defined as "switched" period). The main adverse reaction resulting from these events was Level 1 hypoglycaemic episodes. Medication error during switch from other injectable diabetes therapy is included as an important potential risk in the RMP and the risk for/avoidance of ME are reflected in the SmPC section 4.2 and 4.4.

The remaining AESI i.e., gallbladder related disorders, acute renal failure events, hepatic events, hypersensitivity reactions, injection site reactions, and neoplasm did not reveal any new safety concerns and are considered sufficiently reflected in the SmPC and /or the RMP.

Safety in special populations

Age: The elderly population (≥ 65 years) is sufficient and in line with the ICH E7 guideline. Based on the presented data no new safety concern is revealed for use of Kyinsu in elderly compared to the younger populations. A as often noticed in the elderly population there are some differences in AE profile which also was noted in the Phase 3a pool. Most of these differences are also noted for the comparator. Currently, the differences are not considered clinically significant.

Renal impairment: Kyinsu should not been used in end-stage renal disease and more frequent glucose monitoring is recommended subject with renal impairment (reflected in SmPC section 4.2). For participants in the Kyinsu group with moderate or severe renal impairment at baseline, no pronounced treatment difference of clinical significance in AEs by SOC, and by SOC and PT were observed across baseline renal function groups.

Hepatic impairment: No pronounced clinically significant difference in SAEs, severity and action taken to study drug or in AEs by SOC, and by SOC and PT were observed in the subpopulations.

Other special populations: No pronounced clinically significant difference in SAEs, severity and action taken to study drug or in AEs by SOC, and by SOC and PT were observed in the subpopulations "*Sex"*, "BMI", "*Race*", "*Ethnicity*", "*Region*", "*Baseline HbA1c*", '*Pre-study baseline insulin*" and "*Pre-study baseline dose*".

Action taken to study drug due to AEs

Overall, in the phase 3a pool, there was a larger proportion of participants in the Kyinsu group than in the comparator group that withdrawn study drug (~4% vs ~2%;), interrupted study drug (3.1% vs 2.3%) and reduced dose of study drug (6.0% vs 4.1%; due to AEs. GI events was the major reason for withdrawn, interruption and decrease of study drug.

2.7.10. Conclusions on the clinical safety

No new or unexpected adverse reactions were noted with the fixed combination of insulin icodec and semaglutide compared to the two mono-components. The most common ADRs for Kyinsu were hypoglycaemia, GI events (nausea, diarrhoea and vomiting), decreased appetite, headache, dizziness and diabetes retinopathy.

Compared to semaglutide, use of Kyinsu was associated with similar frequencies of gastrointestinal ADRs, similar frequencies of severe or clinically significant hypoglycaemic events, and slightly higher hyperglycaemic events. Compared to insulin icodec and IGlar+IAsp, use of Kyinsu was associated with higher frequencies of gastrointestinal ADRs, and higher proportion of hyperglycaemic events, but lower frequencies of severe or clinically significant hypoglycaemic events.

These safety concerns are adequately reflected in the SmPC and will be monitored through routine pharmacovigilance activities. The information is reflected in the relevant sections on the Package Leaflet, that also contains a summary of the risk factors, its symptoms and guidance on how to act in case of hypoglycaemia and hyperglycaemia.

There is a known increased risk for complications of diabetes retinopathy in patients with retinopathy when treatment with s.c. semaglutide concomitant with insulin is introduced. In the phase 3a pool, a higher proportion of participants both also without diabetic retinopathy at baseline reported diabetic retinopathy (PT) in the Kyinsu group than in the comparator group after 52 weeks treatment. This safety concern is adequately reflected in the SmPC section 4.4 and 4.8 and will be further evaluated in the ongoing FOCUS study (category 3 PASS). In the meantime, cases without diabetes retinopathy

that reports diabetes retinopathy after treatment with Kyinsu had started, will be followed in the Kyinsu PSURs.

2.8. Risk Management Plan

2.8.1. Safety concerns

Table 69. SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Diabetic retinopathy complications[1]
Important potential risks	Medullary thyroid cancer[1] Pancreatic cancer[1] Medication error due to mix-up with other injectable diabetes treatments[2] Medication error during switch from other injectable diabetes treatments [2]
Missing information	Pregnancy and breastfeeding[1, 2] Patients with severe hepatic impairment[1]

[1] Safety concern included in the EU RMP (version 9.1) for semaglutide. [2] Safety concern included in the EU RMP (version 1.0) for insulin icodec.

2.8.1.1. Discussion on safety specification

Important identified risk:

- *Diabetic retinopathy complications*

The risk of diabetic retinopathy complications was identified for the mono-component semaglutide s.c. based on the findings from the CVOT (SUSTAIN 6), where a total of 3,297 participants with T2D and high cardiovascular risk were included. In the CVOT (SUSTAIN 6), participants with known proliferative retinopathy or maculopathy requiring acute treatment were not excluded.

This safety concern also includes subjects without diabetes retinopathy at baseline concomitant treated with semaglutide and insulin (icodec).

Important potential risks

- *Medullary thyroid cancer*

Medullary thyroid cancer (MTC) is an important potential risk for the GLP-1 RA products based on nonclinical findings of C-cell tumours in rodents. The rodent C-cell tumours are caused by a non-genotoxic, specific GLP-1 receptor mediated mechanism to which rodents are particularly sensitive. The relevance for humans is considered to be low but cannot be completely excluded.

- *Pancreatic cancer*

Pancreatic cancer is included as an important potential risk for semaglutide containing products, based on the EC regulation 726/2004 Article 5(3) referral procedure in 2013 (EMEA/H/A-5(3)/1369).

- *Medication error due to mix-up with other injectable diabetes treatments*

Administration of a wrong product can occur due to a mix-up by the patient, a mix-up by a healthcare professional in a clinical setting, a prescription error, or a dispensing error at the pharmacy. This can lead up to overdose, potentially resulting in hypoglycaemia, or underdose, potentially resulting in hyperglycaemia.

Medication error-related adverse events were reported as part of the phase 3a programme. While characterising this risk, the value of this data is limited since clinical studies do not represent real-world clinical practice. For instance, the appearance of the device (labelling and cartridge colour) used in clinical studies is expected to be different from the actual product post-authorisation. Considering these limitations, post- authorisation data will help characterize this risk.

- *Medication error during switch from other injectable diabetes treatments*

Medication errors may occur due to patient's unawareness of difference between Kyinsu and other injectable diabetes treatments (insulin or GLP-1 RAs). During switch from daily injectable diabetes treatments to weekly Kyinsu treatments, medication errors such as overdose or dosing errors (example, due to lack of awareness around the different dosing terminologies or dosing schedule) can occur. These errors might result in hypoglycaemia and/or other clinical consequences.

Topics of missing information

- *Pregnancy and breastfeeding*

Kyinsu has not been studied in pregnant or lactating women, and the potential risk of Kyinsu treatment during pregnancy and lactation is unknown. No pregnancies were reported in the study period. For semaglutide, nonclinical observations of pregnancy losses and malformations in rats, rabbits and cynomolgus monkeys have been reported with the use of semaglutide. Although the findings are considered unlikely to be of relevance to humans, there is no conclusive evidence supporting a different safety profile in this population.

- *Patients with severe hepatic impairment*

Kyinsu has not been studied in patients with severe hepatic impairment, and the safety profile of Kyinsu (and semaglutide) in this population is unknown. Patients with pronounced hepatic impairment (defined as ALT ≥ 2 .5 times or Bil > 1 .5 times upper normal limit at screening) were excluded from the clinical studies with Kyinsu. In the phase 3a pool, 106 participants with impaired liver function (defined as defined as either AST >UNL or Bil >UNL) were included.

2.8.1.2. Conclusions on the safety specification

Having considered the data in the safety specification the safety concerns listed by the applicant are considered appropriate.

2.8.2. Pharmacovigilance plan

2.8.2.1. Routine pharmacovigilance activities

The applicant reported they aim to minimise the variable quality of the spontaneously reported medically confirmed medication errors. Where information is limited or ambiguous, follow-up attempts with a healthcare professional will be made to ascertain the missing information. There is a series of questions for use in retrieving information required to maximise the evaluation of the data across all of the applicant's insulins or products with insulin as a component. The list of questions is attached in Annex 4 of the RMP and is expected to be developed over time in response to feedback from health authorities and health care professionals. Data retrieved using the follow-up questionnaires will help the applicant in better characterising the risks to patients for "*Medication error due to mix-up with other injectable diabetes treatments"* and "*Medication error during switch from other injectable diabetes treatments*".

No other forms of routine pharmacovigilance activities are proposed.

The applicant has committed to follow new cases of diabetes retinopathy with Kyinsu treatment in future PSURs.

2.8.2.2. Summary of additional PhV activities

No ongoing or planned additional pharmacovigilance activities for Kyinsu are proposed.

Safety findings from the following PASS for the semaglutide mono-component will be assessed for their relevance to Kyinsu.

Table 70.

Safety Concern	PASS
Diabetic retinopathy complications	NN9535-4352: Long-term effects of semaglutide on diabetic retinopathy in participants with T2D [FOCUS])
Pancreatic cancer	NN9535-4447: Epidemiological assessment of the risk for pancreatic cancer associated with the use of semaglutide in patients with T2D
Medullary thyroid cancer	Study MTC-22341: Medullary Thyroid Carcinoma Surveillance Study: a case-series registry

Abbreviations: GLP-1 RA = glucagon-like peptide receptor agonist, PASS = post authorization safety study, s.c. =subcutaneous, T2D = type 2 diabetes.

2.8.2.3. Overall conclusions on the PhV Plan

The PRAC, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

2.8.3. Plans for post-authorisation efficacy studies

There are currently no plans for post-authorisation efficacy studies for Kyinsu, nor have any post-authorisation efficacy studies been imposed.

2.8.4. Risk minimisation measures

2.8.4.1. Routine risk minimisation measures

The applicant described routine risk minimisation measures for all safety concerns specified in the RMP.

2.8.4.2. Summary of additional risk minimisation measures

Table 71. Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Diabetic retinopathy complications	**Routine risk minimisation measures:** SmPC Sections 4.4 and 4.8 and PL Sections 2 and 4. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Patients that do not have a medical history of diabetic retinopathy but develop diabetic retinopathy after initiation of insulin icodec/semaglutide (Kyinsu®) treatment will be monitored in the PSURs **Additional pharmacovigilance activities:** No additional PV activities (including PASS) are planned for insulin icodec/semaglutide (Kyinsu®). If any safety findings arise from the PASS NN9535-4352 (Long-term effects of semaglutide on diabetic retinopathy in participants with T2D [FOCUS]) for the semaglutide mono-component, these will be assessed for their relevance to insulin icodec/semaglutide (Kyinsu®).
Important potential risks		
Medullary thyroid cancer	**Routine risk minimisation measures:** Non-clinical findings are presented in the SmPC Section 5.3 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** No additional PV activities (including PASS) are planned for insulin icodec/semaglutide (Kyinsu®). If any safety findings arise from the PASS MTC-22341 (Medullary Thyroid Carcinoma Surveillance Study: a case-series registry) for the semaglutide mono-component, these will be assessed for their relevance to insulin icodec/semaglutide (Kyinsu®).
Pancreatic cancer	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** No additional PV activities (including PASS) are planned for insulin icodec/semaglutide (Kyinsu®).

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
		If any safety findings arise from the PASS NN9535-4447 (Epidemiological assessment of the risk for pancreatic cancer associated with the use of semaglutide in patients with T2D) for the semaglutide mono-component, these will be assessed for their relevance to insulin icodec/semaglutide (Kyinsu®).
Medication error due to mix-up with other injectable diabetes treatments.	**Routine risk communication:** Section 4.4 of the SmPC and Section 2 and Section 3 of the PL. **Additional risk minimisation measures:** A patient guide will be distributed at the time of launch and will be distributed for the first 2 years to minimise the risk of medication errors due to mix-up with other injectable diabetes therapy (see Annex 6). The patient guide will describe: Information to always check the product label before each injection to avoid accidental mix-ups between insulin icodec/semaglutide (Kyinsu®) and other injectable diabetes treatments.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Standardised follow-up questions (see Annex 4). **Additional pharmacovigilance activities:** None
Medication error during switch from other injectable diabetes treatments.	**Routine risk communication:** Sections 4.2 and 4.4 of the SmPC **Additional risk minimisation measures:** A patient guide will be distributed at the time of launch and will be distributed for the first 2 years to minimise the risk of medication errors during switch from other injectable diabetes therapy (see Annex 6). The patient guide will describe: • Information stating that the dose adjustment of insulin icodec/semaglutide (Kyinsu®) is different from other injectable diabetes treatments. • Information to strictly adhere to weekly dosing regimen as prescribed by the healthcare provider. • Information to check how many dose steps were selected before injecting the weekly dose. • Information to always use the dose counter and the dose pointer to select the dose. Do not count the pen clicks to select dose steps.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Standardised follow-up questions (see Annex 4). **Additional pharmacovigilance activities:** None
Missing information		
Pregnancy and breastfeeding	**Routine risk minimization measures:** SmPC Section 4.6 and PL Section 2. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Patients with severe hepatic impairment	**Routine risk minimisation measures:** SmPC Sections 4.2 and 5.2.	**Routine pharmacovigilance activities beyond adverse reactions reporting and**

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: None	**signal detection:** None **Additional pharmacovigilance activities:** None

Abbreviations: PL = product leaflet; SmPC = Summary of Product Characteristics.

The applicant proposed aRMM in form of patient guide in order to minimize important potential risks *"Medication error due to mix-up with other injectable diabetes treatments"* and *"Medication error during switch from other injectable diabetes treatments"*. The proposed Patient Guide will remind patients about appropriate steps which need to be taken on order to appropriately dose and administer the product as well as reminder to check product label before application in order to avoid mix-up with other injectable therapies. Overall, the format of proposed aRMMs is considered acceptable.

2.8.4.3. Overall conclusions on risk minimisation measures

The PRAC having considered the data submitted was of the opinion that:

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

2.8.5. PRAC outcome (July 2025)

PRAC discussed the assessment of RMP version 0.2 for Kyinsu (insulin icodec/semaglutide) submitted as part of this initial MAAs in the second phase of assessment and agreed on the following comments and recommendations:

Safety specification:

The PRAC noted the CHMP Rapporteur's assessment of the safety specifications and agreed that:

- *Aspiration in association with general anaesthesia and deep sedation* and *Patients with gastroparesis* should not be added to the RMP summary of safety concerns at this stage since these are pending the final assessment of the separate procedures for Kayshild and Ozempic/Rybelsus.
- The missing information *Pregnancy and lactation* should be better reworded to *Pregnancy and breastfeeding.*

The second point is raised for the due consideration of the CHMP Rapporteur's team in the lead for the assessment of the RMP safety specifications.

Pharmacovigilance plan:

The PRAC fully agreed with the PRAC Rapporteur's assessment of the Pharmacovigilance plan consisting of routine pharmacovigilance only among which follow-up questionnaires will be in place to further characterise the important potential risks of *Medication error due to mix-up with other injectable diabetes therapy* and *Medication error during switch from other injectable diabetes therapy.*

Risk minimisation measures:

The PRAC fully endorsed the PRAC Rapporteur's assessment of the risk minimisation measures and concurred that additional risk minimisation measures in a form of a patient's guide are warranted to

mitigate the important potential risks of *Medication error due to mix-up with other injectable diabetes therapy* and *Medication error during switch from other injectable diabetes therapy*, in light of the current knowledge. The PRAC was also of the view that the applicant should remove the reference to a 2-year commitment for the availability of the patient guide following product launch, since there is currently no data to support such timeline to adequately minimize the risk of medication errors.

2.8.6. Conclusion

The CHMP considers that the risk management plan version 0.5 is acceptable.

2.9. Pharmacovigilance

2.9.1. 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.

2.9.2. 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 request alignment of the PSUR cycle with the international birth date (IBD) of semaglutide, one of the component active substances of Kyinsu. The IBD of semaglutide is 5 December 2017. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.10. Product information

2.10.1. 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.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Kyinsu (insulin icodec / semaglutide) is included in the additional monitoring list as the active substances are biological.

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

Kyinsu is intended to be used in the following indication:

"Treatment of adults with type 2 diabetes mellitus insufficiently controlled on basal insulin or glucagon-like peptide 1 (GLP-1) receptor agonists as an adjunct to diet and exercise in addition to oral antidiabetic medicinal products. For study results with respect to combinations, effects on glycaemic control, and the populations studied, see sections 4.4, 4.5 and 5.1."

Kyinsu is a fixed dose combination for weekly subcutaneous administration of insulin icodec and semaglutide. Insulin icodec is a once-weekly basal insulin and semaglutide is a once-weekly GLP-1 agonist, both approved for treatment of adults with type 2 diabetes.

3.1.1. Disease or condition

Type 2 diabetes mellitus is characterised by insulin resistance, impaired insulin secretion, and increased hepatic glucose output due to glucagon dysregulation resulting in chronic 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. Estimates were not separated by diabetes type; however, the overwhelming majority of people with diabetes in 2021 were type 2 diabetes and the increases to 2045 are projected to be mainly type 2 diabetes (IDF 2021).

3.1.2. Available therapies and unmet medical need

The consensus statement from ADA and the EASD for treatment of T2D emphasises individualised care and lifestyle changes as well as pharmacotherapy, while balancing the risks and benefits of each intervention. The person-centred diabetes care should be achieved by managing glycaemic control, weight, cardiovascular risk factors, and the need for cardiorenal protection, with equal importance. Metformin has for many years been the recommended first-line glucose-lowering therapy for the management of type 2 diabetes. However, there is ongoing acceptance that other approaches may be appropriate. Due to the progressive nature of the disease, many people with T2D will in addition to lifestyle modification and treatment with one or more oral antidiabetic agents require the addition of one or more injectable agents, including insulin and/or GLP-1 RA. Treatment intensification increases the complexity and the burden, which are known to negatively impact persistence and adherence. Furthermore, insulin treatment is associated with increased risk of hypoglycaemia and weight gain, which also contributes to poor adherence and therapeutic inertia, i.e., failure to timely initiate or intensify treatment when treatment goals are not met. GLP-1 RA reduces body weight and improves glycaemic control. The combination of a basal insulin analogue and GLP-1 RA may be a way to reduce the burden and complexity of treatment (ADA/EASD 2022). Fixed dose combinations of such compounds have previously been approved in the EU.

3.1.3. Main clinical studies

The efficacy data supporting this application are derived from the three phase 3a studies:

Study 4591 (COMBINE 1)

A 52-week multicentre, randomised (1:1), open-label study (n=1,291) comparing the efficacy and safety of once weekly Kyinsu (700 units/mL+2 mg/mL) and once weekly insulin icodec, both treatment arms with or without oral anti-diabetic drugs, in participants with type 2 diabetes inadequately controlled with daily basal insulin.

Study 4592 (COMBINE 2)

A 52-week multicentre, randomised (1:1), open-label study (n=683) comparing the efficacy and safety of once weekly Kyinsu (700 units/mL+2 mg/mL) and once weekly semaglutide (1.34 mg/mL), both treatment arms with or without oral anti-diabetic drugs, in participants with type 2 diabetes inadequately controlled with a GLP-1 receptor agonist.

Study 4593 (COMBINE 3)

A 52-week multicentre, randomised (1:1), open-label study (n=679) comparing the efficacy and safety of once weekly Kyinsu (700 units/mL+2 mg/mL) and daily insulin glargine (100 units/mL) combined with insulin aspart (100 units/mL), both treatment arms with or without oral anti-diabetic drugs, in participants with type 2 diabetes inadequately controlled with daily basal insulin.

Study 4593 is per se not pivotal for the sought indication.

A treat-to-target approach was applied for Kyinsu in all COMBINE studies as well for the insulin comparators. The titration was based on the last 3 fasting SMPG values prior to dose adjustment.

Table 72. Starting dose, titration, and maximum dose

	Starting dose	**Titration/dose escalation**	**Max. dose**
IcoSema	40 dose steps (40 U insulin icodec and 0.114 mg of semaglutide)	±10 dose steps	350 dose steps (350 U insulin icodec and 1 mg semaglutide)
Insulin icodec	Total daily basal insulin dose before randomisation x 7 x 1.5	±20 U	N/A
Semaglutide	0.25 mg	Increased to 0.5 mg after 4 weeks. Increased to 1 mg after at least 4 additional weeks.	1 mg
Insulin glargine	According to local label	±3 U	N/A
Insulin aspart	4 units per main meal	No titration the first 8 weeks. Then ±1 U twice weekly based on pre-prandial or bedtime SMPGs of the last 3 days.	N/A

Abbreviations: IcoSema=fixed dose regiment insulin icodec/semaglutide.

3.2. Favourable effects

Study 4591 investigated the add-on effect of semaglutide in T2DM patients previously treated with basal insulin, and study 4592 the add-on effect of insulin icodec in patients previously treated with GLP-1 RA. Study 4593 had a different approach and compared Kyinsu with IGlar+IAsp and is per se not pivotal for the sought indication.

The primary hypothesis was that Kyinsu was superior to insulin icodec (study 4591) and to semaglutide (study 4592) and was non-inferior to IGlar+IAsp (study 4593) in terms of mean HbA_{1c} change from baseline to week 52. The non-inferiority margin was pre-specified at 0.3%-point. The

primary endpoint was met in all studies (study 4591: -0.66% [-0.76; -0.57], study 4592: -0.44% [-0.56; -0.33] and study 4593: -0.06% [-0.22; 0.09]).

Multiple testing procedure was in place for "change in body weight" (study 4591 and 4593) and "weekly total insulin dose" (study 4593), which were confirmatory secondary endpoints. The number of level 2 or level 3 hypoglycaemic episodes was a confirmatory endpoint in study 4591 and 4593. Other secondary endpoints were not corrected for multiplicity.

Kyinsu demonstrated superiority with respect to mean change in body weight compared to insulin icodec in study 4591 (ETD: -5.59 kg [-6.14; -5.04]) and to IGlar+IAsp in study 4593 (ETD: -6.72 kg [-7.58; -5.86]). In insulin naïve patients (study 4592), body weight increased in the Kyinsu group (0.84 kg) and decreased in the semaglutide group (-3.7 kg) and the estimated treatment difference was 4.54 kg [-0.12; 1.04].

In 4593, superiority of Kyinsu versus IGlar+IAsp was confirmed for the key secondary endpoint mean weekly total (basal + bolus) insulin dose from week 50 to 52 (ETD: -270 U [-303; -236]). The mean *weekly basal insulin dose f*rom week 50 to 52 was numerically lower for Kyinsu (196 U) compared to IGlar+IAsp (285 U). In study 4591, mean *weekly basal insulin dose* from week 50 to 52 was numerically lower for Kyinsu compared to insulin icodec (ETD: -172 U [-190; -155]).

In study 4592, the mean semaglutide dose of the semaglutide component in Kyinsu ranged from 0.48 to 0.56 mg per week across studies. For participants randomised to semaglutide the actual mean weekly semaglutide dose was 0.99 mg.

In 4592, the mean change in FPG from baseline to end of treatment was numerically larger for Kyinsu than for semaglutide (EDT: -1.07 mmol/L [-1.37; -0.76]). The treatment differences between Kyinsu and comparators in mean FPG reductions was -0.14 mmol/L [-0.38; 0.10] in study 4591 (comparator: insulin icodec) and 0.02 mmol/L [-0.34; 0.38] in study 4593 (comparator: IGlar+IAsp).

Time in target range (TIR) 3.9–10.0 mmol/L, time below range (TBR) <3.0 mmol/L and time above range (TAR) >10.0 mmol/L were supportive secondary endpoints in study 4591 and study 4593. Patients were equipped with a CGM device from week 48 to 52. The CGM data in study 4591 and 4593 were blinded for both subjects and investigators. 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. In study 4591, subjects in the Kyinsu group compared to the insulin icodec group spent more time in target range (73.3% versus 61.8%) and less time above range >10 mmol/L (23.3% vs 37.0%). TBR was <1% and no important differences between treatment groups. In study 4593, there were no important differences between the treatment groups in TIR or TAR and TBR was <1%.

Patient reported outcome (PRO) measures were included as a supportive endpoint in study 4593. The change in DTSQ total score was numerically greater for Kyinsu (31.28) compared to IGlar+IAsp (28.28) and ETD was 3.00 [1.98; 4.02].

In study 4591 and 4593, the responder rate of achieving HbA_{1c} <7% without weight gain and without either level 2 or 3 hypoglycaemia was numerically higher for Kyinsu (50-56%) compared to insulin icodec or IGlar+IAsp (6-10%). In insulin naïve patient (study 4592), the responder rates of achieving HbA_{1c} target without weight gain and without either level 2 or 3 hypoglycaemia was numerically lower for Kyinsu (30.2%) compared to semaglutide (40.5%).

3.3. Uncertainties and limitations about favourable effects

The starting dose of insulin icodec (40 U) for Kyinsu is lower than the starting dose of insulin icodec for the monocomponent Awiqli (70 U). For Awiqli an additional single dose of 50% insulin icodec is recommended for patients switching from daily basal insulin.

In patients previously treated with daily basal insulin, fasting SMPG values increased when initiating treatment with Kyinsu. SMPG values returned to baseline at week 7-9 and reached glycaemic target at week 14-18. Additional antidiabetic treatment, including non-randomised insulin, was needed in approximately 10% of the subjects in the Kyinsu arm in studies 4591 and 4593, of which most treatment was initiated during the first 12 weeks of treatment. The risk of increases in fasting SMPG values when switching from daily basal insulin to Kyinsu has been adequately reflected in section 4.4 of the SmPC. In addition, section 4.2 has been amended with further guidance on adjustment of antidiabetic medication for patients switching from daily basal insulin to Kyinsu.

Across the COMBINE studies, subjects that received an Kyinsu dose ≥350 dose steps (8.1%) did not achieve the treatment goal of HbA1c <7. Information has been included in section 4.2 that the maximum recommended weekly dose for Kyinsu is 35O dose steps.

In insulin naïve patients, body weight decreased in the semaglutide group whereas weight increased in the Kyinsu group. The proportion of patients of achieving HbA_{1c} <7% without weight gain and without level 2 or 3 hypoglycaemia was numerically lower for Kyinsu (30.2%) compared to semaglutide (40.5%). The starting dose of semaglutide is below the lowest dose of semaglutide shown to be efficient (0.144 mg compared to 0.25 mg). Therefore, the full potential of semaglutide in Kyinsu may not being exploited. A responder analysis combining HbA1c target, weight reduction and hypoglycaemia events has been reflected in the SmPC.

The experience from the CV outcomes trial performed with semaglutide can be of interest for the prescriber, and it can therefore be acceptable to include the most important results in section 5.1 for Kyinsu.

3.4. Unfavourable effects

Gastrointestinal adverse events (GIAE)*:* The most common adverse events associated with Kyinsu are gastrointestinal side effects. In the GLP-1RA naïve (pre-basal insulin treated) population*,* the proportion of participants with GIAE was higher for Kyinsu compared to insulin icodec (47.0% vs 21%; study 4591) respectively IGlar+IAsp (43.5% vs 18.3%; study 4593). In the pre-GLP1-RA (basal insulin naïve) population the proportion of participants with and rate of GIAE were slightly lower for Kyinsu compared to semaglutide (31.4% vs 34.2% and 67.09 vs 88.56 events per 100 PYE; study 4592).

The most frequently reported GIAE PTs in the Kyinsu group (phase 3a pool) were*, nausea* (20.1% vs 5.5% for the comparator group), *diarrhoea* (13.8% vs 8.1% for the comparator group) and *vomiting* (9.1% vs 3.7% for the comparator group). Most of the GI disorders events were reported as mild (Kyinsu: 73% and comparator: 80%) or moderate (Kyinsu: 26% and comparator: 19%). GIAE mainly occurred during the initial 8 weeks with a median duration varying between 2 days (vomiting) to 4 days (diarrhoea) in both treatment groups. GIAEs were the major reason for withdrawal (2.7%), interruption (1.7) and decrease (4.2%) of study drug. Dose was increased in 2.7% of the participants treated with Kyinsu due to GIAEs.

Hypoglycemia: In the pre-basal insulin treated populations (study 4591 and 4593), severe (level 3) or clinically significant (level 2) hypoglycaemia were reported by lower proportions and rates for the Kyinsu group compared to the insulin icodec group (study 4591: 7.1% vs 20.8%; 13.77 vs 62.62 per 100 PYE) respectively for the Kyinsu group compared to IGlar+IAsp group (study 4593: 10.0% vs

58.5% and 21.47 vs 222.72 events per 100 PYE). In the insulin naïve (pre GLP1RA-treated) population, the proportion, and rate of severe (level 3) or clinically significant (level 2) hypoglycaemia was similar for Kyinsu and semaglutide (3.5% vs 3.8% and 4.18 vs 3.56 events per 100 PYE; study 4592).

The number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L, confirmed by BG meter) or severe hypoglycaemic episodes (level 3) was secondary confirmatory safety endpoint in study 4591 and 4593 and was a secondary supportive safety endpoint in study 4592. A statistically significant difference in favour of Kyinsu was observed in the rate of level 2 or level 3 hypoglycaemic episodes between Kyinsu and insulin icodec in study 4591 (ETR: 0.22 [0.14; 0.36]) and between Kyinsu and IGlar+IAsp in study 4593 (ETR: 0.12 [0.08; 0.17]). In study 4592, the estimated number of level 2 and 3 hypoglycaemic episodes was low and similar for Kyinsu and semaglutide.

In all three studies hypoglycaemic events were more common at day 2-3 without any large difference compared to days later in the week.

Hyperglycaemia: In the pre-basal insulin treated populations, the PT hyperglycaemia was reported by a higher proportion of participants for Kyinsu than for insulin icodec (3.3% vs 1.2%; study 4591) respectively for Kyinsu than for IGlar+ IAsp (3.8% vs 0.6%). In the insulin naïve (pre-GLP-RA population) a slightly higher proportion of the Kyinsu groups reported the PT hyperglycaemia compared to the semaglutide group (3.5% vs 2.9%; study 4592). In total 32 of the 57 (56%) events in the Kyinsu group were classified as mild, 23 (40%) as moderate and 2 (3.5%) as severe. DKA events were rare without any difference regarding between the two treatment groups. Most of the hyperglycaemic events occurred within the first 12 weeks. In total 32 of the 57 (56%) events in the Kyinsu group were classified as mild, 23 (40%) as moderate and 2 (3.5%) as severe. DKA AEs were rare without any difference between the two treatment groups.

Diabetic retinopathy: In the phase 3a pool a higher proportion of subjects reported AEs related to diabetic retinopathy (predefined MedDRA search) respectively the PT "diabetic retinopathy" in the Kyinsu group than in the comparator group (9.2% vs 8.1%) respectively (6.4% vs 4.8%). Among subjects without diabetic retinopathy or related conditions in medical history at baseline (~75% of the subjects), the difference in the PT diabetes retinopathy was 5.2% vs 3.9%. In this subgroup, most of these events were mild (Kyinsu 82% and comparator 91%). But a slightly higher proportion of the events in the Kyinsu group were reported as moderate or severe compared to the comparator group (18% vs 9.3%). Among subjects with diabetic retinopathy (or related conditions) at baseline (~25% of the subjects) diabetes retinopathy (PT) was reported by 10.2% for Kyinsu and 7.6% for comparator. New data presented do not indicate an increased risk for diabetes retinopathy complications in subjects with diabetes retinopathy at baseline between the two treatment groups. Longer diabetes durations and larger HbA1c (%) reduction from baseline to week 26, were (in both treatment groups) noted for subjects that reported any AEs related to diabetic retinopathy events during the trials.

Acute pancreatitis and cholelithiasis: Acute pancreatitis were reported by 0.2% in the Kyinsu group (none in the comparator group) and gallbladder related disorders including cholelithiasis by 0.8% in the Kyinsu and 0.9% in the comparator group.

Hypersensitivity*:* Adverse events related to hypersensitivity was reported by 3.9% of the participants in the Kyinsu group and 5.1% in the comparator group. Most (91% in the Kyinsu group) of these events were reported as mild. No event of anaphylactic reaction related to Kyinsu was reported.

Immunogenicity*:* Positivity for insulin icodec antibodies any time after baseline was reported with similar (high) frequencies for Kyinsu (~70%) as for insulin icodec as mono-component (78.5%). The immunogenicity results are similar as noted for insulin icodec in the previously basal insulin treated T2D subjects in the development program for insulin icodec (ONWARDS 2; 70.2% positive any time up

to week 31). Anti-semaglutide antibody formation was low (1.4%). The number of cases were too low to allow proper assessments of associations with efficacy and safety parameters.

Medication errors: Medication errors (MEs) were reported by 1.9% of the participants in the Kyinsu group. For Kyinsu most of the ME cases for concerned underdose (0.7%), incorrect dose administration (0.5%) and overdose (0.4%). Approximately, 1/3 of the ME were in in both treatment groups were reported during the first 30 days (defined as "switched" period). The main adverse reaction resulting from these events was Level 1 hypoglycaemic episodes.

Other AESI

The proportions of participants reporting the remaining AESI in the Kyinsu groups: acute renal failure events (0.5%), hepatic events (1.6%), injection site reactions (0.8%).

No events of medullary thyroid carcinoma or pancreatic cancer were reported with Kyinsu.

Safety in special populations

Age**:** In total, 523 subjects ≥ 65 years, including 79 subjects ≥75 years have been exposed to Kyinsu. A higher proportion of subjects of SAEs is reported in the ≥75 years population (18%) compared to the two younger populations (≥65-< 75 years: 12.3% and 18-<65 years: 8.9%) but lower compared to the corresponding age-group in the comparator group (22.3%). Withdrawals due to AEs were more common for Kyinsu in the ≥75 years (11.9%) compared to the younger populations (≥65-< 75 years: 6.1% and 18-<65 years: 2.4%).

Renal impairment at baseline: The proportion of participants with and rate of SAE were higher for those in the Kyinsu group with moderate or severe renal impairment at baseline (20.9% and 38.84 events per 100 PYE) compared to Kyinsu participants with mild (9.9% and 11.64 events per 100 PYE) or normal renal function (8.8% and 11.74 events per 100 PYE) at baseline.

Hepatic impairment: No pronounced clinically significant difference in SAEs, severity and action taken to study drug or in AEs by SOC, and by SOC and PT were observed in the subpopulations.

3.5. Uncertainties and limitations about unfavourable effects

There is a known increased risk for complications of **diabetes retinopathy** in patients **with retinopathy** when treatment with s.c. semaglutide alone or concomitant with insulin is introduced (important identified risk for semaglutide products followed by a category 3 PASS [FOCUS study]). In the Kyinsu phase 3a pool, a higher proportion of participants also **without diabetic retinopathy** at baseline reported diabetic retinopathy (PT) in the Kyinsu group compared to the comparator group. Thus, there are uncertainties regarding the risk for diabetes retinopathy both in subjects with and without diabetes retinopathy when treatment with Kyinsu is introduced. As for semaglutide products "Diabetes retinopathy complications" is included in the Kyinsu RMP as an important identified risk and followed by the FOCUS study. A limited number of patients without diabetic retinopathy or with only microaneurysms at baseline will also be included in the FOCUS study. Thus, results from this study will possibly give some indication, whether there is risk (or not) for development of diabetes retinopathy in subjects also without diabetes retinopathy at baseline co-treated with insulin and semaglutide. When results from the study will become available (LPLT Aug 2027) the need for further safety actions/evaluation for this subgroup should be considered. In the meantime, this risk will be followed in the coming Kyinsu PSURs. The risk is considered adequately reflected in the SmPC section 4.4 and 4.8.

There are uncertainties regarding the risk for **medullary thyroid cancer** and **pancreatic cancer** during use of semaglutide. Both these risks are included in the RMP for semaglutide and Kyinsu as important potential risks followed by category 3 PASS which is considered sufficient.

Medication errors due to mix-up with and during switch from, other injectable diabetes therapy are important potential risks included as safety concerns in the insulin icodec RMP and also for Kyinsu. The risks will be followed in the PSURs.

There is limited experience of use with semaglutide and Kyinsu in patients with **severe hepatic impairment** as well as **use during pregnancy and breastfeeding**. This is reflected in the SmPC, and the topic is included in the RMP as missing information.

3.6. Effects table

Table 73. Effects table for Kyinsu (insulin icodec/semaglutide) indicated for treatment of adults with type 2 diabetes mellitus insufficiently controlled on basal insulin or glucagon-like peptide 1 (GLP-1) receptor agonists as an adjunct to diet and exercise in addition to oral antidiabetic medicinal products. For study results with respect to combinations, effects on glycaemic control, and the populations studied, see sections 4.4, 4.5 and 5.1.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
HbA1c	Mean change in HbA1c from baseline	%	-1.55	-0.89 (insulin icodec)	Primary endpoint, ETD: -0.66 [-0.76; -0.57] Superiority confirmed	Study 4591 [1)]
			-1.35	-0.90 (semaglutide)	Primary endpoint, ETD: -0.44 [-0.56; -0.33] Superiority confirmed	Study 4592 [2)]
			-1.47	-1.40 (insulin glargine + insulin aspart)	Primary endpoint, ETD: -0.06 [-0.22; 0.09] Non-inferiority confirmed	Study 4593 [1)]
Body weight	Mean change in body weight from baseline	kg	-3.70	1.89 (insulin icodec)	Confirmatory secondary endpoint, ETD: -5.59 [-6.14; -5.04] Superiority confirmed	Study 4591 [1)]
			0.84	-3.70 (semaglutide)	Secondary endpoint ETD: 4.54 [3.84; 5.23]	Study 4592 [2)]
			-3.56	3.16 (insulin glargine + insulin aspart)	Confirmatory secondary endpoint, ETD: -6.72 [-7.58; -5.86] Superiority confirmed	Study 4593 [1)]
Weekly insulin dose	Mean weekly insulin dose week 50 to 52	U	182	355 (insulin icodec)	Secondary endpoint, ETD: -172 [-190; -155]	Study 4591 [1)]
			196	466 [3)] (insulin glargine + insulin aspart)	Confirmatory secondary endpoint ETD: -270 [-303; -236] Superiority confirmed	Study 4593 [1)]

			196	285 [4)] (insulin glargine + insulin aspart)	Secondary endpoint, ETD: -89.0 [-109; -68.8]	Study 4593 [1)]
Unfavourable Effects						
Hypo-glycaemia	The number of clinically significant[5)] or severe hypoglycaemic episodes	Episodes per 100 patient-years	15.3	68.4 (insulin icodec)	Confirmatory secondary endpoint, ETR: 0.22 [0.14; 0.36] Superiority confirmed	Study 4591 [1)]
			25.7	218 (insulin glargine + insulin aspart)	Confirmatory secondary endpoint, ETR: 0.12 [0.08; 0.17] Superiority confirmed	Study 4593 [1)]
Hypoglycaemia	Incidence of severe (level 3) or clinically significant (level 2) hypoglycaemic events	%	7.1	20.8 (insulin icodec)		Study 4591 [1)]
			3.5	3.8 (semaglutide)		Study 4592[2)]
			10.0	58.5 (IGlar+IAsp)		Study 4593[1)]
Hyperglycaemia	Incidence of hyperglycaemia (PT)	%	3.3	1.2 (insulin icodec)		Study 4591[1)]
			3.5	2.9 (semaglutide)		Study 4592[2)]
			3.8	0.6 (IGlar+IAsp)		Study 4593[1)]
Gastrointestinal events (GI)	Incidence of GI events (SOC)	%	42.1%	23.8%	Mainly occurred during the initial 8 weeks. Severity of the GI events with IcoSema was mostly mild (73%) or moderate (26%)	Phase 3a safety data pool[6)]
Nausea	Incidence of nausea	%	20.1	5.5	Median duration of the events were 3 days (IcoSema)	Phase 3a safety data pool[6)]
Diarrhea	Incidence of diarrhea	%	13.8	8.1	Median duration of the events (IcoSema) were 4 days	Phase 3a safety data pool[6)]
Vomiting	Incidence of vomiting	%	9.1	3.7	Median duration of the events (IcoSema) were 2 days	Phase 3a safety data pool[6)]
Retinopathy	Diabetic retinopathy (predefined MedDRA search)	%	9.2	8.1		Phase 3a safety data pool[6]
	Incidence of retinopathy (PT)		6.4	4.8		Phase 3a safety data pool[6]
	Incidence of retinopathy (PT)		5.9	3.9		Subjects without retinopathy and related conditions at baseline in; Phase 3a safety data pool[6]

Abbreviations: T2DM=type 2 diabetes mellitus, IcoSema=fixed dose regiment insulin icodec/semaglutide.
Notes: [1)] In T2DM patients insufficiently controlled on basal insulin, [2)] Insulin naïve T2DM patients insufficiently controlled on GLP-1 RA therapy, [3)] Total insulin dose, i.e., basal and bolus insulin, [4)] Basal insulin dose, [5)] Clinically significant hypoglycaemic episodes =<3.0 mmol/L, confirmed by BG meter [6)] The phase 3a safety data pool constituted of the phase 3 study 4591, 4592 and 4593.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Type 2 diabetes mellitus is characterised by a gradual deterioration in beta-cell function with a heterogenicity regarding age at onset, degree of obesity, insulin resistance and tendency to develop complications. When treating the patients, the goal of achieving good metabolic control, including weight management and control of other cardiovascular risk factors, has to be balanced against the risk of hypoglycaemia. The availability of several treatment options is needed to enable an individualised treatment strategy. Concomitant treatment with basal insulin and a GLP-1 RA can be an important treatment option for patients eligible for initiation of insulin treatment as well as those in need of intensified insulin treatment. The benefit of combining basal insulin with GLP-1 RA provides a glycaemic lowering effect with less weight gain and a lower risk of hypoglycaemia compared to an increased dose of insulin. The disadvantages include the risk of GI adverse events associated with GLP-1 RA, although such events are in the majority of the cases transient. Two FRCs with a basal insulin and a GLP-1 RA are already approved, both for once-daily administration. Kyinsu is the first FRC application with a basal insulin and a GLP-1 agonist intended for weekly administration.

In the pivotal trials supporting the proposed therapeutic indication, the glucose lowering effect of Kyinsu was superior to that of both mono-components insulin icodec (study 4591) and semaglutide (study 4592), respectively.

Compared to insulin icodec, a greater effect on HbA1c was achieved with Kyinsu at lower insulin doses and lower rate of hypoglycaemias. In addition, weight reduction was seen with Kyinsu as opposed to the weight gain seen with insulin icodec treatment. Thus, for patients not well controlled on daily basal insulin (and oral antidiabetics), switching to Kyinsu instead of increasing the daily insulin dose may be a relevant treatment option. However, it is noted that there was an initial lower decrease in mean FPG for patients treated with Kyinsu compared to insulin icodec. The posology has been amended with further guidance on adjustment of antidiabetic medication for patients switching from daily basal insulin to Kyinsu.

In insulin-naïve patients not well controlled on GLP-1 RA (and oral antidiabetics), Kyinsu was superior to semaglutide with respect to lowering of HbA1c and the hypoglycaemic rate was comparable between the groups. However, weight loss was observed in the semaglutide group while a small weight gain was noted in the Kyinsu group. In these patients, Kyinsu could be an option to further optimize the glycaemic status, but it may come at a cost of a reduced effect on body weight compared to an optimized dose of semaglutide (possibly with separate insulin treatment). In this context it should be noted that the average weekly dose of semaglutide in Kyinsu was approximately 0.5 mg compared to 1 mg weekly of semaglutide in monotherapy. Further, the maximal approved dose for semaglutide is 2 mg weekly. Thus, the full potential of semaglutide may therefore not be used in Kyinsu.

However, co-administration of two injectable medicinal products in one injection is convenient and could potentially increase compliance.

Considering the results of the CVOT SUSTAIN 6 (performed with semaglutide) the applicant claims that these results are also applicable to Kyinsu. Even if there are overlaps between the exposure of semaglutide and the study populations, it is uncertain if treatment with Kyinsu will have the same cardioprotective effect as was indicated by the results of the SUSTAIN 6 trial. However, the experience from the CV outcomes trial performed with semaglutide can be of interest for the prescriber, and it can therefore be acceptable to include the most important results in section 5.1 for Kyinsu. However, the reference in section 4.1 with respect to effect on CV events is not supported by the data and has been deleted.

The safety profile for Kyinsu is in general similar to the two included mono-components with no indications of additive toxicity. In patients insufficiently controlled on basal insulin, the incidence of subjects with GI AEs was higher and the incidence of patients with hypoglycaemia was lower for Kyinsu compared to basal insulin. In insulin naïve patients previously treated with GLP-1 RA, the incidence of patients with GI AEs and hypoglycaemia was at the same as for semaglutide given as monotherapy.

In subjects with diabetes retinopathy, concomitant use with s.c. semaglutide and insulin has previously been identified to increase the risk for retinopathy complications. In the phase 3a pool, a higher proportion of participants both with and without diabetic retinopathy at baseline reported diabetic retinopathy (PT) in the Kyinsu group than in the comparator group after 52 weeks treatment. The finding that also a higher proportion of subjects **without diabetes retinopathy at baseline** reported diabetes retinopathy after 52 weeks treatment is a new safety concern that now is reflected in the SmPC section 4.4 and 4.8 and will be further evaluated in the FOCUS study and followed in the Kyinsu PSURs.

3.7.2. Balance of benefits and risks

In T2DM patients previously treated with basal insulin, the benefit of achieving a superior reduction of HbA1c with Kyinsu compared to insulin icodec in combination with weight reduction and a lower incidence of hypoglycaemias compared to what would be the result of the higher insulin dose needed to reach the same HbA1c target, is considered to outweigh the additional risks which mainly included transient GI adverse events.

In insulin naïve T2DM patients previously treated with GLP-1 RA, the beneficial effects of Kyinsu are less obvious given that the rates of hypoglycaemia and GI AEs were comparable with semaglutide and, more important, that weight gain was demonstrated for Kyinsu compared to weight loss for semaglutide. The favourable effects of semaglutide in Kyinsu may be diminished by the reduced dose of semaglutide. However, considering the higher glucose-lowering effect with Kyinsu compared to semaglutide, Kyinsu could be a relevant treatment option in some patients not controlled on GLP-1 RA.

3.7.3. Additional considerations on the benefit-risk balance

The clinical data provided is considered as comprehensive.

3.8. Conclusions

The overall benefit/risk balance of Kyinsu is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Kyinsu is favourable in the following indication(s):

> Kyinsu is indicated for the treatment of adults with type 2 diabetes mellitus insufficiently controlled on basal insulin or glucagon-like peptide 1 (GLP-1) receptor agonists as an adjunct to diet and exercise in addition to oral antidiabetic medicinal products.
> For study results with respect to combinations, effects on glycaemic control, and the populations studied, see sections 4.4, 4.5 and 5.1.

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.

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.

The MAH shall provide an education guide prior to launch targeting all patients who will be treated with Kyinsu.

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

Not applicable.