Risk Management Plan

Insulin icodec/Semaglutide (Kyinsu®)

Active substance(s)	Insulin icodec/semaglutide
RMP version number:	0.5
Data lock point for this RMP	14 May 2024
Date of final sign off:	See signature page
Rationale for submitting an updated RMP	Not applicable as this is the 1st RMP submitted for insulin icodec/semaglutide (Kyinsu®) marketing authorisation application.
Summary of significant changes in this RMP	Not applicable as this is the 1st RMP submitted for insulin icodec/semaglutide (Kyinsu®) marketing authorisation application.
Other RMP versions under evaluation	None
Details of the currently approved RMP	Not applicable
QPPV/QPPV Delegate	Lise Grimmeshave
QPPV/QPPV Delegate signature	See signature page

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Abbreviations

ADA	American Diabetes Association
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical code
Bil	bilirrubin
CGM	continuous glucose monitoring
CKD	chronic kidney disease
CNS	central nervous system
CVD	cardiovascular disease
CVOT	cardiovascular outcomes trial
DCCT	diabetes control and complications trial
DDI	drug-drug interaction
DLP	data lock point
DNA	deoxyribonucleic acid
DPP-4i	dipeptidyl peptidase-4 inhibitor
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ESKD	end-stage kidney disease
EU	European Union
EU PI	European Union product information
FRC	fixed-ratio combination
GERD	gastroesophageal reflux disease
GFR	glomerular filtration rate
GI	gastrointestinal
GLP-1 RA	glucagon-like peptide-1 receptor agonist
GVP	good pharmacovigilance practices
HCP	healthcare professional
HF	heart failure
INN	international non-proprietary name
INR	international normalised ratio
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
MACE	major adverse cardiac event
MedDRA	Medical Dictionary for Regulatory Activities
MTC	medullary thyroid cancer
PASS	post-authorisation safety study
PL	package leaflet
PMR	post-marketing requirement
PRAC	Pharmacovigilance Risk Assessment Committee

PSUR	periodic safety update report
PT	preferred term
PV	pharmacovigilance
PYE	patient years of exposure
PYO	patient years of observation
QPPV	Qualified Person responsible for PharmacoVigilance
RMM	risk minimisation measures
RMP	risk management plan
SAE	serious adverse event
SGLT2i	sodium-glucose co-transporter-2 inhibitor
SmPC	summary of product characteristics
SOC	system organ class
SU	sulfonylurea
TZD	thiazolidinedione
UACR	urine albumin-to-creatinine ratio
ULN	upper normal limit
US	United States

1 Product overview

Table 1-1 Product overview

Active substance(s) (INN or common name)	Insulin icodec/semaglutide
Pharmacotherapeutic group(s) (ATC Code)	ATC code is not yet assigned
Marketing authorisation holder/applicant	Novo Nordisk A/S DK-2880 Bagsværd Denmark
Medicinal products to which this RMP refers	All presentations of Kyinsu® (insulin icodec/semaglutide)
Invented name(s) in the European Economic Area (EEA)	Kyinsu® 700 units/mL + 2 mg/mL solution for injection in pre-filled pen
Marketing authorisation procedure	EU Centralised procedure
Brief description of the product	***Chemical class:*** Insulin icodec/semaglutide (Kyinsu®) combines two active substances with complementary mechanisms of action to improve glycaemic control: insulin icodec, a basal insulin analogue, and semaglutide, a GLP-1 receptor agonist.
	Summary of mode of action: <u>*Insulin icodec*</u> The primary action of insulin, including insulin icodec, is to regulate glucose metabolism. Insulin and its analogues lower blood glucose by activating specific insulin receptors to stimulate peripheral glucose uptake, especially by skeletal muscle and fat as well as to inhibit hepatic glucose production. Insulin also inhibits lipolysis and proteolysis and enhances protein synthesis. A slow and steady glucose-lowering effect of insulin icodec is driven by albumin binding as well as reduced insulin receptor binding and clearance. The extended half-life of insulin icodec reflects a depot of insulin icodec in the circulation and in the interstitial compartment, from which insulin icodec is slowly and continuously released and binds specifically to the insulin receptor. When insulin icodec binds to the human insulin receptor it results in the same pharmacological effects as human insulin. <u>*Semaglutide*</u> Semaglutide is a GLP-1 analogue with 94% sequence homology to human GLP-1. Semaglutide acts as a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1. GLP-1 is a physiological hormone that has multiple actions in glucose and appetite regulation, and in the cardiovascular system. The glucose and appetite effects are specifically mediated via GLP-1 receptors in the pancreas and the brain. Semaglutide reduces blood glucose in a glucose dependent manner by stimulating insulin secretion and lowering glucagon secretion when blood glucose is high. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase. During hypoglycaemia, semaglutide diminishes insulin secretion and does not impair glucagon secretion.

Active substance(s) (INN or common name)	Insulin icodec/semaglutide
	Semaglutide reduces body weight and body fat mass through lowered energy intake, involving an overall reduced appetite. In addition, semaglutide reduces the preference for high fat foods. GLP-1 receptors are also expressed in the heart, vasculature, immune system and kidneys. Semaglutide had a beneficial effect on plasma lipids, lowered systolic blood pressure and reduced inflammation in clinical studies. In animal studies, semaglutide attenuates the development of atherosclerosis by preventing aortic plaque progression and reducing inflammation in the plaque.
	Composition Insulin icodec is produced by the fermentation of genetically modified yeast cells (rDNA origin, [redacted]) followed by the attachment of an albumin-binding moiety to the purified molecule. Semaglutide is produced by recombinant DNA technology in [redacted] followed by protein purification.
Hyperlink to the Product Information	Kyinsu® SmPC
Indication(s) in the EEA	**Current (if applicable)** Not applicable
	Proposed (if applicable) Insulin icodec/semaglutide (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.
Dosage in the EEA	**Current (if applicable)** Not applicable
	Proposed (if applicable) This medicinal product is a FRC of the basal insulin, insulin icodec and semaglutide for once-weekly subcutaneous administration. It is intended to be taken on the same day of the week.
Pharmaceutical form(s) and strengths	**Current (if applicable)** Not applicable
	Proposed (if applicable) Solution for injection in pre-filled pen. Clear, colourless or almost colourless isotonic solution with a pH of approximately 7.4.
Is/will the product be subject to additional monitoring in the EU?	Yes

Abbreviations: EEA = European Economic Area, FRC = fixed ratio combination, GLP-1 = glucagon-like peptide 1, SmPC = summary of product characteristics.

2 Safety specification

2.1 Module SI: Epidemiology of the indication(s) and target population

2.1.1 Type 2 diabetes

Type 2 diabetes mellitus (T2D) is a heterogeneous, chronic, progressive disease characterised by insulin resistance, along with relatively impaired beta cell function. In the pre-diabetic state, with increased insulin resistance, beta-cells can produce enough insulin to maintain glucose levels within the normal range. With the progression of the disease, this ability to compensate decreases, beta cells gradually lose their ability to secrete insulin and T2D becomes manifested.

2.1.1.1 Incidence and prevalence

In the International Diabetes Federation's Diabetes Atlas (edition 2021), the estimated worldwide diabetes prevalence was 537 million, with a prediction that by 2045, the number of people with diabetes will have increased to 783 million.[1] Different categories of diabetes mellitus exist with T2D being the most prevalent, accounting for 90-95% of all diabetes.[2]

2.1.1.2 Demographics of the target population – Age, sex, racial and ethnic origin

Type 2 diabetes mellitus

The number of people with diabetes has been on the rise for several decades. Population growth and ageing together with an increase in age-specific prevalence are the main drivers of this increase.[1] The incidence rates of T2D in adults range from 2.3 to 20.2 cases per 1,000 person-years with wide geographical variation.[3-18]. Recent findings showed that the age-adjusted incidence rate (per 100,000 persons) was highest in Oceania (652 persons), followed by Southern sub-Saharan Africa (448 persons) and Central sub-Saharan Africa (447 persons).[19] Magliano et al. (2019) reviewed the trends in the incidence of total or T2D.[20] In the period from 2006 to 2014, the authors found an increase in the incidence of T2D in 33% (11 of 33 populations), a decreased incidence in 36% (12 of 33), and a stable incidence in 30% (10 of 33) of the evaluated separate sex specific or ethnicity specific populations. Therefore, a variable trend in the incidence of T2D was observed.

Prevalence

In 2021, the estimated crude prevalence of diabetes in adults aged 20–79 years was 10.5% globally (the vast majority of cases being T2D).[1] The age-adjusted prevalence varied from one region to another with the highest prevalence in the Middle East and North Africa (16.2%) followed by North America and Caribbean (14%).[1] The lowest prevalence is in Africa (4.5%) followed by Southeast Asia (8.7%).[1] For Europe, the age-adjusted prevalence of diabetes was 9.2%, in general.[1] Turkey (15.9%), Spain (14.8%), Andorra (13.9%) and Portugal (13%) have the highest crude prevalence, and Ireland (4%) and Greenland (4.5%) have the lowest crude prevalence of diabetes.[1] At the global level, Pakistan (30.8%), French Polynesia (25.2) and Kuwait (24.9) have the highest age-adjusted prevalence of diabetes.[1]

From 1990 to 2017, large increase in the age adjusted prevalence rates of diabetes were observed, reaching up to 39.2% in North America and Western sub-Saharan Africa.[19, 21] For T2D, the highest

increase was observed in North America (42.6%), while a decrease by 5.7% was observed in Australasia.[19]

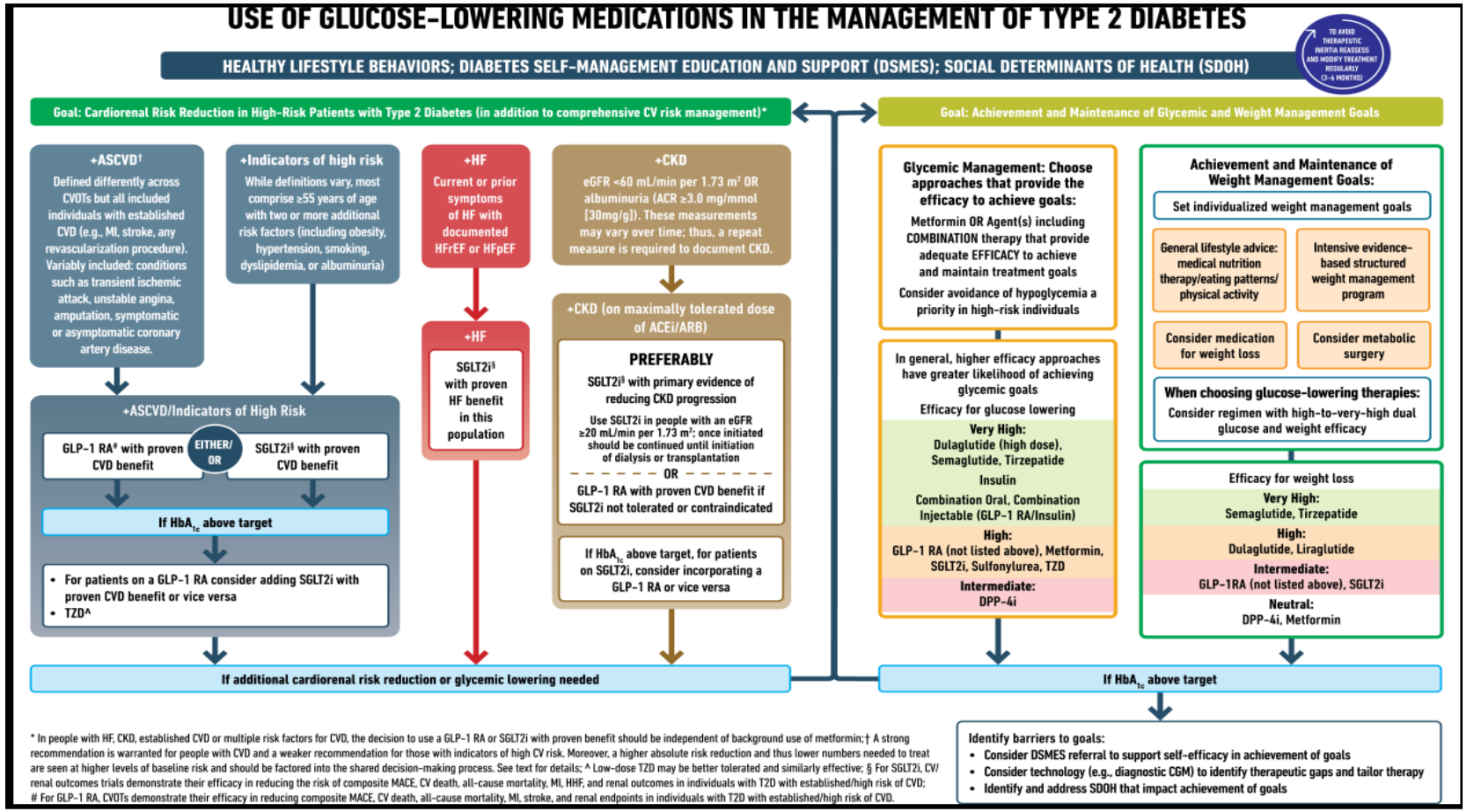
2.1.1.3 Risk factors for the disease

Although the exact causes for the development of T2D are unknown, there are several known risk factors. The most important risk factors are excess body weight (overweight and obesity), physical inactivity, dietary factors and genetics.[1] Additional risk factors include smoking, impaired glucose tolerance, abnormal lipids, hypertension, inflammation, increasing age, male sex, ethnic and genetic pre-disposition, history of gestational diabetes and polycystic ovary syndrome.

2.1.1.4 The main existing treatment options

A hierarchy of the available treatment options for T2D as recommended by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) is presented in Figure 2-1.

Figure 2-1 Glucose-lowering medication in type 2 diabetes: overall approach[22]



Abbreviations: ASCVD = atherosclerotic cardiovascular disease; A_{1C} = haemoglobin A_{1c} / HbA_{1c}; CKD = chronic kidney disease; CVD = cardiovascular disease; CVOT = cardiovascular outcomes trial; DPP-4i = dipeptidyl peptidase-4 inhibitor; eGFR = estimated glomerular filtration rate; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; HFrEF = heart failure reduced ejection fraction; LVH = left ventricular hypertrophy; LVEF = left ventricular ejection fraction; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SU = sulfonylurea; TZD = thiazolidinedione; UACR = urine albumin-to-creatinine ratio

2.1.1.5 Natural history of the indicated condition including mortality and morbidity

T2D is a heterogeneous, chronic and progressive disease characterised by insulin resistance (response to insulin to the target tissues, such as muscle, liver and adipose tissue), along with relatively impaired beta-cell function. The disease usually follows a predictable course. In the early stages, individuals with T2D have sufficient pancreatic reserves to compensate for insulin resistance and can maintain relatively normal blood glucose levels. However, over time, this ability to compensate decreases as beta-cells gradually lose their ability to secrete insulin (beta-cell insufficiency), eventually leading to state of insulin dependency.[23]

The endpoint of the disease process, insulin deficiency, can be absolute or relative in the coexistence of insulin resistance. The result is chronic hyperglycaemia, caused by reduced insulin secretion, decreased insulin utilisation and increased liver glucose production, which in the long run leads to diabetic complications. Diabetes is a leading cause of end-stage kidney disease (ESKD), nontraumatic lower-extremity amputations, adult blindness- and cardiovascular complications.[23-25]

T2D is associated with increased all-cause mortality.[26] Cardiovascular disease is a major cause of death in patients with T2D.[27] Furthermore, cancer patients with diabetes have poorer survival chances and higher cancer mortality rates than cancer patients without diabetes,[28, 29] particularly so for liver, pancreatic, ovary and colorectal cancer.[30] A recent study estimated that in 2021 nearly 40 million years of life lost was due to T2D.[31]

2.1.1.6 Important co-morbidities found in the target population

People with T2D are at a higher risk of developing a number of disabling and life-threatening health problems than people without diabetes.[32] Persistent hyperglycaemia may lead to the development of microvascular pathology in the retina, renal glomerulus and peripheral nerve.[33] As a consequence of its microvascular pathology, diabetes is a leading cause of blindness, ESKD and a variety of debilitating neuropathies. Diabetes is also associated with accelerated atherosclerotic macrovascular disease affecting arteries that supply blood to the heart, brain and lower extremities. As a result, individuals with diabetes have a much higher risk of myocardial infarction, stroke and limb amputation. The important co-morbidities found in the target population are presented in Table 2-1.

Table 2-1 Important co-morbidities found in the target population

Important co-morbidity category	Important co-morbidity sub-category
Macrovascular complications	• Congestive heart failure • Myocardial infarction • Peripheral arterial disease • Stroke
Microvascular complications	• Chronic kidney disease and nephropathy • Peripheral neuropathy • Retinopathy • Extremity ulcers • Autonomic neuropathy
Cancer	• Overall cancer • Liver • Pancreatic • Colorectal
Acute complications	• Diabetic ketoacidosis • Hyperosmolar hyperglycaemic state
Other	• Hypertension • Dyslipidaemia • Pancreatitis • Obesity

2.2 Module SII: Non-clinical safety findings

2.2.1 Important nonclinical safety findings and their relevance to human use

The nonclinical safety programme for insulin icodec/semaglutide (Kyinsu®) relevant for the RMP includes a 13-week toxicity study in rats. Per the GVP module V (revision 2), since insulin icodec/semaglutide (Kyinsu®) is a fixed combination product with no new active substance, this module only presents a summary of important nonclinical findings from the insulin icodec/semaglutide (Kyinsu®) nonclinical study along with an assessment of its relevance in humans are presented in Table 2-2. Important nonclinical safety findings identified in the completed nonclinical programmes for the two mono-components insulin icodec and semaglutide and are presented in the RMPs of the mono-components.

Table 2-2 Important nonclinical safety findings and their relevance to human use

Study type	Key safety findings	Relevance to humans
Acute or repeat-dose toxicity studies	**Hypoglycaemia** Subcutaneous administration of insulin icodec/semaglutide (Kyinsu®) to Sprague-Dawley rats for 13 weeks was generally well tolerated. Findings were consistent with the pharmacological effects of one or both mono-components or were secondary stress-related findings. The death of one male and early termination of one female were most likely due to hypoglycaemic episodes as supported by the low blood glucose levels measured. This required a reduction in the highest dose.	Hypoglycaemia observed in nonclinical studies is a result of the exaggerated pharmacological effect of insulin icodec/semaglutide (Kyinsu®) (the icodec component) in normoglycemic animals. It is observed with all insulin products. Hypoglycaemia is not considered a safety concern in humans as it is well-characterized, and no additional PV or risk management activities are required.
	Brunner's glands in the duodenum Hypertrophy of the Brunner's glands in the duodenum was observed in the majority of treated animals and was considered a response to the treatment with semaglutide. This is due to the abundance of GLP-1 receptors in this tissue.[34, 35] Since the finding was not associated with any inflammatory or cellular damage, either in the Brunner's glands or in the intestinal mucosa, it was considered non-adverse and showed full recovery by the end of the 6-week recovery period. Similar observations were reported from semaglutide repeat-toxicity studies.	Based on low severity and complete recovery observed in rats, the observed changes in Brunner's glands in rodents are not considered to pose a safety concern in humans.
Genotoxicity	Genotoxicity studies have not been performed and are not planned for insulin icodec/semaglutide (Kyinsu®). Genotoxicity toxicity has been evaluated for icodec and semaglutide.	No genotoxic changes observed with icodec or semaglutide. In humans, genotoxicity is not considered a safety concern for insulin icodec/semaglutide (Kyinsu®).
Carcinogenicity	Carcinogenicity studies have not been performed and are not planned for insulin icodec/semaglutide (Kyinsu®). Carcinogenicity has been evaluated for the mono-components.	Based on a comprehensive *in vitro* and *in vivo* evaluation, the carcinogenic potential of insulin icodec was found to be similar to that of human insulin. Based on data for semaglutide and other GLP-1 RAs, the relevance of the rodent thyroid C-cell tumours in humans is considered to be low. The nonclinical finding of the rodent thyroid C-cell tumours is not relevant in humans since published data indicate that the GLP-1 receptor is not expressed in the normal human thyroid C-cells.[35-37]

Study type	Key safety findings	Relevance to humans
		In humans, medullary thyroid cancer is considered an important potential risk for insulin icodec/semaglutide (Kyinsu®) (details in Section 2.7), in alignment with the safety concerns of semaglutide mono-component.
Reproductive and development toxicity	Reproduction toxicity studies have not been performed and are not planned for insulin icodec/semaglutide (Kyinsu®). In the 13-week repeated dose toxicity study, increased incidence of minimal unilateral or bilateral tubular degeneration/atrophy in the testes of high dose males was observed. Reproduction toxicity has been evaluated for the mono-components.	The testicular changes observed for insulin icodec/semaglutide (Kyinsu®) have been associated with hypoglycaemia in normo-glycaemic rats. Hypoglycaemia is not considered a safety concern in humans as it is well characterised and no additional PV or risk management activities are required. For icodec, reproductive and development effects were considered secondary changes to the effect on the maternal blood glucose levels (hypoglycaemia), and without toxicological significance. For semaglutide, the nonclinical observations of pregnancy losses and foetal abnormalities might be either incidental or related to the reduced maternal body weight, but a direct effect of semaglutide could not be excluded. Transfer of semaglutide to milk in lactating rats was observed and therefore due to the possibility of semaglutide transferring into milk, the use of semaglutide while breastfeeding is not recommended. Pregnancy and breastfeeding are included as missing information for insulin icodec/semaglutide (Kyinsu®) (details in Section 2.7).
CNS	CNS toxicity studies have not been performed and are not planned for insulin icodec/semaglutide (Kyinsu®). In the 13-week repeated dose study in rats with insulin icodec/semaglutide (Kyinsu®), treatment-related axonal degeneration in the sciatic nerve was present in a few high dose females and a high dose male that was found dead.	Axonal degeneration in the sciatic nerve is considered related to the exaggerated pharmacological effect of hypoglycemia when normoglycemic animals were treated with insulin icodec/semaglutide (Kyinsu®).

Study type	Key safety findings	Relevance to humans
		Hypoglycaemia is not considered a safety concern in humans as it is well-characterized and no additional PV or risk management activities are required.

Abbreviations: CNS = central nervous system; GLP-1 RA = glucagon-like peptide-1 receptor agonist; PV = pharmacovigilance.

2.2.2 Conclusions on nonclinical data

No safety concerns of relevance to humans were identified from the nonclinical studies of insulin icodec/semaglutide (Kyinsu®) The risks identified from mono-components are presented in Table 2-3.

Table 2-3 Nonclinical summary of safety concerns

Safety concerns
Important identified risks • None
Important potential risks (not refuted by clinical data or which are of unknown significance) • Medullary thyroid cancer (semaglutide)
Missing information • None

2.3 Module SIII: Clinical study exposure

2.3.1 Overall clinical experience with insulin icodec/semaglutide (Kyinsu®)

The development strategy of insulin icodec/semaglutide (Kyinsu®) builds on the extensive knowledge obtained in the clinical development programmes for once-weekly insulin icodec (Awiqli®) and weekly semaglutide s.c. (Ozempic®).

The safety related objectives of the insulin icodec/semaglutide (Kyinsu®) clinical programme were designed to evaluate the following.

- Safety of insulin icodec/semaglutide (Kyinsu®) compared to insulin icodec or semaglutide or daily insulin glargine 100 units/mL combined with insulin aspart in patients with T2D inadequately controlled with daily basal insulin or GLP-1 RA.
- To detect any potential additional safety concerns compared to the known safety profile of the mono-components.

The clinical studies included in this risk management plan (RMP) and their corresponding study IDs and description are listed in Table 2-4.

Table 2-4 Summary of insulin icodec/semaglutide (Kyinsu®) phase 3 study programme by study ID, phase, and study description

Study ID (name)	Phase	Study Description
NN1535-4591 (COMBINE 1)	Phase 3a	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 T2D inadequately controlled with daily basal insulin
NN1535-4592 (COMBINE 2)		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 T2D inadequately controlled with a GLP-1 receptor agonist.

Study ID (name)	Phase	Study Description
NN1535-4593 (COMBINE 3)		A 52-week study comparing the efficacy and safety of once weekly insulin 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 T2D inadequately controlled with daily basal insulin.

Abbreviation: GLP-1 = glucagon-like peptide 1; T2D = type 2 diabetes mellitus.

The 3 phase 3a studies serve as the primary evidence for confirming the efficacy and safety of insulin icodec/semaglutide (Kyinsu®), as these studies investigated insulin icodec/semaglutide (Kyinsu®) in the intended target population and account for most of the total exposure to insulin icodec/semaglutide (Kyinsu®). The populations studied comprise of participants with T2D inadequately controlled with daily basal insulin regimen or a GLP-1 RA.

2.3.2 Clinical exposure to insulin icodec/semaglutide (Kyinsu®) in randomised clinical studies

Cumulatively, until 14 May 2024, a total of 2,637 study participants were exposed to insulin icodec/semaglutide (Kyinsu®) (50.2%) or comparators, that is, insulin icodec, insulin glargine+insulin aspart and semaglutide (49.8%); see Table 2-5. Most of the participants were exposed to insulin icodec/semaglutide (Kyinsu®) or comparators for at least 12 months (see Table 2-6).

Of those exposed to insulin icodec/semaglutide (Kyinsu®), more than half (~61%) of study participants were adults of 18-64 years of age, with additional elderly subpopulations including participants between 65 and 74 years of age (~33% of participants) and those ≥75 years of age (~6%) (see Table 2-7). The participant exposure by sex for those treated with insulin icodec/semaglutide (Kyinsu®) was slightly weighted towards males (3:2 male:female ratio); see Table 2-7. Most of the participants exposed to insulin icodec/semaglutide (Kyinsu®) were of White (~60%) or Asian (~34%) origin; see Table 2-7.

The demographic composition of the participants exposed to comparators was similar to that described above for insulin icodec/semaglutide (Kyinsu®)-treated participants (see Table 2-7).

Table 2-5 Exposure in completed phase 3a studies

	Number of participants (%)	PYE
Insulin icodec/semaglutide (Kyinsu®)	1,325 (50.2%)	1,369.4
All comparators[a]	1,312 (49.8%)	1,376.3
Total	2,637 (100.0%)	2,745.8

Note: The table includes exposure from all studies included in Table 2-4. 1 PYE = 365.25 days.

[a] insulin icodec, insulin glargine+insulin aspart and semaglutide.

Abbreviations: PYE = patient-years of exposure.

Table 2-6 Duration of exposure in completed phase 3a studies

Duration of exposure (at least)	Insulin icodec/semaglutide (Kyinsu®)[a]		All comparators[a]	
	Number of participants	Percentage	Number of participants	Percentage
>0 months	1,318	99	1,305	99.5
3 months	1,264	95.4	1,278	97.4
6 months	1,239	93.5	1,255	95.6
9 months	1,224	92.4	1,231	93.8
12 months	1,149	86.7	1,160	88.4
14 months	3	0.23	1	0.07

Note: The table includes exposure from all studies included in Table 2-4.

[a] insulin icodec, insulin glargine+insulin aspart and semaglutide.

Table 2-7 Exposure by sex, age and race in completed phase 3a studies

	Insulin icodec/semaglutide (Kyinsu®)				All comparators[a]			
	Number of participants		PYE		Number of participants		PYE	
Age group	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
18–64 years	494	308	520.7	323.1	519	347	552.2	363.4
65–74 years	260	184	260.6	188.4	215	146	222.0	153.7
≥75 years	46	33	45.8	30.8	53	32	55.3	29.8
Total	**800**	**525**	**827.1**	**542.3**	**787**	**525**	**829.5**	**546.9**
Race								
White	791		810.1		809		839.2	
Black/African American	49		52.6		48		51.8	
Asian	445		464.5		425		454.5	
Other	8		7.8		9		9.9	
Not reported	32		34.4		21		20.95	
Total	**1,325**		**1,369.3**		**1,312**		**1,376.3**	

Note: The table includes exposure from all studies included in Table 2-4. 1 PYE = 365.25 days.

[a] insulin icodec, insulin glargine+insulin aspart and semaglutide.

Abbreviations: PYE = patient-years of exposure.

2.4 Module SIV: Populations not studied in clinical studies

2.4.1 Exclusion criteria in pivotal clinical studies within the development programme

The phase 3a studies of insulin icodec/semaglutide (Kyinsu®) are considered pivotal clinical studies within the development programme. This section summarises the important exclusion criteria, the reason for exclusion and the rationale for why an exclusion criterion is not classified as missing information for insulin icodec/semaglutide (Kyinsu®) (refer to Table 2-8).

Table 2-8 Exclusion criteria in pivotal clinical studies within the development programme

Criteria	Reason for being an exclusion criterion in the phase 3a programme[a]	Missing information (Yes/No) Rationale if not a missing information
Known or suspected hypersensitivity to the active substances or an excipient.	Known or suspected hypersensitivity to insulin analogues and excipients is not common. If a patient with known or suspected hypersensitivity is exposed to one of these, a severe immunological response with a life-threatening condition could occur.	No Hypersensitivity to insulin icodec/semaglutide (Kyinsu®) or to any of the excipients is listed as a contraindication in the product information for insulin icodec/semaglutide (Kyinsu®) in the SmPC Section 4.3 and Section 2 of the PL. The SmPC includes warning and precautions on hypersensitivity reactions in patients treated with insulin icodec/semaglutide (Kyinsu®). Section 4.4 of the SmPC states that allergic reactions may occur with all protein-based drugs. Immediate-type allergic reactions to either insulin icodec or semaglutide or the excipients may be potentially life-threatening.
History of pancreatitis (acute or chronic) within 180 days before screening	Acute pancreatitis has been observed with the use of GLP-1 receptor agonists and history of pancreatitis is a risk factor for pancreatitis.	No The SmPC includes warning and precautions on the use of insulin icodec/semaglutide (Kyinsu®) in patients with acute pancreatitis. Section 4.4 of the SmPC states that if pancreatitis is suspected in patients treated with insulin icodec/semaglutide (Kyinsu®), it should be discontinued and if confirmed insulin icodec/semaglutide (Kyinsu®) should not be restarted. Caution should be exercised in patients with a history of pancreatitis.
Myocardial infarction, stroke, hospitalisation 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.	These participants are considered vulnerable and excluded from studies in order not to jeopardise their safety and confound the results of the studies.	No

Criteria	Reason for being an exclusion criterion in the phase 3a programme[a]	Missing information (Yes/No) Rationale if not a missing information
Planned coronary, carotid or peripheral artery revascularisation.		The SmPC in section 4.4 states that there is no therapeutic experience in patients with congestive heart failure New York Heart Association (NYHA) class IV. However, there is no medical or scientific rationale to substantiate that a different safety profile would be expected in this population, based on the cumulative knowledge from nonclinical and clinical studies with insulin icodec and semaglutide.
Uncontrolled and potentially unstable diabetic retinopathy or maculopathy.	These participants are considered vulnerable and excluded from studies in order not to jeopardise their safety and confound the results of the studies	No The SmPC includes a warning and precautions on the use of insulin icodec/semaglutide (Kyinsu®) in patients with diabetic retinopathy. The section 4.4 of the SmPC states that patients with a medical history of diabetic retinopathy should be monitored closely and treated according to clinical guidelines. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded.
Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of eGFR <30 mL/min/1.73 m2 as defined by KDIGO 2012.	These participants are considered vulnerable and excluded from studies in order not to jeopardise their safety and confound the results of the studies.	No Section 4.2 of the SmPC states the following recommendation in the Special populations section. Insulin icodec/semaglutide (Kyinsu®) is not recommended for use in patients with end-stage renal disease, due to limited data with the semaglutide component. Based on the limited data available on exposure to the mono-components, semaglutide and insulin icodec in patients with severe renal impairment, the safety profile of insulin icodec/semaglutide (Kyinsu®) is not expected to be different between patients with normal renal function and severe renal impairment.
Pronounced hepatic impairment defined as alanine aminotransferase (ALT) ≥ 2.5 times or bilirubin >1.5 times upper limit of normal at screening	These participants are considered vulnerable and excluded from studies in order not to jeopardise their safety and confound the results of the studies.	Yes The population with severe hepatic impairment is included as missing information in the RMP based on the limited exposure to semaglutide mono-component in this population.

Criteria	Reason for being an exclusion criterion in the phase 3a programme[a]	Missing information (Yes/No) Rationale if not a missing information
		Participants with pronounced hepatic impairment were excluded from the clinical studies with insulin icodec/semaglutide (Kyinsu®). The safety profile of insulin icodec/semaglutide (Kyinsu®) in this population is unknown, therefore, this population with severe hepatic impairment is considered missing information. Details are provided in 2.7.3.7.
History of diabetic ketoacidosis	These participants are considered vulnerable and excluded from studies in order not to jeopardise their safety and confound the results of the studies.	No Untreated hyperglycaemia may eventually lead to diabetic ketoacidosis, which is potentially lethal. Administration of rapid-acting insulin should be considered in situations of severe hyperglycaemia. It is described in the SmPC (section 4.4) that insulin icodec/semaglutide (Kyinsu®) should not be used for the treatment of diabetic ketoacidosis.
Paediatric subpopulation	Insulin icodec/semaglutide (Kyinsu®) is not recommended for use in children and adolescents below 18 years of age. No studies have been performed with insulin icodec/semaglutide (Kyinsu®) in patients below 18 years of age.	No Insulin icodec/semaglutide (Kyinsu®) is currently not indicated in this population. As per the Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Revision 2), excluded populations from the clinical development programme should be included as missing information only when they are relevant for the approved and proposed indications and if the use in such populations might be associated with risks of clinical significance.
Females of childbearing potential who are pregnant, breastfeeding or intend to become pregnant or are not using adequate contraceptive methods.	This population was excluded due to the potential reproductive and developmental toxicity effects of semaglutide, based on observations from nonclinical studies.	Yes Pregnancy and breastfeeding is included as missing information in the RMP based on the limited exposure in this population. The safety profile of insulin icodec/semaglutide (Kyinsu®) in this population is unknown. Details are provided in 2.7.3.6.
Cancer and medical history of cancer 5 years prior to study entry (except basal cell skin cancer or squamous cell skin cancer).	Study participants with cancer or recent history of cancer are usually receiving specialised treatment, with close monitoring. These participants are considered vulnerable and excluded from studies in order not to jeopardise their safety and confound the results of the studies.	No There is no scientific rationale for why a different safety profile would be expected in this population, based on the cumulative knowledge from semaglutide and insulin icodec.

[a]Phase 3a pool from insulin icodec/semaglutide (Kyinsu®) clinical development program includes studies NN1535-4591, 4592, 4593.

Abbreviations: ADR = adverse drug reaction; AE = adverse event; ALT = alanine aminotransferase; eGFR = estimated Glomerular Filtration Rate; EU PI = European Union product information; GLP-1 RA = glucagon-like peptide-1 receptor agonist, GVP = good pharmacovigilance practices, KDIGO = Kidney Disease Improving Global Outcomes, MACE = major adverse cardiac event; PL = product leaflet; RMP= risk management plan, SmPC = Summary of Product Characteristics.

2.4.2 Limitations of ADR detection common to clinical study development programmes

The clinical development programmes are unlikely to detect certain types of adverse reactions, such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

2.4.3 Limitations with respect to populations typically under-represented in clinical study development programmes

Table 2-9 provides an overview of exposure in special populations in the phase 3a clinical studies completed before the data lock point (DLP).

Table 2-9 Exposure of special populations included or not in clinical study development programme

Type of special population	Participants exposed to insulin icodec/semaglutide (Kyinsu®)
Pregnant and breast-feeding women	Pregnant and breast-feeding women were excluded from clinical studies investigating insulin icodec/semaglutide (Kyinsu®) safety and efficacy. This population is considered missing information, refer to Section 2.4.1
Hepatic function	Phase 3a pool[a]
Impaired[b]	106
Renal function (GFR)	Phase 3a pool[a]
Mild (≥60 to <90 mL/min)	588
Moderate (≥30 to <60 mL/min)	133
Cardiac function	Phase 3a pool[a]
Cardiac disorders[c]	285
Vascular disorders[d]	1005
Geriatric age group	Phase 3a pool[a]
≥65 to <75 years	444
≥75 years to <85 years	76
≥85 years	3

[a]Phase 3a pool includes studies NN1535-4591, 4592, 4593. For total exposure in these studies, refer to Section 2.3.

[b]Impaired hepatic function is defined as having baseline total bilirubin > ULN or baseline aspartate aminotransferase > ULN. Baseline refers to evaluation at screening.

[c]Concomitant cardiac disorders at screening were filtered using the SOC Cardiac disorders.

[d]Concomitant vascular disorders at screening were filtered using the SOC Vascular disorders.

Abbreviations: GFR = glomerular filtration rate, RMP = risk management plan, ULN = upper normal limit.

2.5 Module SV: Post-authorisation experience

This section is not applicable, as this RMP for insulin icodec/semaglutide (Kyinsu®) is submitted with the application for marketing authorisation. Hence, no patients have been exposed to insulin icodec/semaglutide (Kyinsu®) in the post-marketing setting.

2.6 Module SVI: Additional EU requirements for the safety specification

2.6.1 Potential for misuse for illegal purposes

There is a potential for misuse or abuse of insulin icodec/semaglutide (Kyinsu®) as observed with all insulin products. Insulin products can be misused by patients with or without diabetes. Examples of misuse are intentional overdoses, suicide attempts and use for anabolic purposes by body builders or endurance athletes. [38-40] No cases of misuse or abuse of insulin icodec/semaglutide (Kyinsu®), insulin icodec and semaglutide were observed in the clinical development programme.

Reports of misuse for illegal purposes will be monitored through routine pharmacovigilance. From the data available, Novo Nordisk does not consider potential for misuse to be a safety concern for insulin icodec/semaglutide (Kyinsu®).

2.7 Module SVII: Identified and potential risks

2.7.1 Identification of safety concerns in the initial RMP submission

2.7.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Risks that are not considered important for the purpose of the risk management plan for insulin icodec/semaglutide (Kyinsu®) are grouped based on the rationale for non-inclusion (see Table 2-10). These risks are considered as well-characterized, appropriately managed and mitigated in the proposed product information for insulin icodec/semaglutide (Kyinsu®).

The overall safety profile of insulin icodec/semaglutide (Kyinsu®) is based on data from the phase 3a clinical studies (NN1535-4591, -4592, -4593) for which study participant exposure is presented in Section 2.3. Since insulin icodec/semaglutide (Kyinsu®) is a fixed-combination product of the mono-components, insulin icodec and semaglutide, the identified and potential risks for the mono-components are indicated as relevant in Table 2-10.

The important potential risk of ‘Aspiration in association with general anaesthesia and deep sedation’ and the missing information regarding ‘Patients with gastroparesis’ have been removed from the list of safety concerns. Per EMA’s request, Novo Nordisk awaits the outcomes of the ongoing semaglutide procedures (Kayshild EMEA/H/C/006426/0000 and EMA/VR/0000249026, EMEA/H/C/004953) to update the Risk Management Plan (RMP) for these safety concerns.

Table 2-10 Risks not considered important for inclusion in the list of safety concerns

Risk	Benefit−risk impact
Risks with minimal clinical impact on patients in relation to the severity of the indication treated	
Injection site reactions	Injection site reactions are listed in the SmPC as an ADR with uncommon frequency. The proportion of participants with AEs within injection site reactions were same between the insulin icodec/semaglutide (Kyinsu®) group and comparator group (0.8% in each group). All events were non-serious across the phase 3a programme. Injection site reactions are considered expected for any drug administered by subcutaneous injection such as insulin icodec/semaglutide (Kyinsu®). Additionally, given the reduction in injection frequency with the once weekly injection regimen for insulin icodec/semaglutide (Kyinsu®), the frequency of injection site reactions is expected to further reduce when compared to that with daily injection regimens. The impact of the injection site reactions on the benefit-risk balance is considered minimal based on the mild severity and the transient nature of these adverse events. Injection site reactions are considered to have minimal clinical consequences and are therefore, considered a non-important risk for insulin icodec/semaglutide (Kyinsu®).
Peripheral oedema	Peripheral oedema is listed as an ADR with uncommon frequency in the SmPC. It was observed in a higher proportion of participants in the comparator group than in the insulin icodec/semaglutide (Kyinsu®) group (0.6%, 11 events for insulin icodec/semaglutide (Kyinsu®) vs 2.1%, 27 events for comparators). All the events in the phase 3a pool were non-serious and did not result in treatment withdrawal. The risk of peripheral oedema has minimal impact on the patients due to the mild severity and non-seriousness of the AEs. This, combined with the transient nature of these adverse events, is consistent with minimal clinical consequence and is, therefore, considered a non-important risk for insulin icodec/semaglutide (Kyinsu®).
Dizziness	Dizziness is listed in the SmPC as a common ADR. It was observed in a higher proportion of participants with insulin icodec/semaglutide (Kyinsu®) treatment (4.5%, 68 events) versus the comparator (2.9%, 47 events). The majority of events were non-serious. Therefore, dizziness is considered to have minimal clinical impact and hence is a non-important risk for insulin icodec/semaglutide (Kyinsu®).
Fatigue	Fatigue is listed in the SmPC as a common ADR. It was observed in a higher proportion of participants on insulin icodec/semaglutide (Kyinsu®) treatment (3.2%, 49 events) versus the comparator (2.0%, 28 events). Majority of the events were non-serious. Therefore, fatigue is considered to have minimal clinical impact and hence is a non-important risk for insulin icodec/semaglutide (Kyinsu®).
Increased heart rate	Increased heart rate is listed in the SmPC as a common ADR since in the phase 3a data pool for insulin icodec/semaglutide (Kyinsu®). It was observed in higher proportion of participants on insulin icodec/semaglutide (Kyinsu®) treatment (1.3%, 18 events) versus the comparator group (0.5%, 6 events). All these events were non-serious, mild to moderate. One event in the insulin icodec/semaglutide (Kyinsu®) group led to treatment withdrawal. Therefore, increased heart rate is considered to have minimal clinical impact and hence is a non-important risk for insulin icodec/semaglutide (Kyinsu®).
Decreased appetite	Decreased appetite is listed in the SmPC as a common ADR. It was observed in a higher proportion of participants on insulin icodec/semaglutide (Kyinsu®) treatment (5.4%, 130 events) versus the comparator (1.3%, 73 events). All decreased appetite events were non-serious and 1 event led to treatment withdrawal. Therefore, decreased appetite is considered to have minimal clinical impact and hence is a non-important risk for insulin icodec/semaglutide (Kyinsu®).
Headache	Headache is listed in the SmPC as a common ADR. It was observed in a higher proportion of participants in the insulin icodec/semaglutide (Kyinsu®) group (5.1%, 100 events) versus the comparator group (2.4%, 39 events). Majority of events in the phase 3a pool were non-serious and 1 event resulted in treatment withdrawal. Therefore, headache is considered to have minimal clinical impact and hence is a non-important risk for insulin icodec/semaglutide (Kyinsu®).

<table>
<tr><th>Risk</th><th>Benefit−risk impact</th></tr>
<tr><td>Dysgeusia</td><td>Dysgeusia is listed in the SmPC as an uncommon ADR. Dysgeusia was reported by a higher proportion of participants in the insulin icodec/semaglutide (Kyinsu®) group than the comparator group (0.5%, 10 events for insulin icodec/semaglutide (Kyinsu®) vs 0.1%, 1 event for comparator). All the events in the phase 3a pool were non-serious and did not result in treatment withdrawal. Therefore, dysgeusia is considered to have minimal clinical impact and it is, therefore, considered a non-important risk for insulin icodec/semaglutide (Kyinsu®).</td></tr>
<tr><td>Delayed gastric emptying</td><td>Delayed gastric emptying is listed in the SmPC as an ADR with unknown frequency. It was not observed in the phase 3a pool for insulin icodec/semaglutide (Kyinsu®). It is a risk for semaglutide and since insulin icodec/semaglutide (Kyinsu®) is a fixed combination product of semaglutide and insulin icodec, delayed gastric emptying is classified as a non-important identified risk for insulin icodec/semaglutide (Kyinsu®). It is related to the mode of action of semaglutide but the effect could also be perceived as adverse by patients.</td></tr>
<tr><td>Abdominal pain
Constipation
Dyspepsia
Gastroesophageal reflux disease (GERD)
Gastritis
Abdominal distention
Flatulence
Eructation</td><td>Gastrointestinal AEs (including abdominal pain, constipation, dyspepsia, gastroesophageal reflux disease, gastritis, abdominal distention, flatulence, eructation) are listed in the SmPC as ADRs with a common frequency.

These events were reported in higher proportion of participants in the insulin icodec/semaglutide (Kyinsu®) group as compared to the comparator group (refer Table 1 below). Most of these events were non-serious and mild to moderate in severity. The proportion of participants with serious and severe GI AEs were low and comparable between insulin icodec/semaglutide (Kyinsu®) and comparator treatment groups. In all treatment groups, the majority of GI AEs were resolved and did not lead to drug withdrawal.

Therefore, GI adverse reactions (abdominal pain, constipation, dyspepsia, gastroesophageal reflux disease, gastritis, abdominal distention, flatulence, eructation) are considered to have minimal clinical impact and are therefore, considered non-important risks for insulin icodec/semaglutide (Kyinsu®).

Table 1: GI AEs reported in the phase 3a data pool from the insulin icodec/semaglutide (Kyinsu®) clinical development program
<table>
<tr><th rowspan="2">Gastrointestinal adverse reactions</th><th colspan="2">Insulin icodec/semaglutide (Kyinsu®)</th><th colspan="2">Comparator</th></tr>
<tr><th>% Participants</th><th>Events</th><th>% Participants</th><th>Events</th></tr>
<tr><td>Total GI AEs</td><td>42.1</td><td>1717</td><td>23.8</td><td>639</td></tr>
<tr><td>Abdominal pain</td><td>3.2</td><td>50</td><td>1.9</td><td>27</td></tr>
<tr><td>Constipation</td><td>4.4</td><td>77</td><td>2.5</td><td>43</td></tr>
<tr><td>Dyspepsia</td><td>4.7</td><td>83</td><td>1.4</td><td>20</td></tr>
<tr><td>Gastroesophageal reflux disease</td><td>2.6</td><td>37</td><td>1.1</td><td>17</td></tr>
<tr><td>Gastritis</td><td>1.0</td><td>16</td><td>0.8</td><td>13</td></tr>
<tr><td>Abdominal distention</td><td>2.0</td><td>32</td><td>0.8</td><td>10</td></tr>
<tr><td>Flatulence</td><td>1.7</td><td>26</td><td>0.5</td><td>8</td></tr>
<tr><td>Eructation</td><td>1.3</td><td>27</td><td>0.2</td><td>3</td></tr>
</table>
Abbreviations: AE = adverse event.</td></tr>
<tr><td>Hypersensitivity</td><td>Hypersensitivity is listed in the SmPC as a common ADR. Hypersensitivity to insulin icodec/semaglutide (Kyinsu®) or any of the excipients is included as a contraindication in the SmPC Section 4.3.

In the phase 3a pool, the proportion of participants with hypersensitivity reactions was lower in the insulin icodec/semaglutide (Kyinsu®) group (3.9%, 56 events) as compared</td></tr>
</table>

Risk	Benefit−risk impact
	to the comparator group (5.1%, 78 events). Majority of the events were non-serious and mild to moderate in severity. Majority of these events were considered unlikely related to the trial product by the investigator and did not lead to any change in treatment dose. Two events in insulin icodec/semaglutide (Kyinsu®) group led to withdrawal of trial product. In both groups, majority of the events were reported resolved. Hence, hypersensitivity is considered a non-important risk for insulin icodec/semaglutide (Kyinsu®).
Drug-drug interaction (DDI) with warfarin and other coumarin derivatives	DDI with warfarin and other coumarin derivatives is described in Section 4.5, Interaction with other medicinal products and other forms of interaction, of the SmPC. No events of DDI with warfarin and other coumarin derivatives were reported from the phase 3a pool for insulin icodec/semaglutide (Kyinsu®). It is a risk for the mono-component semaglutide and since insulin icodec/semaglutide (Kyinsu®) is a fixed combination product of semaglutide and insulin icodec, DDI is classified as a non-important potential risk for insulin icodec/semaglutide (Kyinsu®). The update was based on post-marketing cases of decreased INR. On 11 Jan 2024, in connection with the final assessment report for the semaglutide PSUR (period 01-JUN-2023 – 31-MAY-2023), PRAC requested inclusion of cases of drug-drug interaction between acenocoumarol and semaglutide to section 4.5 of Ozempic®/ Wegovy®/ Rybelsus® SmPCs.
Risks where serious consequences occur at low frequencies and therefore considered to be acceptable in relation to the severity of the indication being treated	
Increased amylase and lipase	Lipase increased and amylase increased are listed as ADRs with unknown frequency in the SmPC. In the insulin icodec/semaglutide (Kyinsu®) clinical studies, 2 events of lipase increased were reported in the insulin icodec/semaglutide (Kyinsu®) treatment arm. These events were non-serious and assessed as probably related to study drug. No events of amylase increased were reported. Increased amylase and lipase are risks for the semaglutide mono-component and since insulin icodec/semaglutide (Kyinsu®) is a fixed combination product of semaglutide and insulin icodec, lipase increased, and amylase increased are classified as non-important identified risks for insulin icodec/semaglutide (Kyinsu®). The elevations of lipase or amylase activities observed with semaglutide s.c. for T2D were not predictive of the development of pancreatitis in the absence of other signs or symptoms of pancreatitis. Therefore, these ADRs are not considered a safety concern.
Known risks that require no further characterisation, and the potential clinical consequences will be monitored via routine pharmacovigilance namely through signal detection and adverse reaction reporting	
Gastrointestinal adverse reactions (nausea, vomiting, diarrhoea)	Gastrointestinal adverse reactions (nausea, vomiting and diarrhoea) are a class effect for GLP-1 RAs and are listed as ADRs with very common frequency (nausea and diarrhoea) and common frequency (vomiting). In addition, a warning is included in the SmPC Section 4.4 stating that gastrointestinal adverse reactions can cause dehydration, which in rare cases can lead to deterioration of renal function. Nausea, vomiting and diarrhoea were reported with higher event rates in the insulin icodec/semaglutide (Kyinsu®) group as compared to the comparator group. Most of these events were non-serious. The proportion of serious events was lower in the insulin icodec/semaglutide (Kyinsu®) group when compared to the comparator group. Overall, severe AEs were higher in the insulin icodec/semaglutide (Kyinsu®) group when compared to the comparator groups (refer Table 2 below). The median durations of these events with insulin icodec/semaglutide (Kyinsu®) were 3 days (nausea), 4 days (diarrhoea) and 2 days (vomiting) and were the same as that observed in the comparator groups. Therefore, gastrointestinal adverse reactions are not considered important for inclusion in the list of safety concerns in the RMP. However, considering its potential impact, the risk of gastrointestinal adverse reactions (nausea, vomiting and diarrhoea) will be monitored and presented as a separate topic in future PSURs.

<table>
<tr><th>Risk</th><th>Benefit−risk impact</th></tr>
<tr><td></td><td>

Table 2: Nausea, vomiting and diarrhoea events reported in the phase 3a data pool from the insulin icodec/semaglutide (Kyinsu®) clinical development program

<table>
<tr><td rowspan="2">Nausea, vomiting and diarrhoea</td><td colspan="2">Insulin icodec/semaglutide (Kyinsu®)</td><td colspan="2">Comparator</td></tr>
<tr><td>% Participants</td><td>Events</td><td>% Participants</td><td>Events</td></tr>
<tr><td>Total AEs</td><td>43</td><td>1,107</td><td>17.3</td><td>361</td></tr>
<tr><td>Serious AEs</td><td>0.5</td><td>3</td><td>1.2</td><td>6</td></tr>
<tr><td>Severe AEs</td><td>0.8</td><td>11</td><td>0.1</td><td>1</td></tr>
</table>

Abbreviations: AE = adverse event.
</td></tr>
<tr><td>Cholelithiasis</td><td>Cholelithiasis is listed in the SmPC as an ADR with an uncommon frequency. No difference between groups was observed (0.5%, 7 events in insulin icodec/semaglutide (Kyinsu®) vs. 0.5%, 6 events in the comparator group). Most of the events were mild or moderate in severity and unlikely related to the trial product. None of the events led to withdrawal of the trial product. Therefore, this risk is not considered important for inclusion in the list of safety concerns in the RMP. However, considering its potential impact, the risk will be monitored and presented in the future PSURs.</td></tr>
<tr><td>Acute pancreatitis</td><td>Acute pancreatitis is included the SmPC as an uncommon ADR and the class labelling text is included in Section 4.4.

Three (3) events of acute pancreatitis in 2 participants in the insulin icodec/semaglutide (Kyinsu®) group were identified in the phase 3a pool. Two (2) events were assessed as probably/possibly due to insulin icodec/semaglutide (Kyinsu®) treatment while 1 event was assessed as unlikely related to insulin icodec/semaglutide (Kyinsu®).

Since there is no evidence of an increased risk of acute pancreatitis with insulin icodec/semaglutide (Kyinsu®), this risk is not considered important for inclusion in the list of safety concerns in the RMP. However, it will be monitored and presented in the future PSURs.</td></tr>
<tr><td>Intestinal obstruction</td><td>Intestinal obstruction is listed as ADR with unknown frequency in the SmPC as it is considered a class effect for the GLP-1 RA drug class. No safety concern was identified based on the current data from completed clinical studies with semaglutide, post-marketing cases and literature cases. No events of intestinal obstruction were reported with insulin icodec/semaglutide (Kyinsu®) in the phase 3a pool.

Therefore, intestinal obstruction is not considered important for inclusion in the list of safety concerns in the RMP. However, considering its potential impact, the risk will be monitored and presented as a separate topic in the future PSURs.</td></tr>
<tr><td>Hypoglycaemia</td><td>Hypoglycemia is a risk well characterized and associated with all insulins. It is listed as an ADR with very common frequency in the SmPC.

A statistically significant difference in favour of insulin icodec/semaglutide (Kyinsu®) was observed in the rate of severe (level 3) or clinically significant (level 2) hypoglycaemic episodes between insulin icodec/semaglutide (Kyinsu®) and insulin icodec in study NN1535-4591 (treatment rate ratio: 0.22 [95% CI: 0.14; 0.36; p-value <0.0001 for superiority]) and between insulin icodec/semaglutide (Kyinsu®) and basal-bolus insulin in study NN1535-4593 (treatment rate ratio: 0.12 [95% CI: 0.08; 0.17; p value <0.0001 for superiority]).

In the post GLP-1 RA population (study NN1535-4592), the proportion of participants with events and event rates of severe (level 3) or clinically significant (level 2) hypoglycaemic episodes were similar between insulin icodec/semaglutide (Kyinsu®) (3.5%, 4.18 events per 100 PYE) and the semaglutide groups (3.8% participants; event rate, 3.56 events per 100 PYE). Therefore, hypoglycaemia is not included as a safety concern in the RMP. However, considering its potential impact, the risk will be monitored and presented as a separate topic in the future PSURs.</td></tr>
</table>

Risk	Benefit−risk impact
	For prolonged hypoglycaemia, the data based on continuous glucose monitoring (CGM) from NN1535-4591 and NN1535-4593 demonstrated no concern regarding prolonged hypoglycaemia during treatment with insulin icodec/semaglutide (Kyinsu®) versus comparators (insulin icodec and insulin glargine + insulin aspart). In both studies, the median duration of periods with <3.0mmol/L blood glucose levels were shorter for insulin icodec/semaglutide (Kyinsu®) when compared to the comparators.
Antibody formation leading to changes in clinical effect	The risk of antibody formation is mentioned under the Warnings and precautions section of the SmPC. In participants treated with insulin icodec/semaglutide (Kyinsu®), the proportion of participants with anti-semaglutide antibodies was low (1.4% to 5.9%). The anti-semaglutide antibodies response did not appear to influence semaglutide pharmacokinetics, safety or efficacy. Therefore, the risk for antibody formation leading to changes in the clinical effect is not considered a safety concern in the RMP. This risk will be monitored and presented as a separate topic in future PSURs.
Serious allergic reactions (including anaphylactic reaction and angioedema)	Allergic reaction is a hypothetical risk for all protein-based drugs. Anaphylactic reaction and angioedema are listed in the SmPC as ADRs with unknown frequency. In the insulin icodec/semaglutide (Kyinsu®) group, one event of anaphylactic shock due to wasp stings was reported and therefore was assessed as unrelated to the trial product. No events of angioedema have been observed in participants in any of the treatment groups in phase 3a pool. Serious allergic reactions are not considered important for inclusion in the list of safety concerns in the RMP. However, considering their potential impact, these risks will be monitored and presented as a separate topic in future PSURs.

Abbreviations: ADR = adverse drug reaction, CGM = continuous glucose monitoring, DDI = drug-drug interaction, GLP-1 RA = glucagon like peptide-1 receptor agonist, INR= international normalised ratio, PSUR = periodic safety update report, RMP = risk management plan, s.c.= subcutaneous, SmPC = summary of product characteristics, T2D = type 2 diabetes.

2.7.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

The risks included in Table 2-11 are considered the important risks for inclusion in the list of safety concerns for insulin icodec/semaglutide (Kyinsu®). They are further characterized in Section 2.7.3.

Table 2-11 Brief presentation of important safety concerns

Safety concerns	Benefit−risk impact
Important identified risks	
Diabetic retinopathy complications	The risk is included as an important identified risk based on the findings in the semaglutide s.c. clinical development programme. There was no increased risk of diabetic retinopathy with insulin icodec/semaglutide (Kyinsu®). The rates and proportions of diabetic retinopathy events were comparable between insulin icodec/semaglutide (Kyinsu®) and comparator groups. Most events were non-serious and mild or moderate in severity. The events related to diabetic retinopathy complications observed in the phase 3a pool likely represent the natural progression of T2D and are considered expected in a population with prevalent risk factors for diabetic retinopathy such as long diabetes duration, poor glycaemic control and predisposing comorbidities. In addition, a higher proportion of participants with diabetic retinopathy events had a history of diabetic retinopathy when compared to the participants without events.

Safety concerns	Benefit−risk impact
	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.
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. No events were reported in the phase 3a data pool from the insulin icodec/semaglutide (Kyinsu®) development program. Considering the fact that MTC is a rare event, a post-approval active surveillance programme for MTC has been established to monitor for any signal indicating a possible association between treatment with long-acting GLP-1 RAs and development of MTC. If any safety findings arise from the following PASS for the semaglutide mono-component, these will be assessed for their relevance to insulin icodec/semaglutide (Kyinsu®).
Pancreatic cancer	The risk is included as an important potential risk for semaglutide, based on the outcome of the EC regulation 726/2004 Article 5(3) referral procedure in 2013 (EMEA/H/A-5(3)/1369). Pancreatic metaplastic changes have been observed in animal models following administration of incretin mimetic drugs, which may suggest that prolonged exposure to incretin mimetic drugs lead to an increased risk of pancreatic cancer. Therefore, the risk is included as an important potential risk for semaglutide. Since, insulin icodec/semaglutide (Kyinsu®) is a fixed combination product of semaglutide and insulin icodec, pancreatic cancer is a potential risk for insulin icodec/semaglutide (Kyinsu®). There was no indication of an increased relative risk in the insulin icodec/semaglutide (Kyinsu®) treatment group versus. comparator in the phase 3a pool. No events of pancreatic cancer were reported in the insulin icodec/semaglutide (Kyinsu®) treatment group while 3 events were reported in the comparator group. A post authorization epidemiological study is ongoing to assess the risk of pancreatic cancer associated with the use of semaglutide in patients with T2D. If any safety findings arise from the following PASS 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	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. Overall, in the phase 3a pool, medication errors were reported in 25 participants (2.12 events per 100 PYE) from the insulin icodec/semaglutide (Kyinsu®) group, compared to 55 participants (5.45 events per 100 PYE) from the comparator groups. In the insulin icodec/semaglutide (Kyinsu®) group, none of the events were serious, most of them were mild in severity.

Safety concerns	Benefit−risk impact
	In 13 of the 25 participants, causality was assessed as probably/possibly related to insulin icodec/semaglutide (Kyinsu®) treatment. Medication errors due to mix-up cover the following PTs: Incorrect product formulation administered, Product dispensing error, Product prescribing error, Wrong device selected, Wrong drug, Wrong product administered. In the phase 3a programme, a total of 7 events of medication errors due to mix-up were reported and all were coded with the PT 'Wrong product administered'. One event was reported in the insulin icodec/semaglutide (Kyinsu®) group, while 6 events were reported in the comparator group. Medication errors are a known risk for many insulin products and can result in loss of glycaemic control depending on the nature of the mix-up. Serious clinical consequences related to over- or under-dosing due to product mix-ups represent an important consideration for the benefit-risk assessment. Any impact of this risk on the benefit–risk balance of insulin icodec/semaglutide (Kyinsu®) is anticipated to be reduced by the measures taken in the labelling and product appearance and the additional risk minimization measure in the form of a patient guide. Standardised follow-up questionnaires for post-marketing reporting of medication errors will be used to further characterise this risk in the post-marketing setting.
Medication error during switch from other injectable diabetes treatments	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. During switch from other injectable diabetes treatments to weekly insulin icodec/semaglutide (Kyinsu®) treatment, medication errors such as overdose or dosing errors (example, due to lack of awareness around the different dosing terminologies or dosing schedule) can occur. Since this risk is specific to insulin icodec/semaglutide (Kyinsu®), it is not meaningful to compare the parameters of this risk with the comparator group, as some of the comparators are for daily administration and/or use a different dosing terminology such as unit or mg. A period of 30 days from the initiation of insulin icodec/semaglutide (Kyinsu®) treatment is considered relevant to assess medication errors during switch from other injectable diabetes treatments. A total of 8 events (8 participants) of medication errors were reported during switch from other injectable diabetes treatments to insulin icodec/semaglutide (Kyinsu®). In these 8 participants, 3 participants administered insulin icodec/semaglutide (Kyinsu®) once daily instead of once weekly (for 1, 13 and 39 days, respectively), 2 participants continued pre-trial insulin along with insulin icodec/semaglutide (Kyinsu®) (for 16 and 41 days, respectively) while 3 participants reported underdosing (60 instead of 70 dose steps, 40 instead of 60 dose steps, and no insulin icodec/semaglutide (Kyinsu®) for 4 weeks as the participant failed to remove the second safety cap from the needle).

Safety concerns	Benefit−risk impact
	In relation to the medication errors during switch from other injectable diabetes treatments to insulin icodec/semaglutide (Kyinsu®), the following AEs were reported: • In 1 participant administering insulin icodec/semaglutide (Kyinsu®) daily, two level 1 hypoglycaemic episodes were reported. • In 2 participants continuing pre-trial insulin, one participant reported two level 1 hypoglycaemic episodes while three were reported in the other participant. • In 5 participants that erroneously administered high doses, 1 participant reported a GI AE; that is, a case of nausea 6 days after the medication error had occurred. None of the 3 participants reporting underdosing were observed to co-report hyperglycaemia in relation to the medication errors. Medication errors are a known risk for many insulin products and can result in loss of glycaemic control depending on the nature of the medication error. Serious clinical consequences related to over-dosing during switch from other injectable diabetes treatments represent an important consideration for the benefit-risk assessment. Any impact of this risk on the benefit–risk balance of insulin icodec/semaglutide (Kyinsu®) is anticipated to be reduced by the measures taken in the product information to mitigate this risk and the additional risk minimization measure in the form of a patient guide. Standardised follow-up questionnaires for post-marketing reporting on medication errors will be used to further characterise this risk in the post-marketing setting.
Missing information	
Pregnancy and breastfeeding	Insulin icodec/semaglutide (Kyinsu®) has not been studied in pregnant or breastfeeding women, and the potential risk of insulin icodec/semaglutide (Kyinsu®) treatment during pregnancy and breast-feeding is unknown. No pregnancies were reported in the study period. Hence, use of insulin icodec/semaglutide (Kyinsu®) in pregnancy and breastfeeding is considered missing information and will be monitored in the post-marketing setting through routine pharmacovigilance activities. If evidence should emerge in the post-marketing setting that indicates a different safety profile of insulin icodec/semaglutide (Kyinsu®) in this population, the impact on the benefit-risk balance will depend on the type and incidence rate of the adverse effects as well as on effectiveness of risk mitigating measures. In section 4.6 of the SmPC, it is stated that insulin icodec/semaglutide (Kyinsu®) should not be used during pregnancy and breast-feeding.
Patients with severe hepatic impairment	Patients with severe hepatic impairment were excluded from the insulin icodec/semaglutide (Kyinsu®) clinical development program and therefore the safety profile of insulin icodec/semaglutide (Kyinsu®) this population is unknown. The limited data from patients with hepatic impairment showed that the safety profile was not affected to a clinically meaningful extent. However, the exposure to insulin icodec/semaglutide (Kyinsu®) in this population is currently limited. Therefore, the population with severe hepatic impairment is considered missing information and will be monitored in the post-marketing setting through routine pharmacovigilance activities.

Safety concerns	Benefit−risk impact
	If evidence should emerge in the post-marketing setting that indicates a different safety profile of insulin icodec/semaglutide (Kyinsu®) in this population, the impact on the benefit-risk balance will depend on the type and incidence rate of the adverse effects as well as on effectiveness of risk mitigating measures. In section 4.2 of the SmPC, it is stated that experience with the use of insulin icodec/semaglutide (Kyinsu®) in patients with severe hepatic impairment is limited and that caution should be exercised when treating these patients with insulin icodec/semaglutide (Kyinsu®).

Abbreviations: CVOT= cardiovascular outcome trial, EU PI = European Union product information, GLP-1 RA = glucagon like peptide-1 receptor agonist, MTC= medullary thyroid cancer.

2.7.2 New safety concerns and reclassification with a submission of an updated RMP

This section is not applicable, as this is the first RMP submitted for insulin icodec/semaglutide (Kyinsu®).

2.7.3 Details of important identified risks, important potential risks, and missing information

2.7.3.1 Important identified risk: diabetic retinopathy complications

Potential mechanisms

This risk was identified based on findings in NN9535-3744 (SUSTAIN 6) (M 5.3.5.4), a CVOT to evaluate the cardiovascular outcomes associated with the use of semaglutide in patients with T2D at high cardiovascular risk. It is well established that a rapid decline in blood glucose can lead to initial worsening of diabetic retinopathy.[41] Analyses from SUSTAIN 6 indicate this as the most likely mechanism underlying the increased risk of diabetic retinopathy complications with semaglutide s.c. treatment. This was primarily seen in the subset of participants characterised by a longer duration of diabetes, history of diabetic retinopathy at baseline, a high baseline HbA1c and insulin use.

Studies have shown that despite initial early worsening, participants experienced substantial long-term benefit from good glycaemic control with respect to diabetic retinopathy.[42]

Evidence source and strength of evidence

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.

Diabetic retinopathy is a risk for insulin icodec/semaglutide (Kyinsu®) based on the findings from the SUSTAIN 6 study. Across the phase 3a trials with insulin icodec/semaglutide (Kyinsu®), there was no increased risk of diabetic retinopathy with insulin icodec/semaglutide (Kyinsu®) (see details below). The rates and proportions of diabetic retinopathy events were comparable between insulin icodec/semaglutide (Kyinsu®) and comparator groups. The events related to diabetic retinopathy

complications observed in the phase 3a pool likely represent the natural progression of T2D and are considered expected in a population with prevalent risk factors for diabetic retinopathy such as long diabetes duration, poor glycaemic control and predisposing comorbidities. In addition, a higher proportion of participants with diabetic retinopathy events had a history of diabetic retinopathy when compared to the participants without events.

The insulin icodec/semaglutide (Kyinsu®) phase 3a studies were not designed to specifically evaluate diabetic retinopathy outcomes. Events were identified during eye examinations performed to assess the presence of diabetic retinopathy at screening and at week 52 (end of treatment visit). Therefore, there is a need to evaluate the long-term effects of semaglutide on diabetic retinopathy in patients with type 2 diabetes (T2D) using validated and standardised ophthalmic assessments. This is the objective of the NN9535-4352 study (FOCUS), a post-authorization safety study for semaglutide. The safety findings from this study will provide evidence to further characterize this risk and will be assessed for its relevance to insulin icodec/semaglutide (Kyinsu®).

Characterisation of the risk

Impact on quality of life

Diabetic retinopathy is reported to significantly reduce health-related quality of life.[43-45] Diabetic retinopathy is often asymptomatic, particularly in the early stages of the disease. For patients experiencing complications in the later stages of the disease, e.g., significantly reduced vision (including blindness), the impact is considered major. However, for most patients, the impact is considered to be low as the condition is manageable with appropriate monitoring and treatment.

Data from clinical trials with insulin icodec/semaglutide (Kyinsu®)

In the phase 3a studies with insulin icodec/semaglutide (Kyinsu®), eye examinations (fundus photography or by slit lamp biomicroscopy examination) were performed at screening and at week 52 (end of treatment visit). No event adjudication was performed.

A MedDRA search capturing all events of retinal disorders and visual impairment was adopted to identify events that are typically associated with the progression of diabetes or for which diabetes constitutes a significant risk factor.

Participants with uncontrolled and potentially unstable diabetic retinopathy or maculopathy were excluded from the clinical trials with insulin icodec/semaglutide (Kyinsu®).

Diabetic retinopathy data are presented from first dose to end of study period. Eye examinations were evaluated based on the on-treatment and in-study period due to the possible long latency between onset and diagnosis of these events.

The number of cases, proportion, number of events and reporting rates of diabetic retinopathy by preferred term are shown in Table 2-12 for insulin icodec/semaglutide (Kyinsu®) and all comparators.

Table 2-12 Events of diabetic retinopathy by preferred term - from first dose to end of study – insulin icodec/semaglutide (Kyinsu®) phase 3a pool[a]

	Insulin icodec/semaglutide (Kyinsu®)				Comparator			
Number of participants	1,325				1,312			
PYO	1,407.72				1,398.25			
Number of participants with diabetic retinopathy reported at baseline	209 (15.8%)				212 (16.2%)			
	N	**%**	**E**	**R**	**N**	**%**	**E**	**R**
Diabetic retinopathy complications[b]	123	9.3	157	11.16	106	8.1	149	10.68
SOC 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

[a]Phase 3a pool includes studies NN1535-4591, 4592, 4593.

[b]PTs with >5 events reported are presented in the table.

Abbreviations: PYO = patient years of observation, SOC = system organ class.

The proportion of participants with AEs within the MedDRA search for diabetic retinopathy and the event rates were comparable between insulin icodec/semaglutide (Kyinsu®) (9.3%, 11.16 events per 100 PYO) and comparators (8.1%, 10.68 events per 100 PYO). Majority of events were non-serious, mild or moderate in severity, judged by the investigator as unlikely related to trial product and did not lead to change in study dose. The outcome for the majority of events was not recovered.

Most of the events were identified in connection with the protocol scheduled end of treatment eye examinations and were not based on emergence of eye-related symptoms.

Data from literature sources: Incidence and prevalence in the background population

The incidence rate of diabetic retinopathy is in the range of 38–125 per 1,000 person-years in patients with T2D and varies with the length of follow-up time and race.[46]

The age-standardised global prevalence of any diabetic retinopathy and proliferative diabetic retinopathy in patients with T2D are 25.2% and 3.0%, respectively.[47]

Risk factors and risk groups

Patient risk factors include increasing age, long duration of diabetes, poor glycaemic control, prior history of diabetic retinopathy and rapid decline in HbA1c.[48]

Preventability

Patients with diabetes should have eye examinations performed as per clinical guidelines and any detected changes in the retina should be appropriately managed in order to prevent further complications of diabetic retinopathy. These patients should be monitored closely and treated according to clinical guidelines. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded. Good long-term glycaemic control decreases the risk of diabetic retinopathy.[41]

Impact on the benefit−risk balance of the product

The proportion of participants with AEs within the MedDRA search for diabetic retinopathy complications and the event rates were comparable between insulin icodec/semaglutide (Kyinsu®) (9.3%, 11.16 events per 100 PYE) and comparators (8.1%, 10.68 events per 100 PYE).

The proportion of participants with a history of diabetic retinopathy (based on the MedDRA search) at baseline was greater in participants with diabetic retinopathy events compared to those without diabetic retinopathy events in both insulin icodec/semaglutide (Kyinsu®) (38.2% vs 22.8%) and comparator groups (43.4% vs 23.5%).

Participants with diabetic retinopathy adverse events had longer diabetes duration compared to participants without diabetic retinopathy adverse events, both for insulin icodec/semaglutide (Kyinsu®) (mean duration 15.7 years vs. 14.2 years) and comparator groups (mean duration 15.2 years vs. 14.4 years). No relevant difference in other risk factors (age, sex, and baseline HbA1c) between participants with and without events were observed.

The results for AEs related to diabetic retinopathy are reflecting a T2D trial population with long disease duration and poor glycaemic control. Given the high prevalence of diabetic retinopathy in patients with diabetes, the rate of events and event types observed in the phase 3a pool, likely represent a natural progression of the disease and is considered expected in the population with long standing diabetes.

Initial worsening of diabetic retinopathy has been seen with intensive treatment with glucose-lowering agents,[49] but continued intensive therapy provided a greater benefit for patients with diabetic retinopathy in the long term. In addition to this, the recently published ACCORD follow-up trial demonstrated a 'legacy effect' with a post-treatment benefit of intensive glycaemic control on the progression of eye disease.[50]

Taken together, the benefits of the long-term improved glycaemic control, including reduction in diabetes complications, are considered to outweigh the risk of diabetic retinopathy complications during diabetes therapy intensification.

Public health impact

The attributed risk (difference between insulin icodec/semaglutide (Kyinsu®) rate and comparator rate) for developing diabetic retinopathy complications when treated with insulin icodec/semaglutide (Kyinsu®) was 0.48 events per 100 PYO in the phase 3a data pool.

Considering the risk factors in relation to the size of the target population, the public health impact is anticipated to be minimal.

2.7.3.2 Important potential risk: medullary thyroid cancer

Potential mechanisms

Medullary thyroid carcinoma (MTC) is a rare thyroid malignancy arising from the parafollicular C cells. Thyroid C-cell tumours were observed in semaglutide carcinogenicity studies in mice and rats. Based on mechanistic data generated by Novo Nordisk and data from the literature, it has been shown that the C-cell tumours induced in mice and rats following dosing of semaglutide are caused by a non-genotoxic, specific GLP-1 receptor-mediated mechanism to which mice and rats are particularly sensitive, whereas monkeys and humans are not (Section 2.2.1).

Evidence source and strength of evidence

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.

No events were reported in the phase 3a data pool from the insulin icodec/semaglutide (Kyinsu®) development program.

Considering the fact that MTC is a rare event, a post-approval active surveillance programme for MTC has been established to monitor for any signal indicating a possible association between

treatment with long-acting GLP-1 RAs and development of MTC. The safety findings from this study will provide evidence to further characterize this risk and will be assessed for its relevance to insulin icodec/semaglutide (Kyinsu®).

Characterisation of the risk

Impact on the individual patient

The management of MTC will impact the patient's quality of life. Surgery is primarily required for the management of MTC, but chemotherapy or radiation therapy may also be required. MTC may result in death. The 10-year overall survival rate in unselected patients with MTC is approximately 75%, but it decreases to 40% or less in patients with locally advanced or metastatic disease.[51]

Data from clinical studies with insulin icodec/semaglutide (Kyinsu®)

In the insulin icodec/semaglutide (Kyinsu®) phase 3 clinical development programme, no events of MTC were reported.

Data from literature sources: Incidence in the general population

Previous studies report that MTC accounts for a small percentage of thyroid cancer overall, with estimates of the proportion ranging from 1–2%.[52-54] Among patients with T2D, the incidence rate of thyroid cancer has been reported to be 0.24 per 1,000 person-years.[55]

No studies evaluating the incidence of MTC in patients with diabetes are available. In the general population, the incidence rate was between 0.0021–0.0028 per 1,000 person-years.[56, 57]

Risk factors and risk groups

Patient risk factors for MTC include family history or medical history of multiple endocrine neoplasia 2 (MEN2), a group of medical disorders associated with tumours of the endocrine system.

Preventability

No causal relationship between insulin icodec/semaglutide (Kyinsu®) or semaglutide and MTC is established therefore preventability is not applicable.

Impact on the benefit−risk balance of the product

The impact on the benefit–risk balance will depend on the size of the attributed risk if a causal relationship is confirmed. Considering that MTC is a rare event in the general population, the absolute risk is expected to be very low, and the potential impact on the benefit–risk balance is expected to be minimal.

Public health impact

Considering that MTC is a rare event in the general population, the absolute risk is expected to be very low, and the potential impact on public health is expected to be minimal.

2.7.3.3 Important potential risk: pancreatic cancer

Potential mechanisms

In 2010, a potential risk of pancreatic cancer was hypothesised for the incretin mimetic class of antidiabetic drugs (GLP-1 RAs and dipeptidyl peptidase 4 [DPP-4] inhibitors).[58] It was suggested that based on the mode of action of incretin mimetic drugs and pancreatic metaplastic changes seen in animal models following administration of incretin mimetic drugs, prolonged exposure to incretin mimetic drugs may lead to an increased risk of pancreatic cancer. An association between the incretin-based therapy class and risk of pancreatic cancer is not supported by findings from the completed CVOTs of other GLP-1 RAs, including lixisenatide[59] and liraglutide,[60]dulaglutide,[61] and DPP-4 inhibitors (saxagliptin, sitagliptin and alogliptin).[62-64]

Evidence source and strength of evidence

Patients with T2D have an increased risk of certain types of cancer such as pancreatic cancer. There is no evidence from clinical studies, including insulin icodec/semaglutide (Kyinsu®) studies, that GLP-1 RA based therapies increase the risk of pancreatic cancer. However, 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).

Characterisation of the risk

Impact on quality of life

Pancreatic cancer severely impacts the patient's quality of life. Treatment can involve chemotherapy, radiation therapy and/or surgery. More than 50% of the patients are diagnosed at an advanced stage with a 5-year survival rate less than 5%.[65]

Data from clinical studies with insulin icodec/semaglutide (Kyinsu®)

There is no indication of an increased relative risk in the insulin icodec/semaglutide (Kyinsu®) treatment group (0 events per 100 PYE) versus comparator (3 events per 100 PYE). Pancreatic cancer is a serious medical condition, therefore, all the investigator-reported events in the phase 3 trials were serious. Two events were reported as 'not recovered' and one event was reported as 'resolving'.

Since the data collection period of the trials is relatively short to assess long-term outcomes of the treatment, this will continue to be monitored in post-marketing data.

Data from literature sources: Incidence and prevalence in the background population

Reported incidence rates of pancreatic cancer range from 0.2 to 2.8 per 1,000 person-years.[66-76]

A claims-based analysis found an incidence rate of pancreatic cancer of 0.20 for users of liraglutide (a GLP-1 RA structurally similar to semaglutide), compared with 0.33 per 1,000 person-years for users of non-incretin-based comparator therapies.[77]

Risk factors and risk groups

Patient risk factors for neoplasms include diabetes, chronic pancreatitis, obesity, physical inactivity, advanced age, smoking, alcohol abuse, environmental factors, history of neoplasms and family history of pancreatic cancer, and other genetic predispositions.

Preventability

No causal relationship has been established between insulin icodec/semaglutide (Kyinsu®) or semaglutide and pancreatic cancer, and therefore preventability is not applicable.

Impact on the benefit–risk balance of the product

Data from the insulin icodec/semaglutide (Kyinsu®) and semaglutide development programmes do not indicate a causal association. Based on this, the risk is considered to have a low impact on the benefit–risk profile of insulin icodec/semaglutide (Kyinsu®).

Public health impact

Considering that pancreatic cancer is a rare event in the general population, the absolute risk is expected to be very low, and the potential impact on public health is expected to be minimal.

2.7.3.4 Important potential risk: Medication error during switch from other injectable diabetes treatments

Potential mechanisms

Medication errors may occur due to patient's unawareness of difference between insulin icodec/semaglutide (Kyinsu®) and other injectable diabetes treatments (insulin or GLP-1 RAs). A period of 30 days from the initiation of insulin icodec/semaglutide (Kyinsu®) treatment is considered relevant to assess medication errors during switch from other injectable diabetes treatments.

During switch from other injectable diabetes treatments to weekly insulin icodec/semaglutide (Kyinsu®) treatment, 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, hyperglycaemia or gastrointestinal adverse reactions.

Evidence source and strength of evidence

Medication errors are a known risk for many insulin products. 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.

Characterisation of the risk

Impact on quality of life

Incorrect dosing during switch from other injectable diabetes treatments can potentially result in the following adverse events:

- hypoglycaemic events due to overdosing.
- hyperglycaemia events due to underdosing.
- increased GI AEs due to semaglutide overdose.

Data from clinical studies with insulin icodec/semaglutide (Kyinsu®)

While medication error-related adverse events were reported as part of the phase 3a programme, the post-authorisation experience will be more valuable in terms of characterising this risk.

Since this risk is specific to insulin icodec/semaglutide (Kyinsu®), it is not meaningful to compare the parameters of this risk with the comparator group, as some of the comparators are for daily administration and/or use a different dose terminology of unit or mg.

A total of 8 events of medication errors were reported during switch from other injectable diabetes treatments to insulin icodec/semaglutide (Kyinsu®). In these 8 events, 3 participants administered insulin icodec/semaglutide (Kyinsu®) once daily instead of once weekly (for 1, 13 and 39 days, respectively), 2 participants continued pre-trial insulin along with insulin icodec/semaglutide (Kyinsu®) (for 16 and 41 days, respectively) while 3 participants reported underdosing (60 instead of 70 dose steps, 40 instead of 60 dose steps, and no insulin icodec/semaglutide (Kyinsu®) for 4 weeks as the participant failed to remove the second safety cap from the needle).

In relation to the medication errors during switch from other injectable diabetes treatments to insulin icodec/semaglutide (Kyinsu®), the following AEs were reported:

- In 1 participant administering insulin icodec/semaglutide (Kyinsu®) daily, two level 1 hypoglycaemic episodes were reported.
- In 2 participants continuing pre-trial insulin, 1 participant reported two level 1 hypoglycaemic episodes while three episodes were reported by the other participant.
- In 5 participants that erroneously administered high doses, 1 participant reported a GI AE; that is, a case of nausea 6 days after the medication error had occurred.

None of the 3 participants reporting underdosing were observed to co-report hyperglycaemia in relation to the medication errors.

Risk factors and risk groups

Patients with diabetes switching from GLP-1 RAs or insulins to insulin icodec/semaglutide (Kyinsu®) represent the most significant risk group.

Preventability

The instructions included in the EU-PI are expected to limit the frequency of this kind of medication errors. These instructions in the EU-PI are designed for insulin icodec/semaglutide (Kyinsu®) usage in a post-marketing setting (details provided in Section 5).

Impact on the benefit–risk balance of the product

While medication errors in clinical studies are not necessarily predictive of what the post-marketing experience will be, the occurrence of these errors during clinical studies indicates a potential for related errors in a post-marketing setting. Further, while the clinical consequences to a large dosing error could be significant, the impact on the benefit–risk balance of insulin icodec/semaglutide (Kyinsu®) is anticipated to be lessened based on the measures taken in the product information and product differentiation strategy to mitigate this risk.

Public health impact

The public health impact is anticipated to be sufficiently minimised through the EU-PI and the product differentiation strategy.

2.7.3.5 Important potential risk: Medication error due to mix-up with other injectable diabetes treatments

Potential mechanisms

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.

Evidence source and strength of evidence

Medication errors are a known risk for many insulin products. 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.

Characterisation of the risk

Impact on quality of life

Administration of a wrong product can potentially result in the following adverse events:

- hypoglycaemic events due to overdosing
- hyperglycaemic events in the case of underdosing.

Data from clinical studies with insulin icodec/semaglutide (Kyinsu®)

While medication error-related adverse events were reported as part of the phase 3a programme, the post-authorisation experience is required to characterise this risk.

Overall medication error events that were reported in the phase 3a programme of insulin icodec/semaglutide (Kyinsu®) are presented in Table 2-13. Medication errors were reported in 25 participants (2.12 events per 100 PYE) from the insulin icodec/semaglutide (Kyinsu®) group compared to 55 participants (5.45 events per 100 PYE) from the comparator groups. For insulin icodec/semaglutide (Kyinsu®), all the events were non-serious and mild to moderate in severity. In 13 of the 25 cases, causality was assessed as probably/possibly related to insulin icodec/semaglutide (Kyinsu®) treatment.

Table 2-13 Overall medication errors incl. misuse and abuse (MedDRA search) – on-treatment - phase 3a pool[a]

	Insulin icodec/semaglutide (Kyinsu®)				**Comparator**			
Number of participants	1,325				1,312			
PYE	1,369.43				1,376.35			
	N	**%**	**E**	**R**	**N**	**%**	**E**	**R**
Medication errors	25	1.9	29	2.12	55	4.2	75	5.45
SOC Injury, poisoning and procedural complications	25	1.9	29	2.12	55	4.2	75	5.45
Underdose	9	0.7	9	0.66	5	0.4	9	0.67
Incorrect dose administered	6	0.5	8	0.58	15	1.1	24	1.79
Overdose	5	0.4	6	0.44	17	1.3	19	1.38
Wrong product administered	3	0.2	3	0.22	6	0.5	6	0.45
Product administration error	1	0.1	1	0.07	1	0.1	1	0.07
Inappropriate schedule of product administration	1	0.1	1	0.07	0	0	0	0
Medication error	1	0.1	1	0.07	4	0.3	4	0.30
Accidental overdose	0	0	0	0	7	0.5	10	0.73
Wrong dose	0	0	0	0	2	0.2	2	0.15

[a]Phase 3a pool includes studies NN1535-4591, 4592, 4593.

Note: 1 PYE = 365.25 days.

Abbreviations: PYE = patient years of exposure, SOC = system organ class.

The frequency of medication errors due to mix-up with other injectable diabetes treatments was low. One event (0.07 events per 100 PYE) was reported in the insulin icodec/semaglutide (Kyinsu®) group, while 6 events (0.45 events per 100 PYE) were reported in the comparator group. All the events reported were non-serious, mild or moderate in severity, and reported outcomes were recovered or recovering. All the events were reported under the PT Wrong product administered.

Risk factors and risk groups

Patients with diabetes treated with insulin (or other injectable medicine), patients with diabetes living with another person with diabetes, and visually impaired or colour- blind patients may be at a higher risk.

Preventability

The EU-PI describing the medicinal product, and the product differentiation strategy are expected to limit the frequency of this kind of medication errors (details provided in Section 5).

Impact on the benefit–risk balance of the product

While medication errors in clinical studies are not necessarily predictive of what the post-marketing experience will be, the occurrence of these errors during clinical studies indicates a potential for related errors in a post-marketing setting. Further, while the clinical consequences to a large dosing error could be significant, the impact on the benefit–risk balance of insulin icodec/semaglutide (Kyinsu®) is anticipated to be lessened based on the measures taken in the product information and product differentiation strategy to mitigate this risk.

Public health impact

The public health impact is anticipated to be sufficiently minimised through the product information, product label and the product differentiation strategy.

2.7.3.6 Missing information: pregnancy and breastfeeding

Evidence source

Insulin icodec/semaglutide (Kyinsu®) has not been studied in pregnant or women breastfeeding, and the potential risk of insulin icodec/semaglutide (Kyinsu®) treatment during pregnancy and breastfeeding 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 (Table 2-2). 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.

Population in need of further characterisation

Exposure to insulin icodec/semaglutide (Kyinsu®) or the mono-components, semaglutide and insulin icodec, during pregnancy and breastfeeding is limited. The safety profile of insulin

icodec/semaglutide (Kyinsu®) or the mono-components has not been established in pregnant or breastfeeding patients with diabetes mellitus.

The relevance of the nonclinical observations with semaglutide mono-component to humans cannot be excluded.

The anticipated use in this population is low based on the prescription-only status of the insulin icodec/semaglutide (Kyinsu®) and because the SmPC clearly specifies that insulin icodec/semaglutide (Kyinsu®) should not be prescribed to this population. Novo Nordisk will continue to monitor the population of pregnant patients in the post-marketing setting by routine pharmacovigilance activities.

2.7.3.7 Missing information: patients with severe hepatic impairment

Evidence source

Insulin icodec/semaglutide (Kyinsu®) has not been studied in patients with severe hepatic impairment, and the safety profile of insulin icodec/semaglutide (Kyinsu®) 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 insulin icodec/semaglutide (Kyinsu®). In the phase 3a pool, 106 participants with impaired liver function (defined as defined as either AST >UNL or Bil >UNL) were included. insulin icodec/semaglutide (Kyinsu®) was safe and well-tolerated in these participants. The data showed that the safety profile was not affected to a clinically meaningful extent by hepatic impairment, however, the exposure in this population is limited.

Population in need of further characterisation

The exposure of insulin icodec/semaglutide (Kyinsu®) in patients with T2D and severe hepatic impairment is currently limited.
Novo Nordisk will continue to monitor the population of patients with severe hepatic impairment in the post-marketing setting by routine pharmacovigilance activities.

2.8 Module SVIII: Summary of safety concerns

Risks considered important for inclusion in the list of safety concerns for further evaluation as part of the pharmacovigilance plan or risk minimisation activities and their benefit−risk impact are briefly discussed in Table 2-14. Further details on the safety concerns are presented in section 2.7.3.
The safety concerns for insulin icodec/semaglutide (Kyinsu®) are based on the risks of the two mono-components; semaglutide s.c. for T2D and insulin icodec.

Table 2-14 Summary of safety concerns – insulin icodec/semaglutide (Kyinsu®)

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.

3 Pharmacovigilance plan

3.1 Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection

3.1.1 Specific adverse reaction follow-up questionnaires

Novo Nordisk aims 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 Novo Nordisk's insulins or products with insulin as a component. The list of questions is attached in Annex 4A 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 Novo Nordisk 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".

3.1.2 Other forms of routine pharmacovigilance activities

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.

3.2 Additional pharmacovigilance activities

There are currently no ongoing or planned additional pharmacovigilance activities for insulin icodec/semaglutide (Kyinsu®).

Safety findings from the following PASS for the semaglutide mono-component will be assessed for their relevance to insulin icodec/semaglutide (Kyinsu®).

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. =sub-cutaneous, T2D = type 2 diabetes.

4 Plans for post-authorisation efficacy studies

There are currently no plans for post-authorisation efficacy studies for insulin icodec/semaglutide (Kyinsu®) nor have any post-authorisation efficacy studies been imposed.

5 Risk minimisation measures

5.1 Routine risk minimisation measures

Table 5-1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation measures
Important identified risks	
Diabetic retinopathy complications	**Routine risk communication:** SmPC Sections 4.4 and 4.8 and PL Sections 2 and 4. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** A recommendation to closely monitor patients with a history of diabetic retinopathy treated with insulin icodec/semaglutide (Kyinsu®) is included in the SmPC (Section 4.4). Instructions to inform the HCP about eye disorders are included in the PL (Section 2 and Section 4). **Other risk minimisation measures beyond the Product Information:** By the legal status of the product; prescription only. 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.
Important potential risks	
Medullary thyroid cancer	**Routine risk communication:** SmPC Section 5.3 (Nonclinical findings). **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None. **Other risk minimisation measures beyond the Product Information:** By the legal status of the product; prescription only.
Pancreatic cancer	**Routine risk communication:** None. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None. **Other risk minimisation measures beyond the Product Information:** By the legal status of the product; prescription only.
Medication error due to mix-up with other injectable diabetes treatments	***Routine risk communication:*** • The risk of mix-ups is presented in Section 4.4 of the SmPC and Section 2 and Section 3 of the PL. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • Instructions for avoidance of medication errors due to mix-up are described in Section 4.4 of the SmPC and Section 2 of the PL • Recommendations in Section 4.4 of the SmPC and Section 3 of the PL indicates that patients with impaired vision require assistance from a person with good vision. • Product appearance is described in Section 6 of the PL to prevent misidentification of the product. ***Other risk minimisation measures beyond the Product Information:***

Safety concern	Routine risk minimisation measures
	• This medicine will only be available by prescription. • Product differentiation strategy to reduce misidentification; includes trade name, label text, colour branding of the carton, container label and cartridge holder.
Medication error during switch from other injectable diabetes treatments	***Routine risk communication:*** • The risk related to switching from insulin products or GLP-1 RAs is presented in Sections 4.2 and 4.4 of the SmPC. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** • Instructions for switching from other injectable blood glucose lowering agents to insulin icodec/semaglutide (Kyinsu®) are presented in Section 4.2 of the SmPC. • Prescribers are instructed to inform patients that they must verify the dialled dose steps on the dose counter of the pen (Section 4.4 of the SmPC) • Patients who are uncertain about the correct dose must be instructed to consult their physician/pharmacist/nurse for further guidance (Section 3 of the PL) • Frequent glucose monitoring is recommended during switch and in the subsequent weeks (Section 4.2 of SmPC). • Recommendations in Section 4.4 of the SmPC and Section 3 of the PL indicates that patients with impaired vision require assistance from a person with good vision. ***Other risk minimisation measures beyond the Product Information:*** • This medicine will only be available by prescription only
Missing information	
Pregnancy and breastfeeding	**Routine risk communication:** SmPC Section 4.6 and PL Section 2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** It is stated in the SmPC and PL that insulin icodec/semaglutide (Kyinsu®) should not be used during pregnancy and breastfeeding and should be discontinued at least 2 months in advance if a patient wishes to become pregnant. **Other risk minimisation measures beyond the Product Information:** By the legal status of the product; prescription only.
Patients with severe hepatic impairment	**Routine risk communication:** SmPC Sections 4.2 and 5.2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** It is stated in the SmPC that caution should be exercised when treating patients with severe hepatic impairment. **Other risk minimisation measures beyond the Product Information:** By the legal status of the product; prescription only.

Abbreviations: GLP-1 RA = glucagon-like peptide 1 receptor agonist; HCP = healthcare professional; PL = product leaflet; SmPC = Summary of Product Characteristics.

5.2 Additional risk minimisation measures

Details of additional risk minimisation measure in the form of a patient/carer guide (referred to as "patient guide" throughout the document) to mitigate medication errors during switch or due to mix-up with other injectable diabetes treatments are included in Section 5.2.1.

5.2.1 Patient guide to mitigate medication errors during switch or due to mix-up with other injectable diabetes treatments.

Objectives

The patient guide aims at increasing awareness about the weekly dosing and the dose adjustments for insulin icodec/semaglutide (Kyinsu®) while describing the key points of use to minimise medication errors during switch from other injectable diabetes treatments and the risk of medication errors due to mix-up with other injectable diabetes treatments.

Rationale for the additional risk minimisation activity

It is necessary to educate patients on the weekly dosing and the dose adjustments specific to insulin icodec/semaglutide (Kyinsu®) when compared to the other injectable diabetes therapies that the patients are currently using or used in the past. This additional risk minimisation measure is being performed to minimise the risk of medication errors with medication errors during switch from other injectable diabetes treatments and the risk of medication errors due to mix-up with other injectable diabetes treatments.

Target audience and the planned distribution path

Novo Nordisk provides patient guide either as digital or hard copies for patients/carers of patients prescribed insulin icodec/semaglutide (Kyinsu®).

A patient guide will emphasise on the following:

For medication errors during switch from other injectable diabetes treatments

- Information stating that the dose adjustment of insulin icodec/semaglutide (Kyinsu®) is different from other injectable diabetes treatments.
- Information to strictly adhere to a weekly dosing regimen as prescribed by healthcare professional.
- 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 steps
- Information stating that dose steps should not be selected by counting pen clicks.

For medication errors due to mix-up

- 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.

Plans to evaluate the effectiveness of the interventions and criteria for success

The process indicators for assessing the effectiveness of information dissemination include tracking the delivery/return of hard copies and downloads of digital patient guides. Actions pertaining to returned emails or hard copies should be documented while evaluating dissemination. The dissemination process shall be monitored, and its effectiveness will be evaluated at least biannually following launch. Subsequently, the frequency of monitoring and dissemination process will be modified based on evaluation.

The effectiveness indicators include routine pharmacovigilance and safety surveillance activities, evaluation of the risk of medication errors, types of medication errors reported, and medication error reporting rates. The effectiveness assessment results are documented in the aggregate reports. Overall reporting rate of medication errors is one of the indicators of effective risk minimization.

Based on the effectiveness of risk minimisation, the process and content of the patient guide will be revised as necessary or alternative activities will be proposed if required.

5.3 Summary table of pharmacovigilance and risk minimisation activities by safety concern

Table 5-2 Pharmacovigilance 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

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
		Additional pharmacovigilance activities: No additional PV activities (including PASS) are planned for insulin icodec/semaglutide (Kyinsu®). If any safety findings arise from the PASS NN9535-4447 (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 to minimise the risk of medication errors due to mix-up with other injectable diabetes treatments (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 4A). **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 to minimise the risk of medication errors during switch from other injectable diabetes treatments (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 professional. • Information to check how many dose steps were selected before injecting the weekly dose.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Standardised follow-up questions (see Annex 4A). **Additional pharmacovigilance activities:** None

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
	• 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.	
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. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Abbreviations: PL = product leaflet ; SmPC = Summary of Product Characteristics.

6 Summary of the risk management plan for insulin icodec/semaglutide (Kyinsu®)

This is a summary of the risk management plan (RMP) for Kyinsu®. The RMP details important risks of Kyinsu®, how these risks can be minimised, and how more information will be obtained about Kyinsu®'s risks and uncertainties (missing information).

Kyinsu®'s summary of product characteristics (EU-PI) and its package leaflet give essential information to healthcare professionals and patients on how Kyinsu® should be used.

This summary of the RMP for Kyinsu® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the EPAR.

Important new concerns or changes to the current ones will be included in updates of Kyinsu®'s RMP.

6.1 The medicine and what it is used for

Kyinsu® is used in the treatment of type 2 diabetes in adults when insufficiently controlled with basal insulin or glucagon-like peptide 1 (GLP-1) receptor agonists. Kyinsu® is an adjunct to diet and exercise in addition to oral antidiabetic medicinal products. It is injected once a week. It

contains insulin icodec and semaglutide as the active substances and it is given as a subcutaneous injection.

Further information about the evaluation of Kyinsu®'s benefits can be found in insulin Kyinsu®'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: *link to the EPAR summary landing page*.

6.2 Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Kyinsu®, together with measures to minimise such risks and the proposed studies for learning more about Kyinsu®'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and EU-PI addressed to patients and healthcare professionals,
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimises its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Kyinsu®, these measures are supplemented with *additional risk minimisation* measures mentioned under relevant risks, below.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*. If important information that may affect the safe use of Kyinsu® is not yet available, it is listed under 'missing information' below.

6.2.1 List of important risks and missing information

Important risks of Kyinsu® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Kyinsu®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

The important potential risk of 'Aspiration in association with general anaesthesia and deep sedation' and the missing information regarding 'Patients with gastroparesis' have been removed from the list of safety concerns. Per EMA's request, Novo Nordisk awaits the outcomes of the

ongoing semaglutide procedures (Kayshild EMEA/H/C/006426/0000 and EMA/VR/0000249026, EMEA/H/C/004953) to update the Risk Management Plan (RMP) for these safety concerns.

Table 6-1 List of important risks and missing information

Safety concerns	Title
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.

6.2.2 Summary of important risks and missing information

6.2.2.1 Important identified risks

The important identified risks for Kyinsu® are presented in Table 6-2.

Table 6-2 Diabetic retinopathy complications

Important identified risk: Diabetic retinopathy complications	
Evidence for linking the risk to the medicine	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.
Risk factors and risk groups	Patient risk factors include increasing age, long duration of diabetes, poor glycaemic control, prior history of diabetic retinopathy and rapid decline in HbA_{1c}.
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Sections 4.4 and 4.8 and PL Sections 2 and 4. ***Additional risk minimisation measures:*** 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 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®).

Abbreviations: CVOT = cardiovascular outcomes trial; PL = package leaflet; s.c. = subcutaneous; SmPC = Summary of Product Characteristics; T2D = type 2 diabetes.

6.2.2.2 Important potential risks

The important potential risks for Kyinsu® are presented in Table 6-3, Table 6-4, Table 6-5, and Table 6-6,

Table 6-3 Medullary thyroid cancer

Important potential risk: Medullary thyroid cancer	
Evidence for linking the risk to the medicine	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. No events were reported in the phase 3a data pool from the insulin icodec/semaglutide (Kyinsu®) development program.
Risk factors and risk groups	Patient risk factors for MTC include family history or medical history of multiple endocrine neoplasia 2 (MEN2), a group of medical disorders associated with tumours of the endocrine system.
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Section 5.3 ***Additional risk minimisation measures:*** 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®).

Abbreviations: GLP-1 RA = glucagon-like peptide 1 receptor agonist; MEN2 = multiple endocrine neoplasia 2; MTC = medullary thyroid cancer; SmPC = Summary of Product Characteristics.

Table 6-4 Pancreatic cancer

Important potential risk: Pancreatic cancer	
Evidence for linking the risk to the medicine	Patients with T2D have an increased risk of certain types of cancer such as pancreatic cancer. There is no evidence from clinical studies, including insulin icodec/semaglutide (Kyinsu®) studies, that GLP-1 RA based therapies increase the risk of pancreatic cancer. However, 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).
Risk factors and risk groups	Patient risk factors for neoplasms include diabetes, chronic pancreatitis, obesity, physical inactivity, advanced age, smoking, alcohol abuse, environmental factors, history of neoplasms and family history of pancreatic cancer and other genetic predispositions.
Risk minimisation measures	***Routine risk minimisation measures:*** None ***Additional risk minimisation measures:*** 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 NN9535-4447 (Epidemiological assessment of the risk for pancreatic cancer associated with the use of semaglutide

Important potential risk: Pancreatic cancer	
	in patients with T2D) for the semaglutide mono-component, these will be assessed for their relevance to insulin icodec/semaglutide (Kyinsu®).

Abbreviations: GLP-1 RA = glucagon-like peptide 1 receptor agonist; T2D = type 2 diabetes.

Table 6-5 Medication error due to mix-up with other injectable diabetes treatments

Important potential risk: Medication error due to mix-up with other injectable diabetes treatments	
Evidence for linking the risk to the medicine	Medication errors are a known risk for many insulin products. Medication error-related adverse events were reported as part of the clinical studies. 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.
Risk factors and risk groups	Patients with diabetes treated with insulin (or other injectable treatments), patients with diabetes living with another person with diabetes, and visually impaired or colour-blind patients may be at a higher risk.
Risk minimisation measures	**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 to minimise the risk of medication errors due to mix-up with other injectable diabetes treatments (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.

Abbreviations: PL = product leaflet; SmPC = Summary of Product Characteristics.

Table 6-6 Medication error during switch from other injectable diabetes treatments

Important potential risk: Medication error during switch from other injectable diabetes treatments	
Evidence for linking the risk to the medicine	Medication errors are a known risk for many insulin products. Medication error-related adverse events were reported as part of the clinical studies. While characterising the 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.
Risk factors and risk groups	Patients with diabetes switching from GLP-1 RAs or insulins to insulin icodec/semaglutide (Kyinsu®), represent the risk group.
Risk minimisation measures	**Routine risk communication:** Sections 4.2 and 4.4 of the SmPC

Important potential risk: Medication error during switch from other injectable diabetes treatments	
	Additional risk minimisation measures: A patient guide will be distributed at the time of launch to minimise the risk of medication errors during switch from other injectable diabetes treatments (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 professional. • 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.

Abbreviations: GLP-1 RA = glucagon-like peptide 1 receptor agonist; SmPC = Summary of Product Characteristics.

6.2.2.3 Missing information

The missing information for Kyinsu® is presented in Table 6-7 and Table 6-8.

Table 6-7 Pregnancy and breastfeeding

Missing information: Pregnancy and breastfeeding	
Risk minimisation measures	**Routine risk minimization measure** SmPC Section 4.6 and PL Section 2. **Additional risk minimization measure** None

Abbreviations: PL = package leaflet; SmPC = Summary of Product Characteristics.

Table 6-8 Patients with severe hepatic impairment

Missing information: Patients with severe hepatic impairment	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.2 and 5.2. **Additional risk minimisation measures:** None

Abbreviations: SmPC = Summary of Product Characteristics.

6.2.3 Post-authorisation development plan

6.2.3.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of insulin icodec/semaglutide (Kyinsu®).

6.2.3.2 Other studies in post-authorisation development plan

There are no studies required for insulin icodec/semaglutide (Kyinsu®). Safety findings from the following PASS for the semaglutide mono-component will be assessed for their relevance to insulin icodec/semaglutide (Kyinsu®).

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. =sub-cutaneous, T2D = type 2 diabetes.

7 Annexes

Table 7-1 Annexes

Annex	Title	Included (Yes/No)
1	EudraVigilance interface	No
2	Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	No
3	Protocols for proposed and ongoing studies in Categories 1–3 of the section "Summary table of additional pharmacovigilance activities" in RMP Part 3	No
4	Specific adverse event follow-up forms 4A: Proposed follow-up questions for post-marketing surveillance of medication errors	Yes
5	Protocols for proposed and ongoing studies in RMP part IV	No
6	Details of proposed additional risk minimisation measures	Yes
7	Other supporting data (including referenced material)	No
8	Summary of changes to the risk management plan over time	Not applicable

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Annex 4A: Proposed follow-up questions for post-marketing surveillance of medication errors

1 Standard questions concerning medication errors

- Has the patient recently switched from another product (within last 3 months)?
- Is this the first time that the patient is treated for this indication?
- Did the patient experience the same medication error in the past?
- Was the product received in the original packaging? If no, please specify.
- Persons involved in the medication error? (e.g. physician, pharmacist, nurse, patient/caregiver or others?)
- At which stage did the medication error occur?
    - When the product was prescribed by physician
    - When the product was dispensed, e.g. at pharmacy
    - When the product was prepared to be administered.
    - When the product was administered.
    - An error in the monitoring required to administer the product correctly (e.g. recommendations in the label were not followed).
    - Other (please specify)
- Why do you think the medication error occurred?
    - Miscalculation of dose
    - Products look alike
    - Wrong instructions for product use by physician or pharmacist
    - Distraction
    - Drug names are alike
    - Insufficient lighting
    - Poor eyesight/colour blindness
    - Insufficient training

- Misunderstanding of product label information (please specify)
- Other (please specify)

- Please describe the reason for the error in your own words
- Did the patient experience any AEs as a consequence of the medication error?
  - If yes, please specify

2 Questions concerning the risk "Medication error during switch from other injectable diabetes treatments"

- When did the medication error occur?
  - Did the medication error happen during switch from injectable diabetes treatments?
- Did the patient experience any AE/hypoglycaemic event/hyperglycaemic event as a consequence of the medication error?
  - If yes, please specify, if possible, the severity, seriousness, event outcome, and eventual causal relationship between the event and the medication error
- At which stage did the medication error occur?
  - When the product was prescribed by physician.
  - When the product was dispensed, e.g. at pharmacy.
  - When the product was prepared to be administered.
  - When the product was administered.
  - An error in the monitoring required to administer the product correctly (e.g. recommendations in the label were not followed).
  - Other (please specify).
- Why do you think the medication error occurred?
  - Miscalculation of dose
  - Wrong instructions for product use by physician or pharmacist
  - Distraction
  - Poor eyesight/colour blindness/insufficient lighting

- Insufficient training
- Misinterpretation of product label information (please specify)
- Other (please specify)

- Please describe the reason for the error in your own words

Annex 6: Details of proposed additional risk minimisation measures

Novo Nordisk provides a patient/carer guide (referred to as "patient guide" throughout the document) for patients with type 2 diabetes mellitus who are prescribed insulin icodec/semaglutide (Kyinsu®) or their carers.

The patient guide aims at increasing awareness about the weekly dosing and the dose adjustments for icodec/semaglutide (Kyinsu®) while describing the key points of use to minimise the medication error during switch from other injectable diabetes treatments and the risk of medication error due to mix-up with other injectable diabetes treatments.

The patient guide is distributed at the time of launch of icodec/semaglutide (Kyinsu®) to help mitigate the medication errors during switch from other injectable diabetes treatments and due to mix up with other injectable diabetes treatments.

The patient guide will be available either as digital or hard copies. The patient guide contains information and instructions related to the following key elements:

Medication errors due to switch from other injectable diabetes treatments

- Instructions stating that the dose adjustment of icodec/semaglutide (Kyinsu®) is different from other injectable diabetes treatments.
- Instructions to strictly adhere to a weekly dosing regimen as prescribed by the healthcare professional.
- Instructions to check how many dose steps were selected before injecting the weekly dose.
- Instructions to always use the dose counter and the dose pointer to select the dose steps. Do not count the pen clicks to select dose steps.

Medication errors due to mix-up

- Instructions to always check the product label before each injection to avoid accidental mix-ups between icodec/semaglutide (Kyinsu®) and other injectable diabetes treatments.

Dissemination:

- Patient guide will be available in the local language online.
- For patients who prefer hard copy and/or have challenges accessing online material; hardcopy version can be distributed if required, upon agreement with national competent authorities.
- As the implementation of this patient guide takes place at the national level, the dissemination plans are tailored in accordance with national legal requirements and local healthcare systems.

Effectiveness:

The effectiveness of the additional risk minimisation activities will be measured by process and effectiveness indicators.

Process indicators will include:

- Tracking of delivery/return of hard copies in countries where needed, to assess the effectiveness of patient guide dissemination.
- Tracking the total downloads/webpage views of the digital copies of patient guide to assess the effectiveness of online dissemination.
- The frequency of tracking the dissemination is established within each EU member state and agreed upon with the National Competent Authority. However, the dissemination shall be tracked at least semi-annually following the launch. Subsequently, the frequency will be adjusted, as necessary.
- Targets or thresholds for assessing the effectiveness of dissemination are established at the national level considering the extent of dissemination required for each EU member state. In case the target is not achieved, a reevaluation of the dissemination process is warranted.
- Actions pertaining to returned emails or hard copies should be documented while evaluating dissemination.

Effectiveness indicators will include:

- Routine pharmacovigilance and safety surveillance activities conducted through adverse events monitoring and subsequent documentation of effectiveness assessment results in aggregate reports.
- Overall reporting rate of medication errors is one of the indicators of effective risk minimization.
- Based on the effectiveness of risk minimisation, the process and content of the patient guide will be revised as necessary or alternative activities will be proposed if required.