インスリン イコデク（遺伝子組換え）

2.7.2.5 付録
1. 臨床薬理試験における薬物動態エンドポイント及び薬力学的作用エンドポイント

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List of abbreviations

AUC	area under the curve
C_{max}	maximum concentration
CL	clearance
CO	crossover
CV	coefficient of variation
DB	double blind
dose norm.	dose normalised (endpoint values divided by the individual dose in kilograms)
ESRD	end-stage renal disease
F	fraction when used in endpoints, and otherwise female
geom. mean	geometric mean
GIR	glucose infusion rate
GIR_{max}	maximum glucose infusion rate
Ico	insulin icodec
M	male
MD	multiple dose
MRT	mean residence time
N	number of subjects
NA	not applicable
OL	open label
PG	parallel group
RND	randomised
s.c.	subcutaneous(ly)
SD	single dose when used in endpoints, and otherwise standard deviation
SS	steady state
$t_{½}$	terminal elimination half-life
t_{max}	time to maximum concentration
U	unit
V	volume of distribution

1 Pharmacokinetic endpoints

1.1 Insulin icodec steady state pharmacokinetic endpoints

1.1.1 Subjects with T2D

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

1.1.2 Subjects with T1D

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

1.2 Insulin icodec first dose or single dose pharmacokinetic endpoints

1.2.1 Subjects with T2D

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

1.2.2 Subjects with T1D

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

1.2.3 Renal or hepatic impairment

Trial ID, report location, design	**N (M/F) Race**	**Treatment and insulin icodec s.c. dose**	**$AUC_{Ico,0-168h,SD}$ Geom. mean (CV%) (pmol*h/L)**	**$C_{max,Ico,SD}$** Geom. mean (CV%) (pmol/L)	**$t_{max,Ico,SD}$** Median (mean [SD]) (h)	**$t_{½,Ico,SD}$** Geom. mean (CV%) (h)	**$MRT_{Ico,SD}$ Geom. mean (CV%)** (h)	**$CL/F_{Ico,SD}$** Geom. mean (CV%) (mL/(h*kg))	**$Vz/F_{Ico,SD}$** Geom. mean (CV%) (mL/kg)
4226, Trial 4226 (M 5.3.3.3), OL, PG, SD	58 (39/19) *Renal:*	Single doses.							
	Normal: 12	• 1.5 U/kg normal	17,390,878 (14.3)	84,704 (17.1)	15.0 (22.8 [18.6])	139.4 (11.2)	204.8 (10.4)	0.507 (14.2)	102 (8.7)
	Mild: 12	• 1.5 U/kg mild	19,888,308 (9.8)	90,707 (14.6)	15.0 (15.5 [1.7])	160.1 (9.0)	231.2 (6.8)	0.442 (9.8)	102 (9.4)
	Moderate: 12	• 1.5 U/kg moderate	21,366,414 (8.2)	91,100 (24.9)	21.0 (27.0 [16.9])	169.1 (7.6)	248.5 (9.6)	0.408 (8.2)	99 (9.9)
	Severe: 12	• 1.5 U/kg severe	19,857,044 (36.6)	76,893 (48.1)	21.1 (28.3 [16.5])	178.1 (18.6)	260.8 (17.2)	0.437 (36.8)	112 (45.1)
	ESRD: 10	• ESRD	18,590,836 (16.2)	80,426 (18.4)	18.1 (29.3 [26.0])	170.6 (9.0)	244.6 (8.5)	0.466 (15.6)	115 (16.5)
4570, Trial 4570 (M 5.3.3.3), OL, PG, SD	25 (12/13) *Hepatic:*	Single doses.							
	Normal: 6	• 1.5 U/kg normal	16,871,624 (8.6)	78,614 (13.4)	22.5 (21.0 [5.0])	134 (12.3)	197 (10.6)	0.52 (9.5)	101 (12.0)
	Mild: 6	• 1.5 U/kg mild	18,084,678 (18.4)	82,632 (24.1)	17.9 (18.5 [5.2])	134 (7.1)	192 (5.7)	0.50 (20.4)	96 (14.3)
	Moderate: 6	• 1.5 U/kg moderate	18,676,172 (15.1)	80,417 (27.8)	25.5 (29.0 [16.2])	148 (14.5)	214 (14.9)	0.47 (14.8)	102 (22.9)
	Severe: 7	• 1.5 U/kg severe	15,695,274 (18.6)	73,230 (19.8)	27.0 (26.5 [7.2])	161 (6.8)	223 (8.3)	0.56 (17.3)	130 (19.6)

2 Pharmacodynamic endpoints

2.1 Insulin icodec steady state pharmacodynamic endpoints

2.1.1 Subjects with T2D

Trial ID, report location, design	**N (M/F) Race**	**Treatment and insulin icodec s.c. dose**	**$AUC_{GIR,tau,SS,model}$** Geom. mean (CV%) (mg/kg)	**$GIR_{max,SS,model}$** Geom. mean (CV%) (mg/kg/min)	**$tGIR_{max,SS,model}$** Median (h)
4314, Trial 4314 (M 5.3.4.2), RND, DB, MD	50 (43/7) Caucasian	Five once-weekly doses. Dose at end of trial:			
		• 2.0 U/kg/week	NA	NA	NA
		• 3.3 U/kg/week	NA	NA	NA
		• 4.0 U/kg/week	NA	NA	NA
4569, Trial 4569 (M 5.3.4.2), OL, MD	46 (35/11) Caucasian	Six once-weekly doses. Mean (SD) at end of trial:			
		• 2.9 (1.16) U/kg/week	21983 (27)	2.8 (21.2)	46.5

2.1.2 Subjects with T1D

Trial ID, report location, design	**N (M/F) Race**	**Treatment and insulin icodec s.c. dose**	**$AUC_{GIR,tau,SS,model}$** Geom. mean (CV%) (mg/kg)	**$GIR_{max,SS,model}$** Geom. mean (CV%) (mg/kg/min)	**$tGIR_{max,SS,model}$** Median (h)
4225, Trial 4225 (M 5.3.4.2), RND, OL, CO, MD	66 (56/10) Caucasian	Eight once-weekly doses. Mean (SD) at end of trial:			
		• 1.9 (0.44) U/kg/week (all subjects)	8668 (52.7)	1.5 (40.6)	46
4422, Trial 4422 (M 5.3.4.2), RND, OL, CO, MD	24 (14/10) Japanese	Eight once-weekly doses. Mean (SD) at end of trial:			
		• 1.7 (0.45) U/kg/week (all subjects)	8330 (40.7)	8330 (40.7)	24

2.2 Insulin icodec single dose pharmacodynamic endpoints

2.2.1 Subjects with T2D

Trial ID, report location, design	**N (M/F) Race**	**Treatment and insulin icodec s.c. dose**	**$AUC_{GIR,30\text{-}60h,SD}$** Geom. mean (CV%) (mg/kg)
4572, Trial 4572 (M 5.3.1.2), RND, OL, CO, SD	25 (22/3) Caucasian	Single doses: • 5.6 U/kg abdomen • 5.6 U/kg upper arm • 5.6 U/kg thigh	 2,130 (51.6) 2,391 (39.6) 1,961 (51.3)

インスリン イコデク（遺伝子組換え）

2.7.2.5 付録
2. 個々の試験の叙述

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List of abbreviations

CHO	Chinese hamster ovary
COLO-205	human colon adenocarcinoma cell line
DPP4i	dipeptidyl peptidase 4 inhibitors
EDTA	ethylenediaminetetraacetic acid
F	female
hIR	human insulin receptor
HMEC	human mammary epithelial cells
IDeg	insulin degludec
IGF-1	insulin-like growth factor-1
IGlar	insulin glargine
M	male
MCF-7	human mammary adenocarcinoma cell line
PRO	patient-reported outcome
s.c.	subcutaneous(ly)
SGBS	Simpson-Golabi-Behmel disease
T1D	type 1 diabetes
T2D	type 2 diabetes
U	unit

5.2.1 Summary of individual in vitro studies with human biomaterials

Study ID[a], study location	Title of Study	Tissues tested	Overall conclusion
212035, Study 212035 (M 4.2.1.1)	*In vitro* binding to mouse, rat, rabbit, dog and human plasma proteins	EDTA plasma pools from CD1 mice (male and female), Spraque Dawley rats (male and female), New Zealand White rabbits (female), Beagle dogs (male and female) and humans (male and female).	The vast majority of insulin icodec was bound to plasma constituents with more than 99% bound for all species.
212036, Study 212036 (M 4.2.1.1)	*In vitro* binding of human serum albumin	Human serum albumin (96-99%) and essentially fatty acid free human serum albumin	Mean unbound insulin icodec fraction was less than 0.1%.
[redacted]120427, Study [redacted]120427 (M 4.2.1.1)	Binding to human serum albumin	Human albumin	Displacement of insulin icodec from albumin by palmitate is considered unlikely due to the high albumin concentration
[redacted]120428, Study [redacted]120428 (M 4.2.1.1)	Binding to albumin from various species	Rabbit, rat, dog, pig, and human albumin.	Binding affinity of insulin icodec albumin is different and in the following order: human ≥ pig ≥ rabbit > dog > rat.
316976, Study 316976 (M 4.2.1.1)	Serum metabolites in human (multiple dose)	Human serum (male subjects with T2D)	Insulin icodec was the most abundant fraction at trial day 1 and 29 after s.c. injection
211508, Study 211508 (M 4.2.1.1)	Species comparison in hepatocytes	Mouse, rat, rabbit, dog and human hepatocytes	No unique insulin icodec metabolites were found in human hepatocytes
214386, Study 214386 (M 4.2.1.1)	*In vitro* metabolism with human insulin degrading enzyme	Human insulin and recombinant human insulin degrading enzyme	Insulin icodec metabolites were primarily products from multiple cleavages in the B-chain while the human insulin metabolites were products from cleavage in both A- and B-chains.
[redacted] 12-11-2010, Study [redacted]_12-11-2010 (M 4.2.1.1)	Binding to solubilized human insulin receptors	Recombinant human insulin receptors.	Relative affinity of insulin icodec compared to human insulin was below 1%. Relative affinity decreased further in the presence of human serum albumin.
[redacted]120424, Study [redacted]120424 (M 4.2.1.1)	Binding to membrane-associated recombinant rat, pig and human insulin receptors	Recombinant rat, pig and human insulin receptors	Insulin icodec has identical affinities for the short (A) and long (B) isoform of insulin receptors of rat, pig and human origin. Presence of human serum albumin reduced affinity in a concentration-dependent manner.

Study ID[a], study location	Title of Study	Tissues tested	Overall conclusion
[redacted]120425, Study [redacted]120425 (M 4.2.1.1)	Binding to endogenous rat, dog, pig and human insulin receptors from liver	Endogenous rat, dog, pig and human insulin receptors from liver	Insulin icodec was found to bind with the same affinity to insulin receptors from rat, dog, pig and human livers.
[redacted]110524, Study [redacted]110524 (M 4.2.1.1)	Binding to solubilized human IGF-1 receptors	Recombinant human IGF-1 receptors	The affinity of insulin icodec for the IGF-I receptors in the absence of human serum albumin was determined to be 0.14% relative to human insulin.
[redacted]120426, Study [redacted]120426 (M 4.2.1.1)	Binding to membrane-associated recombinant human IGF-1 receptors	Recombinant human IGF-1 receptors	Insulin icodec have a very low affinity for human IGF-1 receptors relative to human insulin in experiments performed in the presence of 0.1% human serum albumin and a relative potency compared to human insulin could not be determined
[redacted]120429, Study [redacted]120429 (M 4.2.1.1)	Insulin receptor binding kinetics	Recombinant human insulin receptors	The association rate of insulin icodec to the human insulin receptor is similar to that of human insulin. The dissociation rate of insulin icodec from the human insulin receptor is faster than that of human insulin
[redacted]111101, Study [redacted]111101 (M 4.2.1.1)	Insulin receptor and PKB phosphorylation in CHO-hIR cells	Recombinant human insulin receptors	The results demonstrate that insulin icodec stimulates the same signalling events as native human insulin albeit with a lower potency.
[redacted] 20110524.2, Study [redacted] 20110524.2 (M 4.2.1.1)	Glucose uptake in SGBS human fat cells	Human SGBS adipocytes and rat adipocytes	Insulin icodec has retained the same biological effects as human insulin in fat cells, stimulating glucose uptake and conversion into lipids to the same extent as human insulin.
211021, Study 211021 (M 4.2.1.1)	*In vitro* mitogenic potency in human mammary adenocarcinoma (MCF-7)	^{3}H-thymidine incorporation in MCF-7 cells.	The *in vitro* mitogenic potency of insulin icodec compared to human insulin was 0.5%.
[redacted] 110406, Study [redacted] 110406 (M 4.2.1.1)	Metabolic effects in MCF-7 cells	^{14}C-labeled glucose in MCF-7 cells	Insulin icodec stimulated glycogen synthesis. Relative potency compared to human insulin was calculated to 0.26%.
211431, Study 211431 (M 4.2.1.1)	*In vitro* mitogenic potency in human colon adenocarcinoma (COLO-205)	^{3}H-thymidine incorporation in COLO-205 cells.	The *in vitro* mitogenic potency of insulin icodec compared to human insulin was 2.0%.

Study ID[a], study location	Title of Study	Tissues tested	Overall conclusion
301435, Study 301435 (M 4.2.1.1)	*In vitro* mitogenic potency in rat L6 myoblasts transfected with the human insulin receptor (L6-hIR)	^{3}H-thymidine incorporation in L6-hIR cells.	The *in vitro* mitogenic potency of insulin icodec compared to human insulin was 0.6%.
215074, Study 215074 (M 4.2.1.1)	*In vitro* mitogenic potency in primary human mammary epithelial cells (HMEC)	^{3}H-thymidine incorporation in HMEC cells	The *in vitro* mitogenic potency of insulin icodec compared to human insulin was 0.2%.

[a] only studies on human biomaterials that supported the interpretation of PK and PD data are included.

5.2.2 Summary of individual clinical pharmacology trials

Trial ID	Population	N (M/F)	Trial design and objectives	Dose and treatment	Overall conclusions
4314	T2D Caucasian	50 (43/7)	Single-centre, randomised, double dummy, double blind, active-controlled, multiple-dose, dose escalation trial investigating safety and tolerability of multiple fixed once-weekly doses of insulin icodec in subjects with T2D, to compare PK and PD properties of insulin icodec with insulin degludec at steady state.	Multiple, predefined doses. Insulin icodec (s.c., once weekly, 5 weeks): • 2.0 U/kg/week • 3.3 U/kg/week • 4.0 U/kg/week IDeg (s.c. once daily, 5 weeks): • 0.4 U/kg/day	• Insulin icodec was well-tolerated and no safety issues were identified • Insulin icodec exposure was well-distributed across a one-week dosing interval and the half-life supports once-weekly dose administration. • The duration of glucose-lowering effect of insulin icodec covered one week at clinically relevant doses.
4569	T2D Caucasian	46 (35/11)	Single-centre, open-label, one-period, multiple-dose trial investigating PK and PD properties of once weekly insulin icodec in subjects with T2D at steady state.	Multiple, individualised doses. Titration with IDeg for at least seven days run-in to reach stable, fasting SMPG 4.4-7.0 mmol/L (80-126 mg/dL), and titration after switch to insulin icodec if target SMPG was not fulfilled.[b] Insulin icodec (s.c., once weekly, 8 weeks): • Mean dose at start of trial: 2.6 U/kg/week (SD: 1.07) • Mean dose at end of trial: 2.9 U/kg/week (SD: 1.16)	• Insulin icodec exposure is well-distributed across one week and half-life supports a once-weekly administration • Insulin icodec demonstrates an even distribution of glucose-lowering effect within the dosing interval of one week • The duration of glucose-lowering effect of insulin icodec covers one week at clinically relevant doses
4571	T2D Chinese	24 (12/12)	Single-centre, open-label, single-group, multiple-dose trial investigating PK properties of once-weekly insulin icodec in Chinese subjects with T2D at steady state.	Multiple, individualised doses. Titration with IDeg for at least seven days run-in to reach stable, fasting SMPG 4.4-7.0 mmol/L (80-126 mg/dL).[b] Insulin icodec (s.c., once weekly, 6 weeks): • Mean dose: 2.2 U/kg/week (SD: 0.80)	• Insulin icodec exposure was well-distributed across one week and half-life supported a once-weekly administration

Trial ID	Population	N (M/F)	Trial design and objectives	Dose and treatment	Overall conclusions
4462	T2D Caucasian	43 (31/12)	Single-centre, randomised, open-label, 2-period cross-over, multiple-dose trial comparing the ability of an overdose of insulin icodec versus IGlar to induce hypoglycaemia in subjects with T2D.	Multiple individualised doses. Titration with IGlar for at least three days run-in to reach stable, fasting SMPG 4.4-7.2 mmol/L (80-130 mg/dL).[a] Insulin icodec (s.c., once weekly, 6 weeks): • Mean dose: 2.43 U/kg/week (SD: 1.03) IGlar (s.c. once daily, 12 days): • Mean dose: 0.35 U/kg/day (SD: 0.15) Individual dose was used to calculate double and triple doses of insulin icodec and IGlar.	• A double or triple dose of insulin icodec did not lead to an increased risk of hypoglycaemia as compared with IGlar • During hypoglycaemia, a comparable symptomatic and cognitive response and a moderately greater endocrine response were seen for insulin icodec as compared with IGlar • Insulin icodec was well-tolerated and no safety issues were identified in this trial
4572	T2D Caucasian	25 (22/3)	Single-centre, randomised, open-label, three-periods, cross-over trial comparing PK and PD properties of single dose insulin icodec when administered in abdomen, upper arm and thigh in subjects with T2D.	Single, predefined doses. Insulin icodec (single s.c.): • 5.6 U/kg	• Total exposure of insulin icodec was comparable across s.c. administration in the thigh, the abdomen and the upper arm • Maximum concentration of insulin icodec was slightly higher after s.c. administration in the abdomen and the upper arm compared to the thigh • Partial glucose-lowering effect of insulin icodec was similar after s.c. administration in the thigh, the abdomen and the upper arm
4225	T1D Caucasian	66 (56/10)	Single-centre, randomised, open-label, 2-period crossover, multiple-dose trial investigating PK and PD properties of insulin icodec at steady state across one dosing interval.	Multiple, individualised doses. Titration with IGlar for at least two days run-in to reach stable, fasting SMPG 4.4-7.2 mmol/L (80-130 mg/dL).[a] Insulin icodec (s.c., once weekly, 8 weeks): • Mean dose: All: 1.9 U/kg/week (SD: 0.44) Sufficiently dosed: 2.0 U/kg/week (SD: 0.46) IGlar (s.c., once daily, 2 weeks): • Mean dose: 0.3 U/kg/day (SD: 0.07)	• Insulin icodec exposure was well-distributed across one week and the half-life of insulin icodec supports once-weekly administration. • The duration of the glucose-lowering effect of insulin icodec covered one week at clinically relevant doses. • No new safety issues were identified in relation to insulin icodec in this trial.

Trial ID	Population	N (M/F)	Trial design and objectives	Dose and treatment	Overall conclusions
4422	T1D Japanese	24 (14/10)	Single-centre, randomised, open-label, 2-period cross-over, multiple-dose trial investigating PK, PD and safety properties of insulin icodec at steady state across one dosing interval in Japanese subjects with T1D.	Multiple, individualised doses. Titration with IGlar for at least two days run-in to reach stable, fasting SMPG 4.4-7.2 mmol/L (80-130 mg/dL).[a] Insulin icodec (s.c., once weekly, 8 weeks): • Mean dose: All: 1.7 U/kg/week (SD: 0.45) Sufficiently dosed: 1.6 U/kg/week (SD: 0.29) IGlar (s.c. once daily, 2 weeks): • Mean dose: 0.2 U/kg/day (SD: 0.07)	• Insulin icodec exposure was well-distributed across one week and half-life supported once weekly administration • Duration of glucose-lowering effect of insulin icodec covered one week at clinically relevant doses • Insulin icodec was well-tolerated by Japanese subjects with T1D and no new safety issues were identified in this trial
4226	Subjects with various degrees of renal impairment	58 (39/19)	Single-centre, open-label, parallel-group, single dose trial investigating PK exposure, PK properties and safety profile of a single dose of insulin icodec in subjects with various degrees of renal impairment.	Single, predefined doses. Insulin icodec (s.c.): • 1.5 U/kg	• Total exposure of insulin icodec was larger in subjects with impaired renal function compared to subjects with normal renal function • Maximum concentration of insulin icodec was comparable across all groups after a single dose, whereas model-predicted maximum concentration at steady state was larger in subjects with impaired renal function compared to subjects with normal function • No new safety issues were identified in relation to insulin icodec in this trial

Trial ID	Population	N (M/F)	Trial design and objectives	Dose and treatment	Overall conclusions
4570	Subjects with various degrees of hepatic impairment	25 (12/13)	Multi-centre, open-label, single-dose, parallel-group trial investigating the PK properties of a single dose of insulin icodec in subjects with various degrees of hepatic impairment.	Single, predefined doses. Insulin icodec (s.c.): • 1.5 U/kg	• The total exposure was slightly higher and maximum concentration of insulin icodec was comparable in subjects with mild and moderate impaired hepatic function compared to subjects with normal hepatic function. The differences in total exposure are considered of limited clinical relevance. • The total exposure and maximum concentration of insulin icodec were similar in severe hepatic impaired patients and subjects with normal hepatic function. • No new safety issues were identified in relation to insulin icodec in this trial.

[a] Insulin glargine (IGlar) was administered once daily during the run-in period. Dose of insulin icodec was seven times the dose of IGlar administered at the end titration run-in period.
[b] Insulin degludec (IDeg) was administered once daily during the run-in period. Dose of insulin icodec was seven times the dose of IDeg administered at the end titration run-in period.

5.2.3 Summary of confirmatory therapeutic trials with clinical pharmacology endpoints

Trial ID Population	Trial design and primary objective	N randomised (M/F)	Treatment and dose
4383 T2D	A 26-week, randomised, double-blind, double-dummy, active-controlled, parallel-group, stratified, multicentre, multinational, treat-to-target trial comparing the efficacy and safety of treatment with insulin 287 once weekly vs insulin glargine once daily in insulin-naive subjects with T2D inadequately controlled on metformin with or without DPP4i. To investigate the effect on glycaemic control after 26 weeks treatment of once weekly insulin 287 versus once daily IGlar both in combination with metformin with or without DPP4i in insulin-naïve T2DM subjects inadequately treated with metformin with or without DPP4i.	247 (139/108)	Multiple doses. Insulin icodec (s.c., once weekly, 26 weeks): • Geometric mean dose last 2 weeks: 2.58 U/kg/week IGlar (s.c., once daily, 26 weeks): • Geometric mean dose last 2 weeks: 3.11 U/kg/week
4478 T2D	A 26-week randomised, open label, active-controlled, parallel group, multicentre, multinational, treat-to-target trial investigating the effect on glycaemic control, safety and PROs of treatment with once weekly insulin icodec versus once daily insulin degludec, in basal insulin treated subjects with T2D inadequately controlled on once or twice daily insulin with or without non-insulin anti-diabetic drugs. To demonstrate the effect on glycaemic control of once weekly insulin icodec, with or without non-insulin anti-diabetic drugs, in subjects with T2D treated with basal insulin. This includes comparing the difference in change from baseline in HbA1c between insulin icodec and insulin degludec after 26 weeks of treatment to a non-inferiority limit of 0.3%.	526 (302/224)	Multiple doses. Insulin icodec (s.c., once weekly, 26 weeks): • Geometric mean dose last 2 weeks: 3.10 U/kg/week IDeg (s.c., once daily, 26 weeks): • Geometric mean dose last 2 weeks: 3.21 U/kg/week
4479 T2D	A 26-week, randomised, stratified, double blinded, double dummy, active-controlled, parallel-group, multicentre, multiregional, treat-to-target trial with 2 treatment arms comparing the effect on glycaemic control and safety of treatment with once weekly insulin icodec versus once daily insulin degludec 100 units/mL, both in combination with non-insulin anti-diabetic drugs insulin naïve T2D subjects in need of insulin initiation. To demonstrate the effect on glycaemic control of once weekly insulin icodec in combination with non-insulin anti-diabetic drugs insulin-naïve subjects with T2D. This includes comparing the difference in change from baseline in HbA1c between insulin icodec and insulin degludec after 26 weeks of treatment to a non-inferiority limit of 0.3%.	588 (369/219)	Multiple doses. Insulin icodec (s.c., once weekly, 26 weeks): • Geometric mean dose last 2 weeks: 2.39 U/kg/week IDeg (s.c., once daily, 26 weeks): • Geometric mean dose last 2 weeks: 2.24 U/kg/week

Trial ID Population	Trial design and primary objective	N randomised (M/F)	Treatment and dose
4480 T2D	A 26-week randomised, open label, active-controlled, parallel group, multicentre, multinational, treat-to-target trial investigating the effect on glycaemic control and safety of treatment with once weekly insulin icodec compared to once daily insulin glargine 100 units/mL, both in combination with insulin aspart with or without non-insulin anti-diabetic drugs in subjects with T2D on a basal-bolus regimen. To demonstrate the effect on glycaemic control of once weekly insulin icodec in combination with insulin aspart, with or without non-insulin anti-diabetic drugs, in subjects with T2D on a basal-bolus regimen. This includes comparing the difference in change from baseline in HbA1c between insulin icodec and insulin glargine after 26 weeks of treatment to a non-inferiority limit of 0.3%.	582 (304/278)	Multiple doses. Insulin icodec (s.c., once weekly, 26 weeks): • Geometric mean last 2 weeks: 3.79 U/kg/week IGlar (s.c., once daily, 26 weeks): • Geometric mean last 2 weeks: 3.41 U/kg/week
4625 T1D	A 26-week, randomised, multicentre, multinational, open-label, active-controlled, parallel group, two-armed, treat-to-target trial investigating the effect on glycaemic control and safety of treatment with once weekly insulin icodec compared to once daily insulin degludec, both in combination with insulin aspart in subjects with T1D, with a 26-week extension phase. To confirm the effect on glycaemic control of once weekly insulin icodec in combination with insulin aspart, in subjects with T1D. This includes comparing the difference in change from baseline in HbA1c between once weekly insulin icodec and once daily insulin degludec both in combination with insulin aspart after 26 weeks of treatment to a non-inferiority limit of 0.3%.	582 (337/245)	Multiple doses. Insulin icodec (s.c., once weekly, 26 weeks): • Geometric mean last 2 weeks: 2.29 U/kg/week IDeg (s.c., once daily, 26 weeks): • Geometric mean last 2 weeks: 1.95 U/kg/week

インスリン イコデク（遺伝子組換え）

2.7.2.5 付録
3. 臨床薬理試験に関する帳票

ノボ ノルディスク ファーマ株式会社

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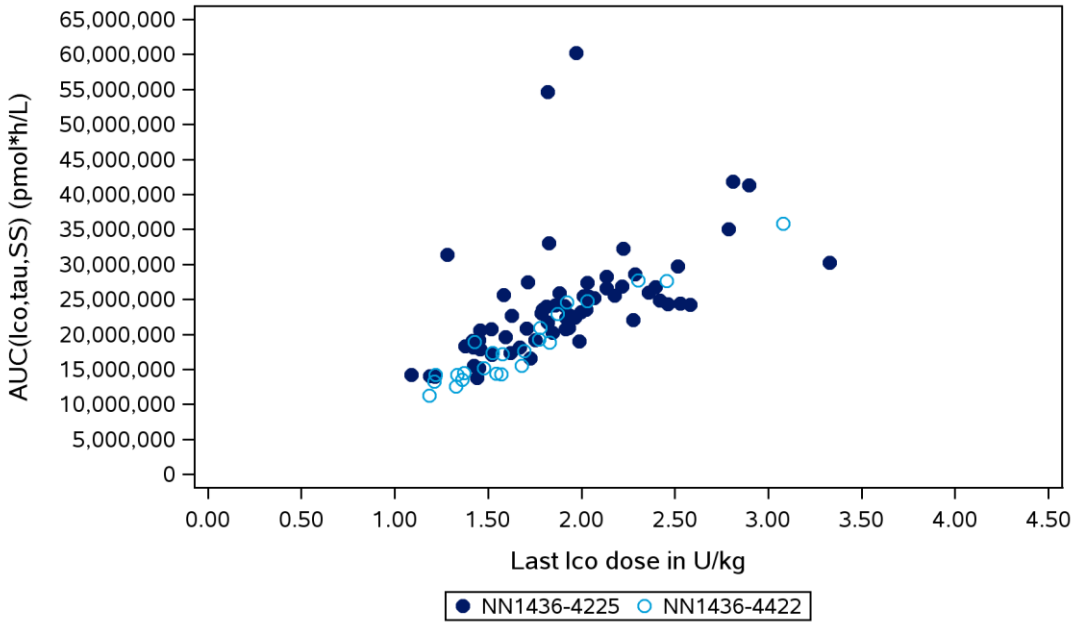
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5.3.1 Insulin icodec PK endpoints - time parameters - summary - full analysis set

	Ico - Abdomen	Ico - Upper Arm	Ico - Thigh
Number of profiles	24	23	23
tmax(Ico,SD) (h)			
N	24	23	23
Mean (SD)	24.1 (6.8)	21.9 (5.8)	35.3 (24.1)
Median	24.0	24.0	27.0
Min ; Max	12.0 ; 48.0	12.0 ; 30.0	21.0 ; 96.0
t1/2(Ico,SD) (h)			
N	24	23	23
Geometric mean (CV%)	150 (15.5)	150 (19.9)	153 (23.5)
Median	147	147	155
Min ; Max	118 ; 234	86 ; 219	70 ; 252

N: Number of profiles, SD: Standard deviation but single dose in PK endpoint names, CV: Coefficient of variation.

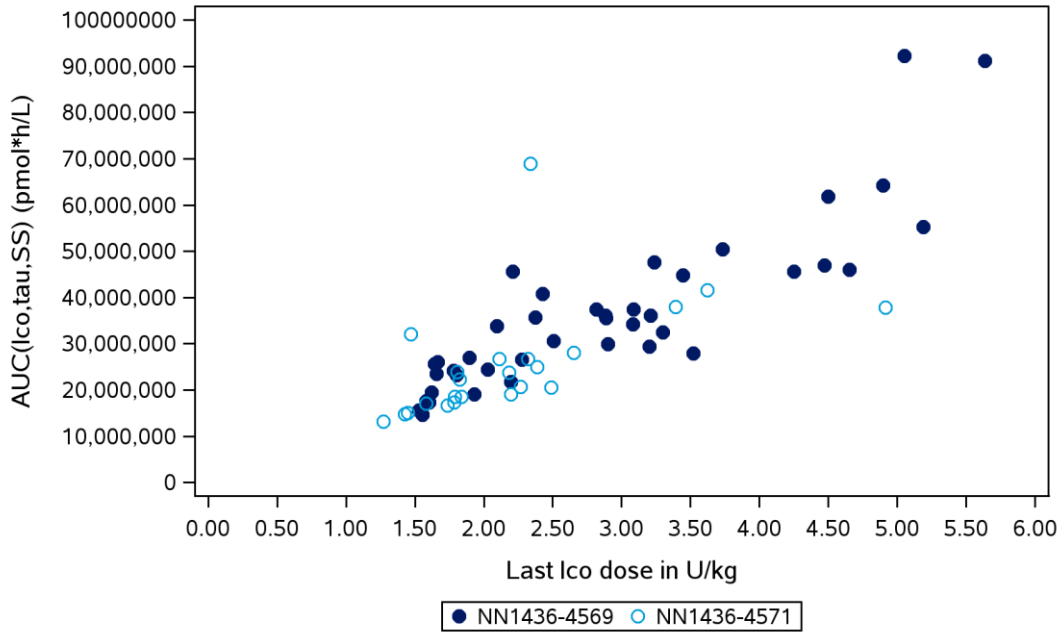
5.3.2 AUC(I287,tau,SS) against last I287 dose - scatter plot - I287 - full analysis set



SS: Steady state.

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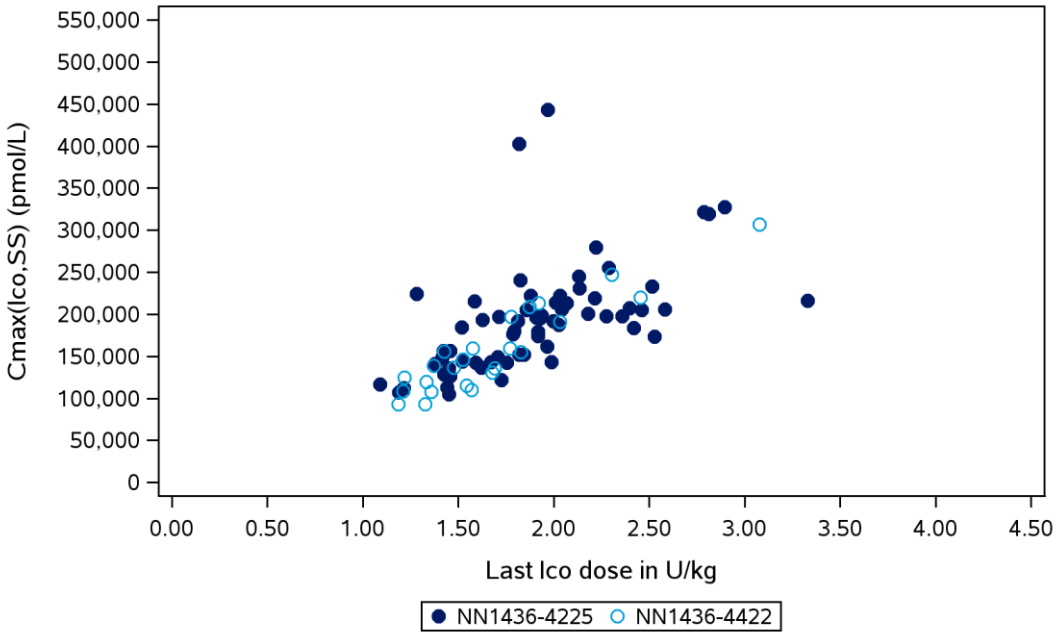
5.3.3 AUC(I287,tau,SS) against last I287 dose - scatter plot - I287 - full analysis set



SS: Steady state.

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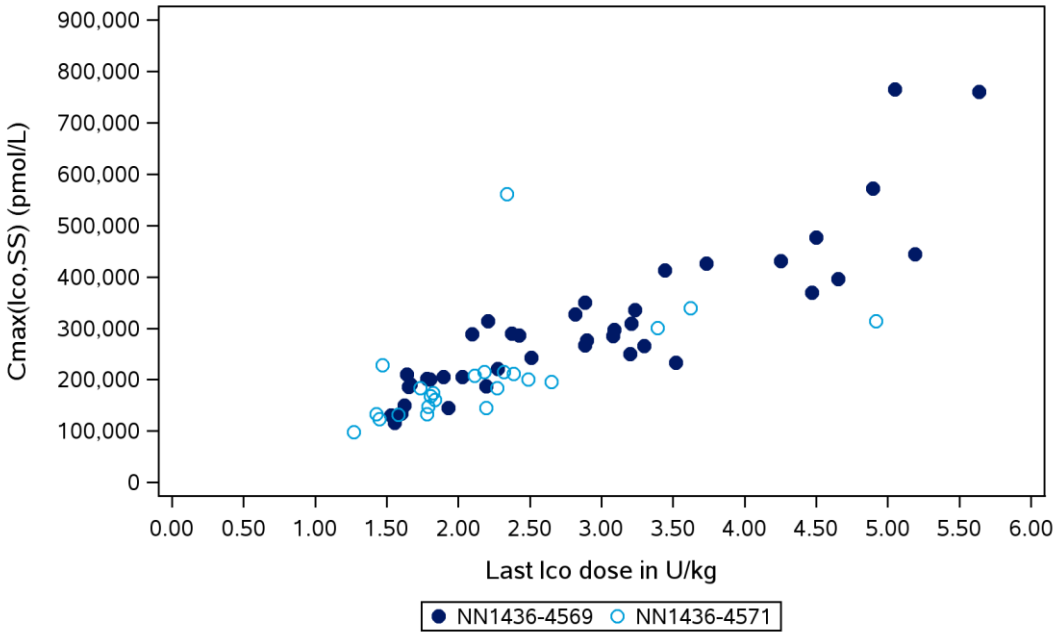
5.3.4 Cmax(I287,SS) against last I287 dose - scatter plot - I287 - full analysis set



SS: Steady state.

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5.3.5 Cmax(I287,SS) against last I287 dose - scatter plot - I287 - full analysis set



SS: Steady state.

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5.3.6 Insulin icodec PK endpoint - t-half across T2D in 4314 and 4569 trials - steady state - summary - full analysis set

	Total
t1/2(Ico,SS) (h)	
N	77
Geometric mean (CV%)	172 (23.6)
Median	170
Min ; Max	123 ; 368

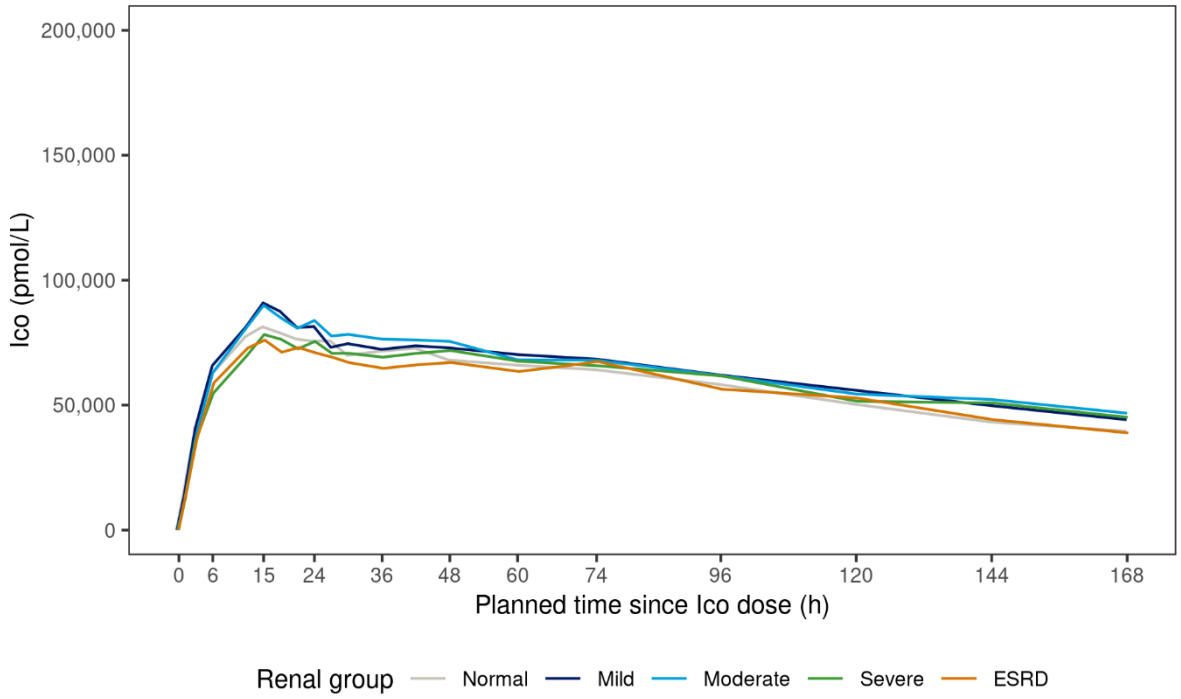
SS: Steady state, N: number of subjects, CV: coefficient of variation.

5.3.7 Insulin icodec PK endpoint - t-half across T1D and T2D in 4314, 4569 and 4225 trials - steady state - summary - full analysis set

	Total
t1/2(Ico,SS) (h)	
N	142
Geometric mean (CV%)	173 (21.6)
Median	170
Min ; Max	123 ; 404

SS: Steady state, N: number of subjects, CV: coefficient of variation.

5.3.8 Ico after single dose - 0-168h (one dosing interval) - mean profiles - linear scale - full analysis set

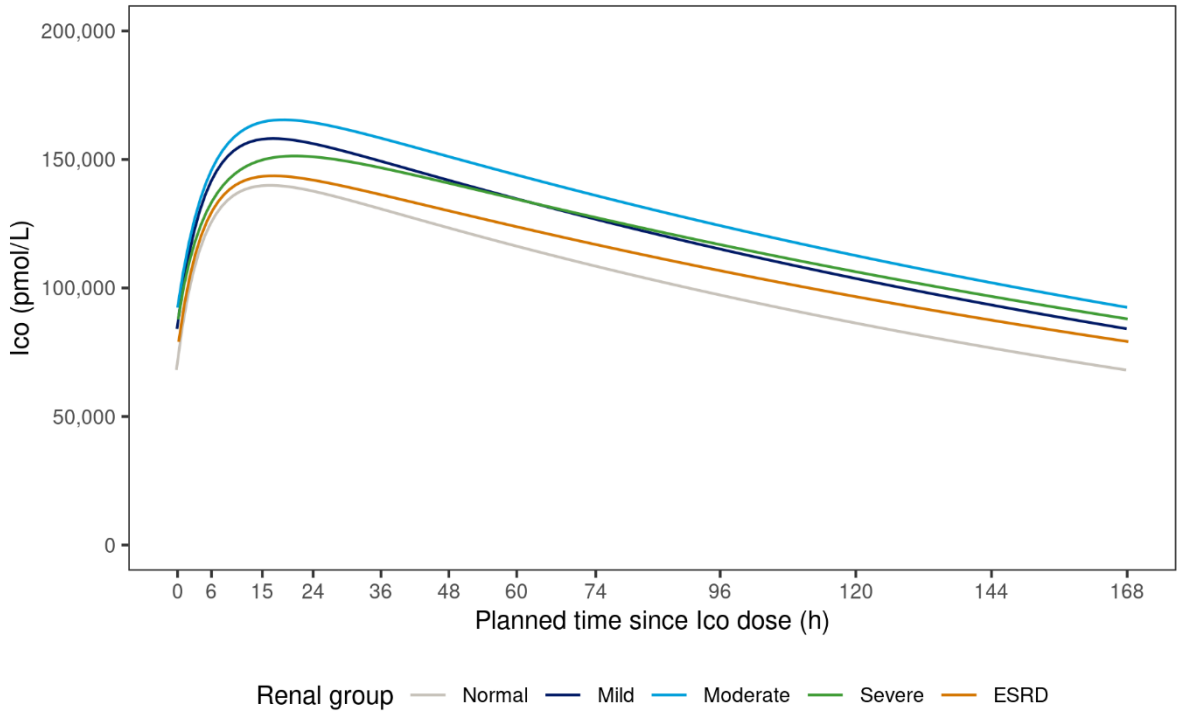


ESRD: End stage renal disease.

adpc.xpt; variable(s): AVAL; criteria: FASFL == "Y" & PARAMCD == "INS287SR" & ANELFL == "Y" & ATPT1N <= 168 & AVISITN != 29999

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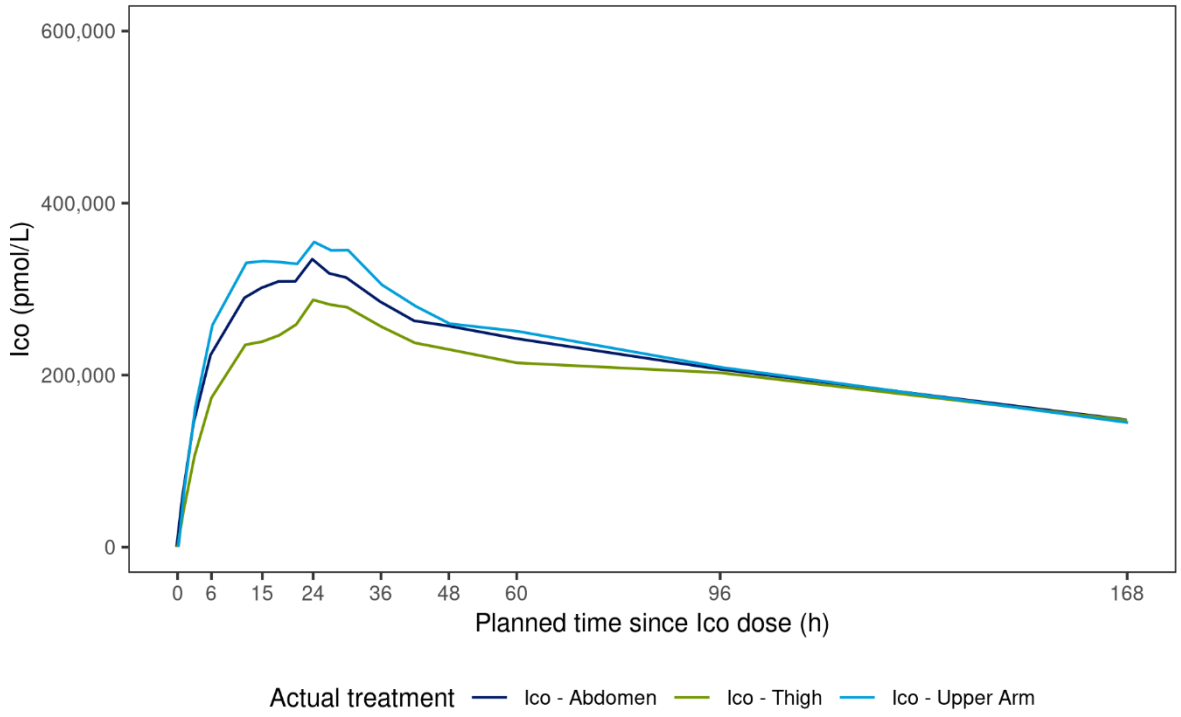
5.3.9 Ico after steady state (modelled) - 0-168h (one dosing interval) - mean profiles - linear scale - full analysis set



ESRD: End stage renal disease.

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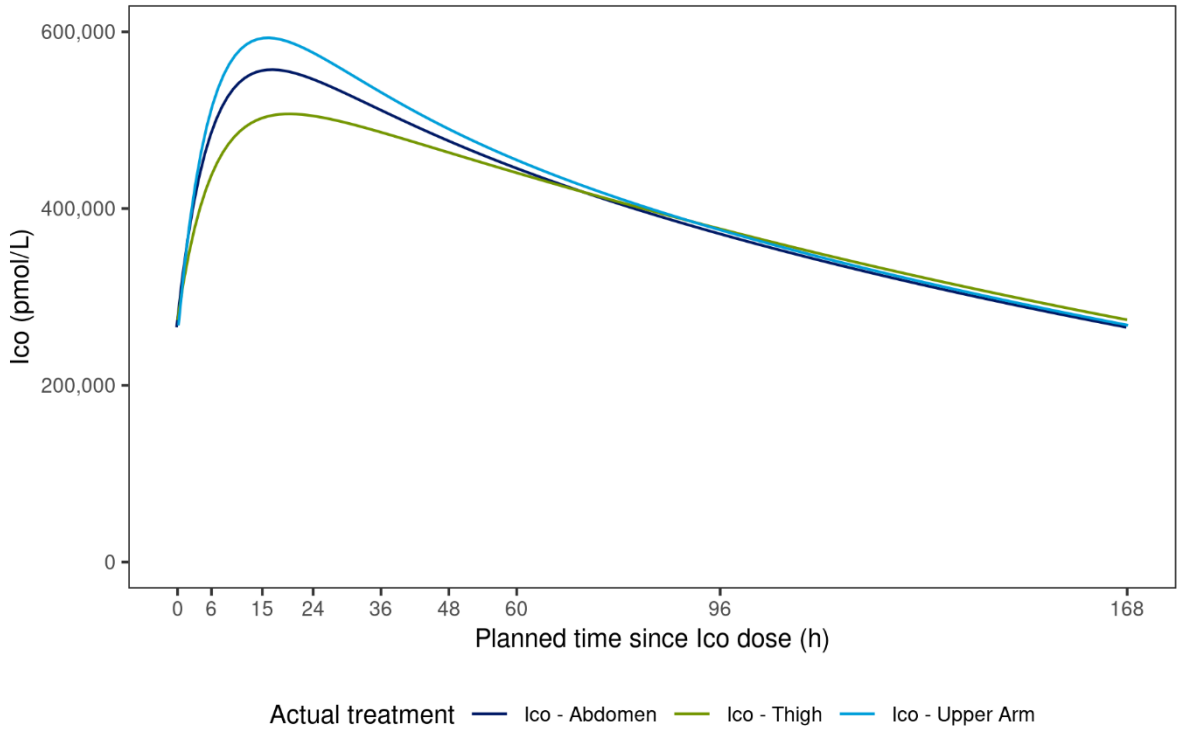
5.3.10 Ico after single dose - 0-168h (one dosing interval) - mean profiles - linear scale - full analysis set



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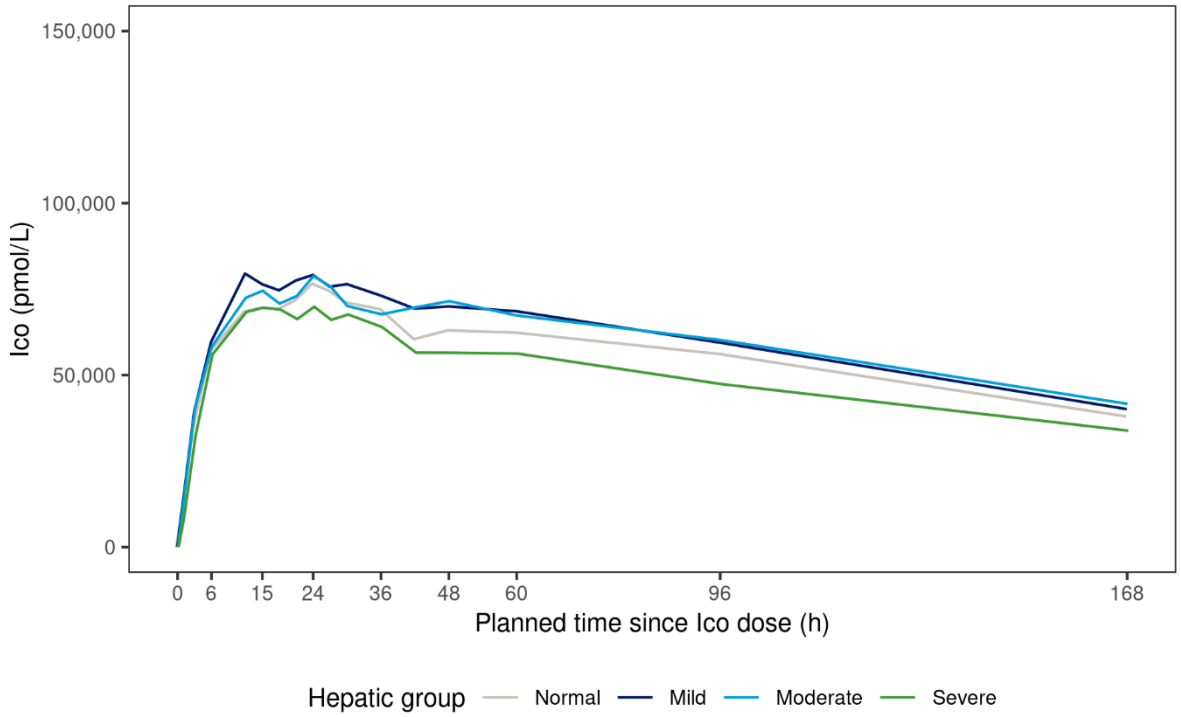
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5.3.11 Ico after steady state (modelled) - 0-168h (one dosing interval) - mean profiles - linear scale - full analysis set



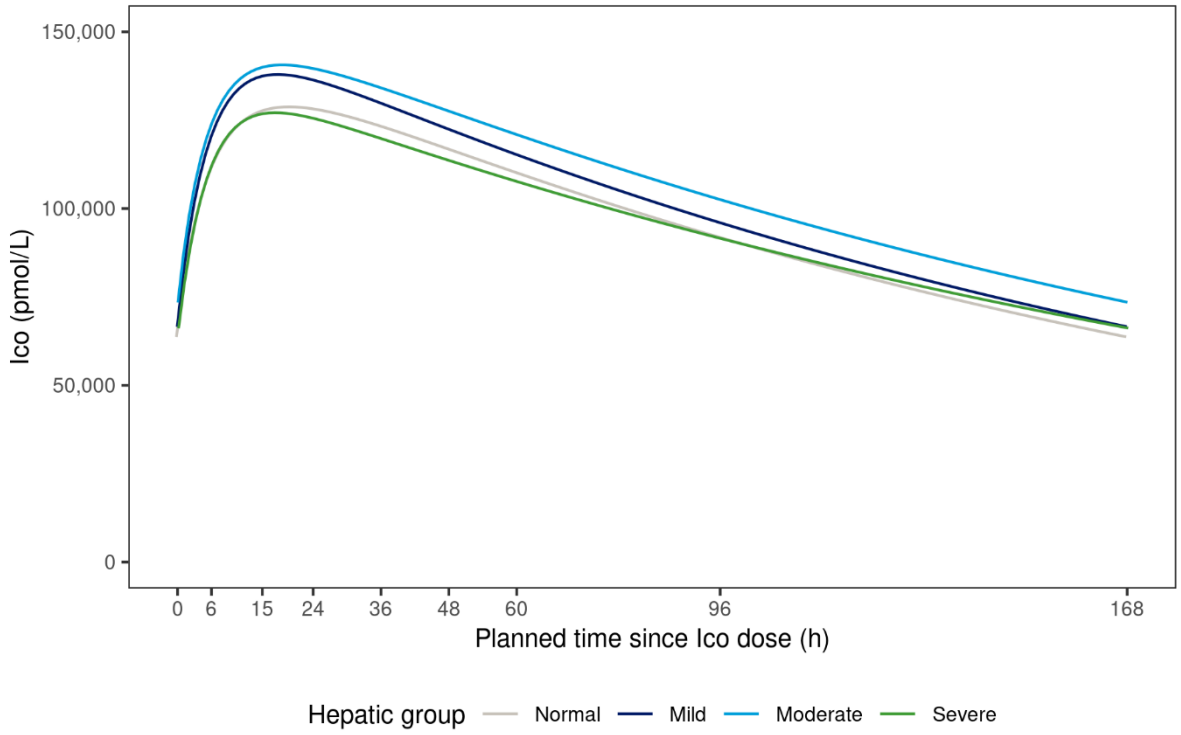
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5.3.12 Ico at steady state - 0-168h (one dosing interval) after last Ico dose - mean profiles - linear scale - full analysis set



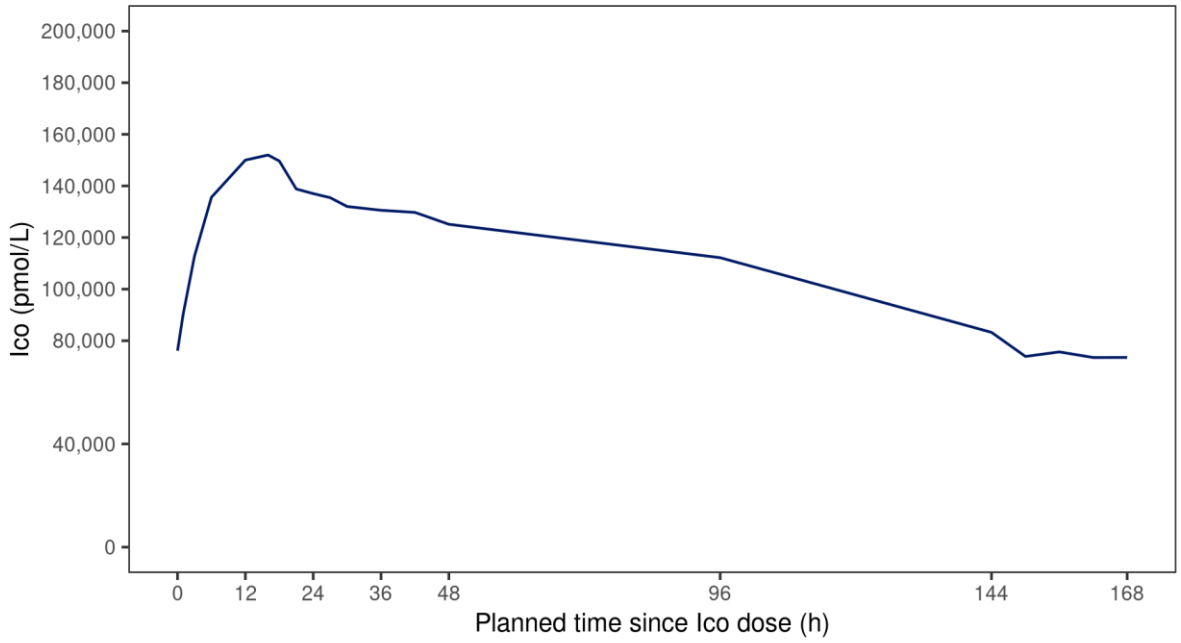
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5.3.13 Ico after steady state (modelled) - 0-168h (one dosing interval) - mean profiles - linear scale - full analysis set



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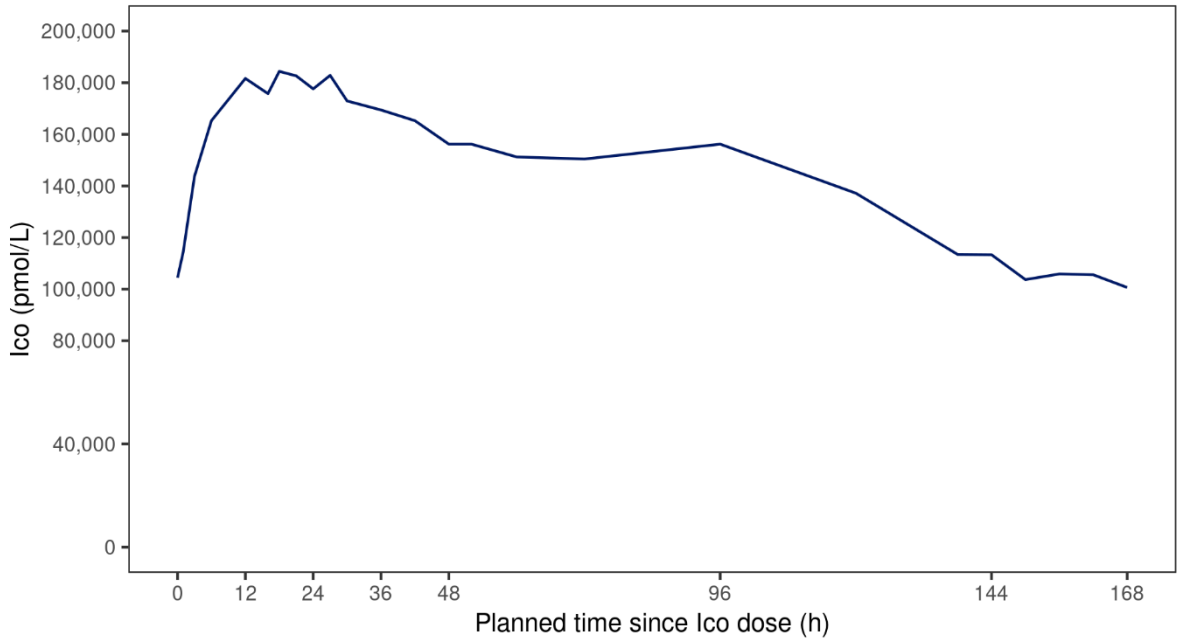
5.3.14 Ico at steady state - 0-168h (one dosing interval) after last Ico dose - mean profile - linear scale - full analysis set



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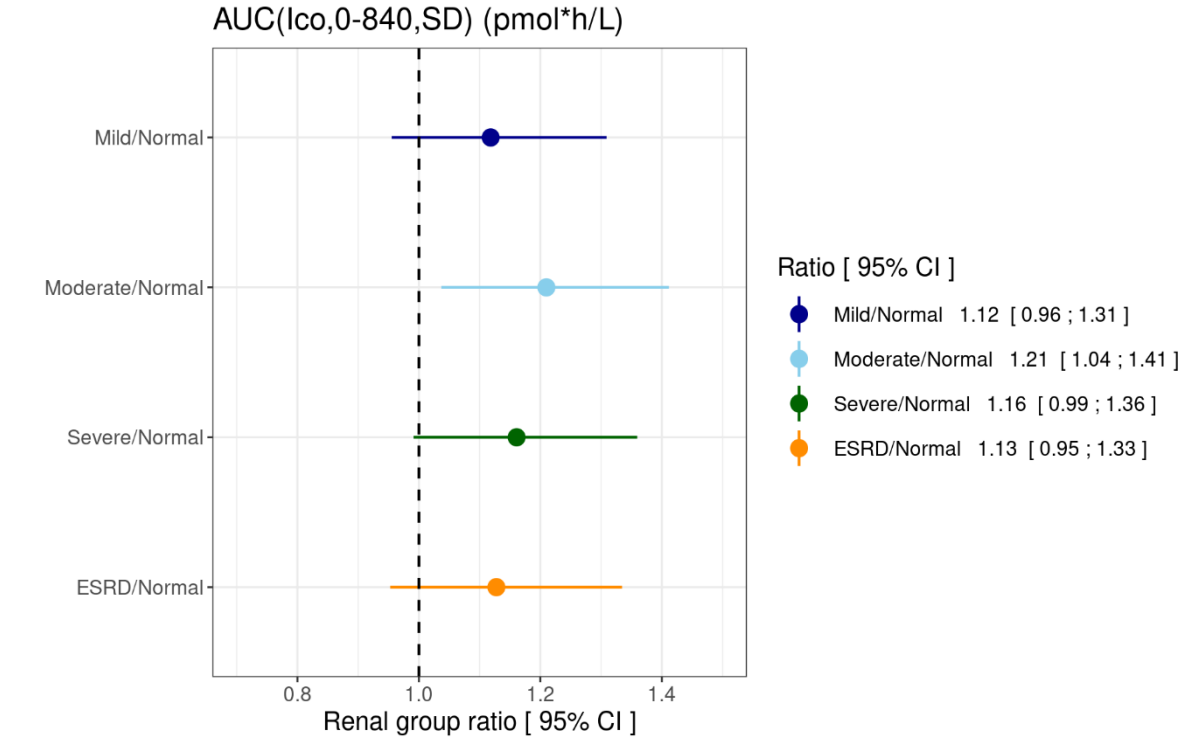
5.3.15 Ico at steady state - 0-168h (one dosing interval) after last Ico dose - mean profile - linear scale - full analysis set



adpc.xpt; variable(s): AVAL; criteria: FASFL == "Y" & PARAMCD == "INS287SR" & TYPE == "SS" & ANELFL == "Y" & TRTPN == 2 & ATPT2N <= 168

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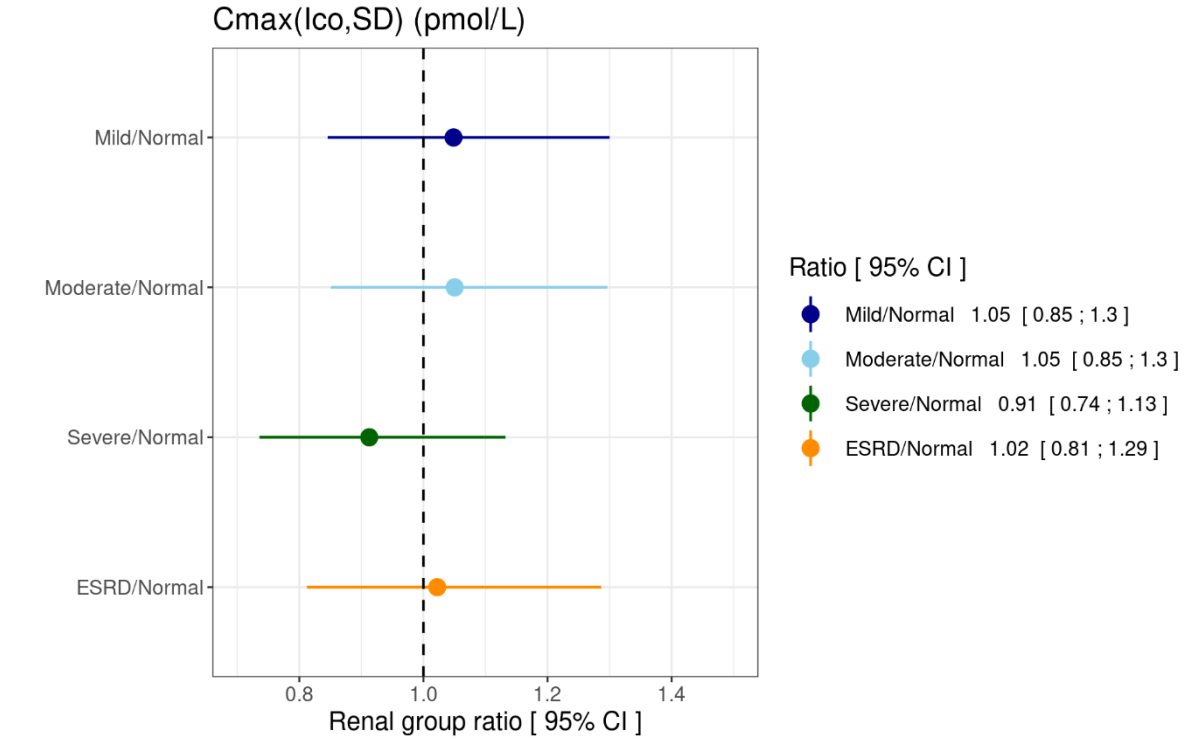
5.3.16 Insulin icodec endpoints - AUC(I287,0-840,SD) - plot of statistical analysis results - full analysis set



SD: Single dose, CI: Confidence interval, ESRD: End stage renal disease.

nn1436/exploratory/pueot001_20221031_er
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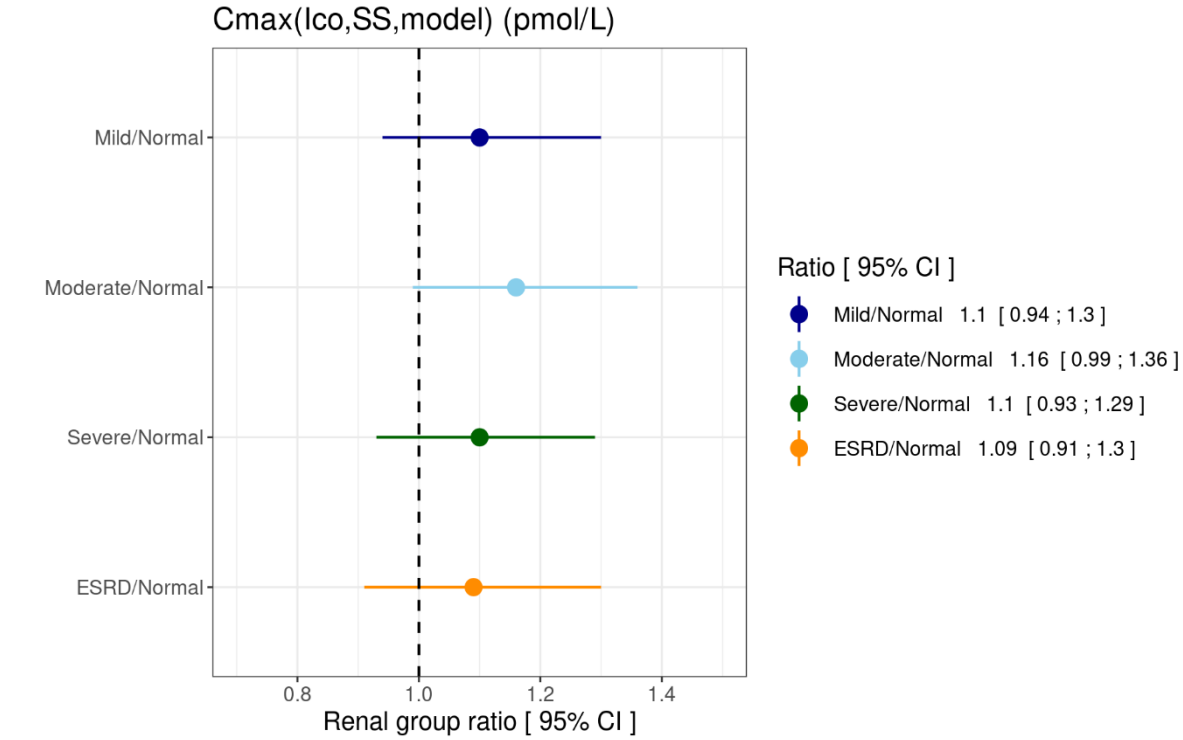
5.3.17 Insulin icodec endpoints - Cmax(I287,SD) - plot of statistical analysis results - full analysis set



SD: Single dose, CI: Confidence interval, ESRD: End stage renal disease.

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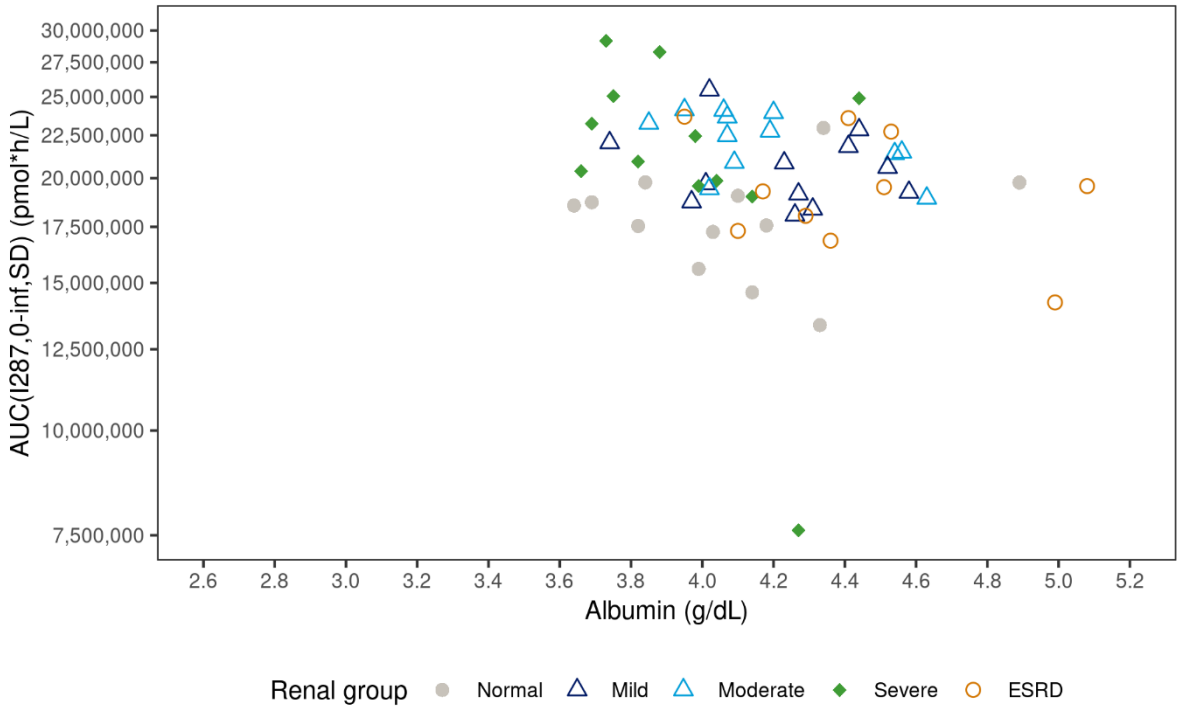
5.3.18 Insulin icodec endpoints - Cmax(I287,SS,model) - plot of statistical analysis results - full analysis set



SS: Steady state, CI: Confidence interval, ESRD: End stage renal disease.

nn1436/exploratory/pueot001_20221031_er
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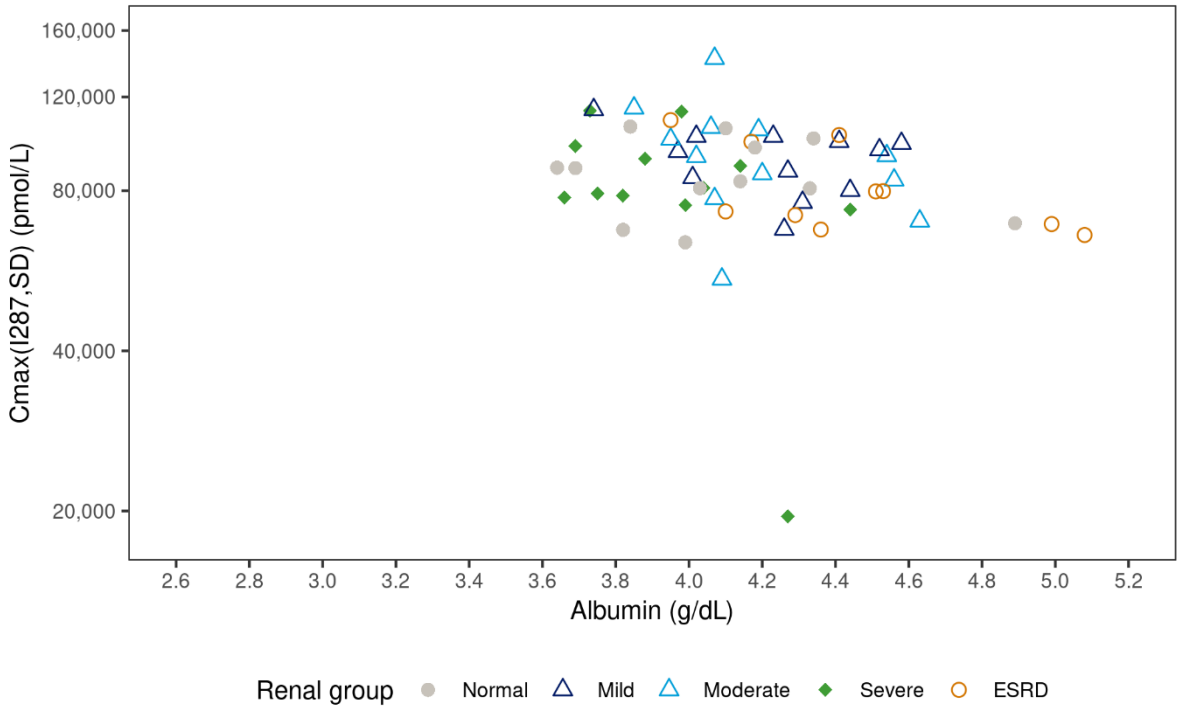
5.3.19 AUC(I287,0-840h,SD) against albumin at baseline - scatter plot - semi-log scale - full analysis set



SD: Single dose, ESRD: End stage renal disease.

nn1436/exploratory/pueot001_20221031_er
02NOV2022:05:52:48 - fscatter/fppscataucvsalbfas.png

5.3.20 Cmax(I287,SD) against albumin at baseline - scatter plot - semi-log scale - full analysis set



SD: Single dose, ESRD: End stage renal disease.

nn1436/exploratory/pueot001_20221031_er
02NOV2022:05:52:50 - fscatter/fppscatcmaxvsalbfas.png

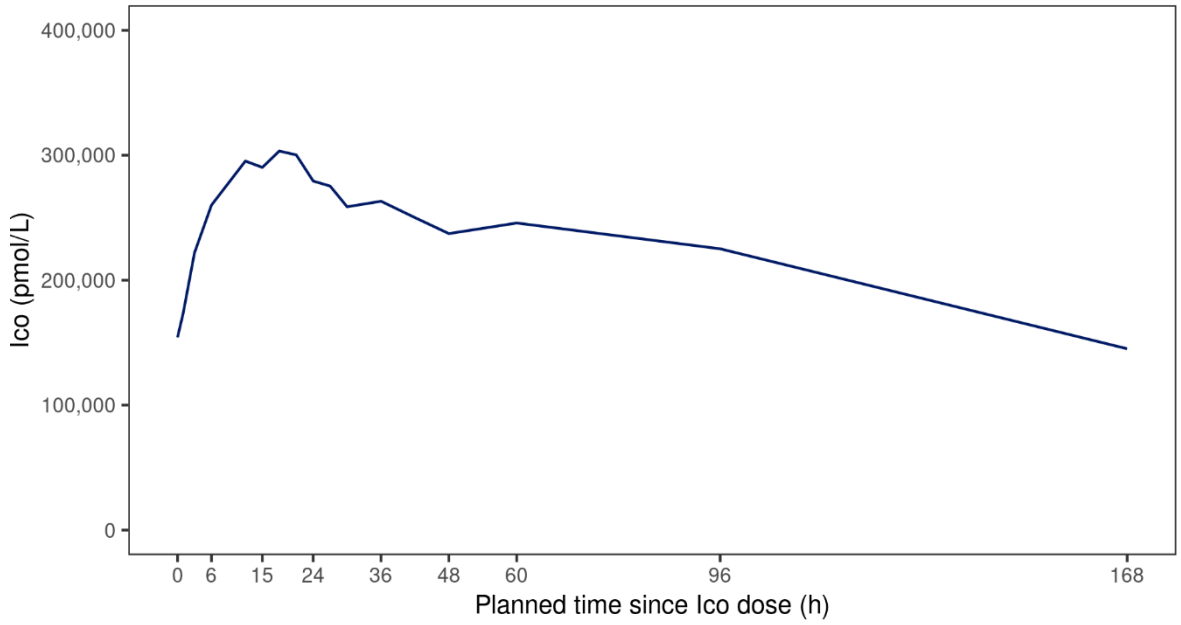
5.3.21 Insulin icodec endpoints - statistical analysis using albumin at baseline - full analysis set

	FAS	N	Estimate	95% CI	p-value
AUC(I287,0-inf,SD) (pmol*h/L)					
Parameter					
Sex (Female)	58	58	0.129	[-0.012 ; 0.269]	
Age	58	58	-0.002	[-0.007 ; 0.003]	
Body weight	58	58	0.456	[0.079 ; 0.833]	
Baseline Albumin	58	58	-0.483	[-1.367 ; 0.401]	0.2782
Cmax(I287,SD) (pmol/L)					
Parameter					
Sex (Female)	58	58	0.209	[0.027 ; 0.390]	
Age	58	58	-0.004	[-0.010 ; 0.003]	
Body weight	58	58	0.582	[0.094 ; 1.069]	
Baseline Albumin	58	58	-0.810	[-1.953 ; 0.333]	0.1611

CI: Confidence interval, FAS: Full Analysis set, N: Number of subjects contributing to the analysis, SD: Single dose. The results are from a normal linear model with log(endpoint) as the dependent variable and log(baseline body weight), age and log(baseline albumin) as covariates and sex as a fixed effect.

nn1436/exploratory/pueot001_20221031_er
02NOV2022:05:52:41 - appcovariate/appcovariatefas.txt

5.3.22 Ico at steady state - 0-168h (one dosing interval) after last Ico dose - mean profile - linear scale - full analysis set

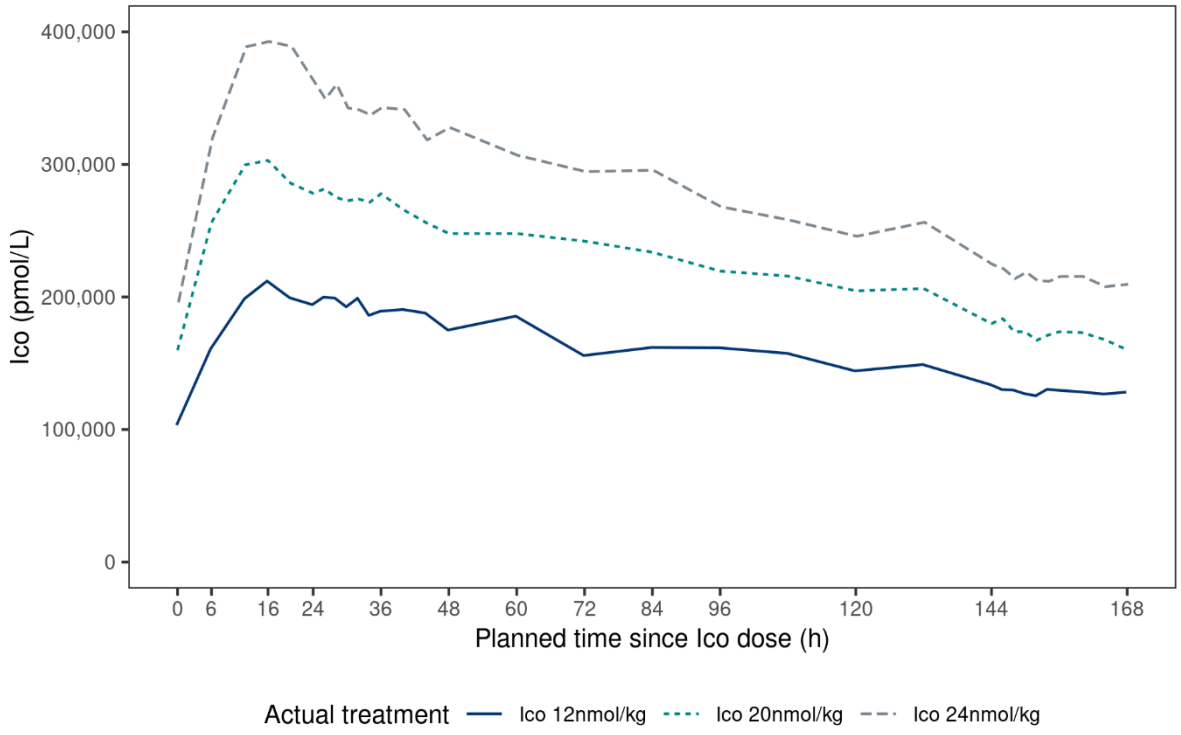


Day 50 - Ico actual dose range (U/kg): 1.53 - 5.64.

adpc.xpt; variable(s): AVAL; criteria: FASFL == "Y" & PARAM == "Ico (pmol/L)" & ANELFL == "Y" & PROFID == "Ico SS" & ATPT2N <= 168

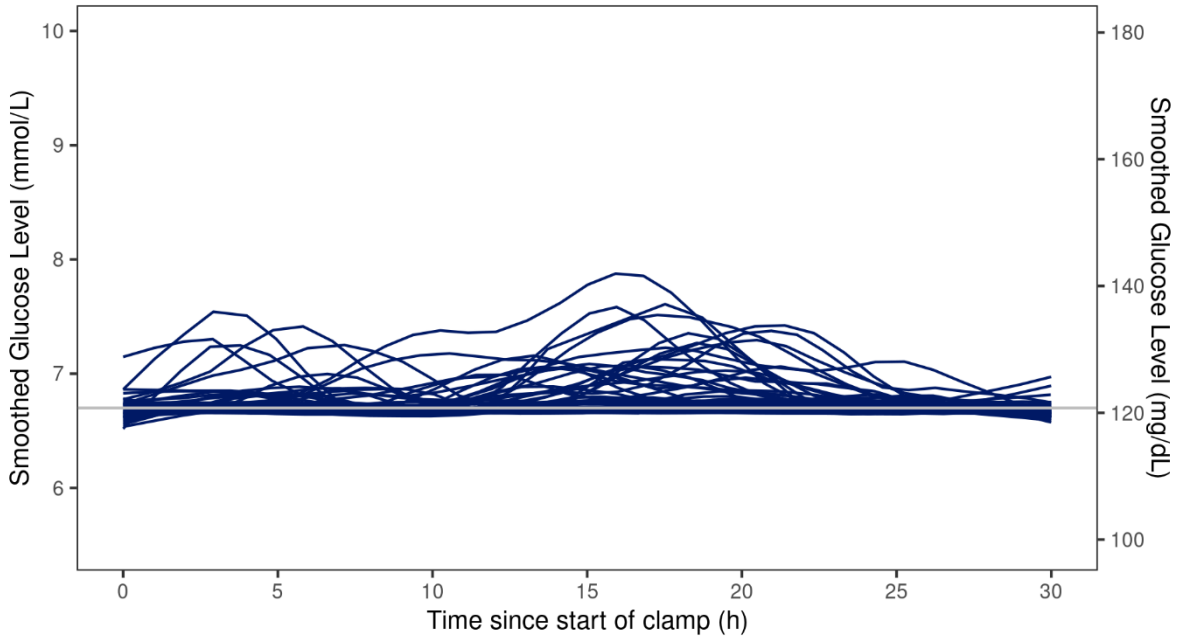
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5.3.23 PK - mean profiles - I287 - steady state (day 29 - day 36) - linear scale - full analysis set



nn1436/exploratory/pueot001_20221031_er
02NOV2022:05:52:51 - fmeantime2/fpci287meansslin4314fas.png

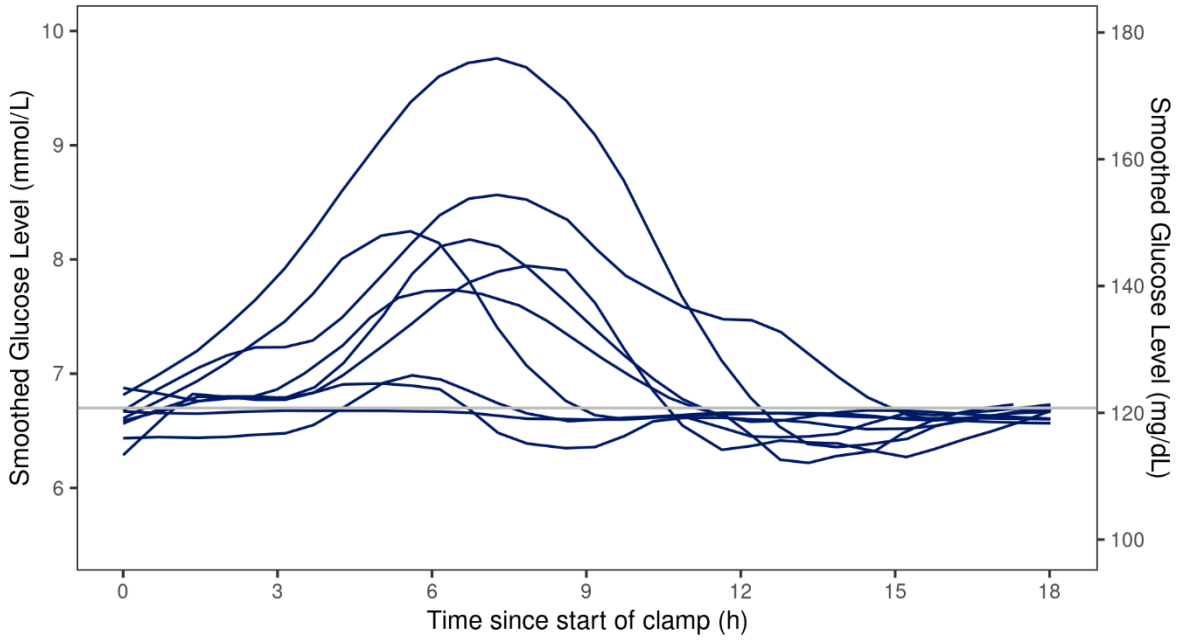
5.3.24 BG (smoothed) during clamp at steady state - 138-168h after last Ico dose - individual profiles - insulin icodec - subjects with sufficient dose - full analysis set



Horizontal grey line at 6.7 mmol/L indicates the clamp target.

nn1436/exploratory/pueot001_20221031_er
02NOV2022:05:52:47 - fpdcindivpg/fpdcsindivpg4225fas.png

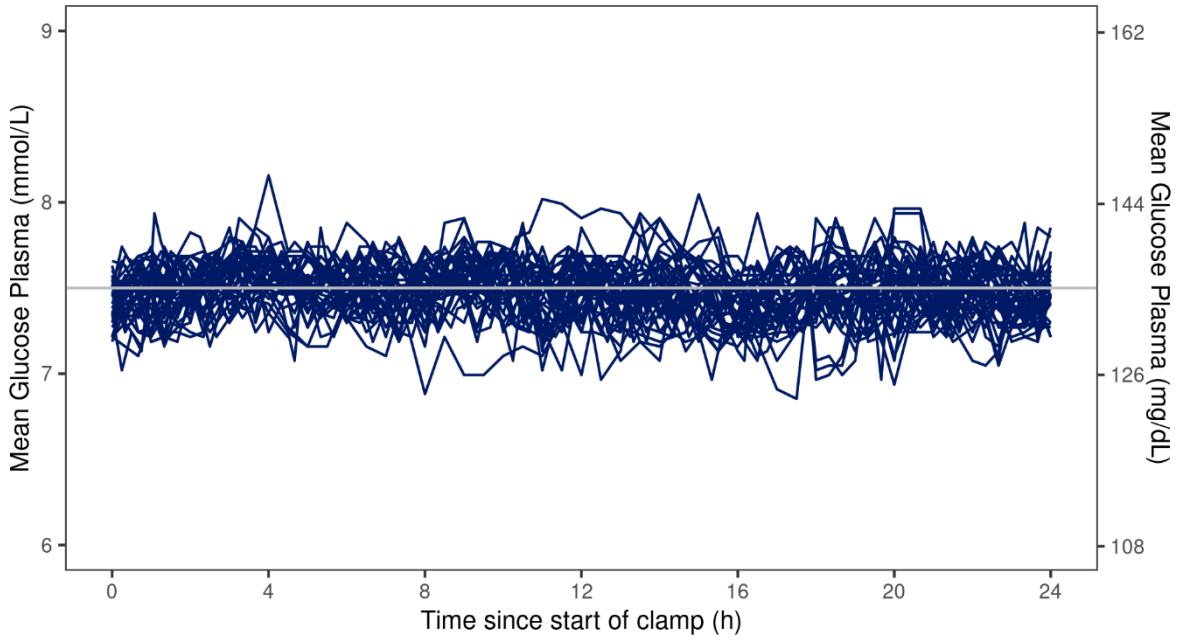
5.3.25 BG (smoothed) during clamp at steady state - 150-168h after last Ico dose - individual profiles - insulin icodec - subjects with sufficient dose - full analysis set



Horizontal grey line at 6.7 mmol/L indicates the clamp target.

nn1436/exploratory/pueot001_20221031_er
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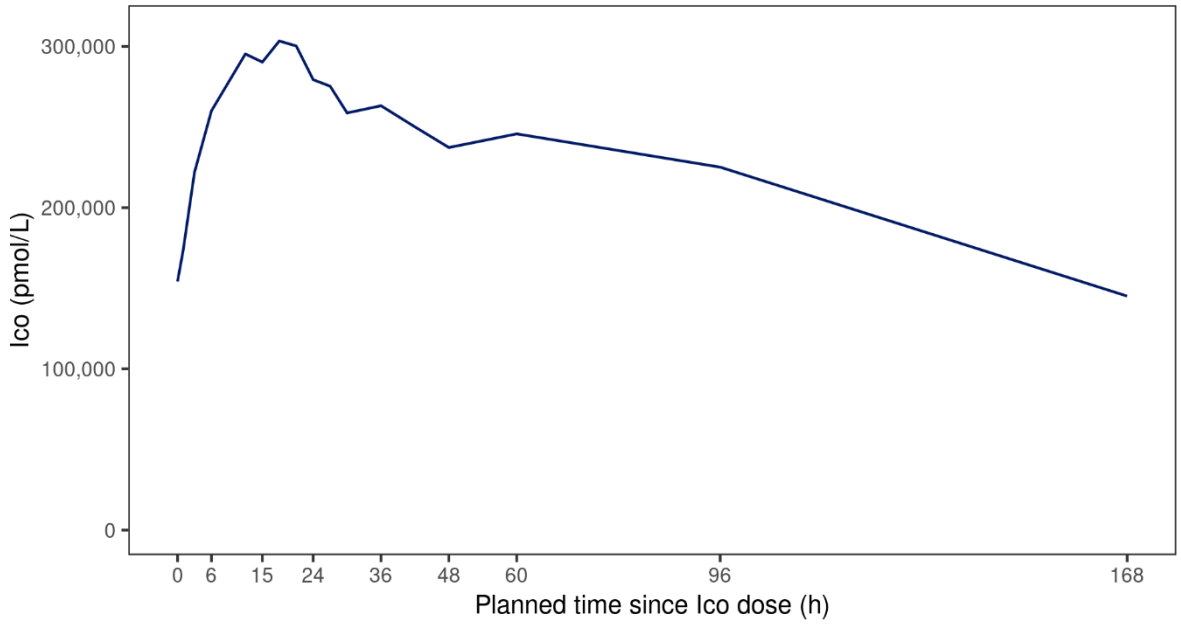
5.3.26 Plasma glucose at steady state - 144-168h after Ico dose day 50 - individual profiles - full analysis set



Horizontal grey line at 7.5 mmol/L indicates the clamp target.

nn1436/exploratory/pueot001_20221031_er
02NOV2022:05:53:24 - fpdcindivpg2/fpdcindvpg144168hicofas.png

5.3.27 Ico at steady state - 0-168h (one dosing interval) after last Ico dose - mean profile - linear scale - full analysis set

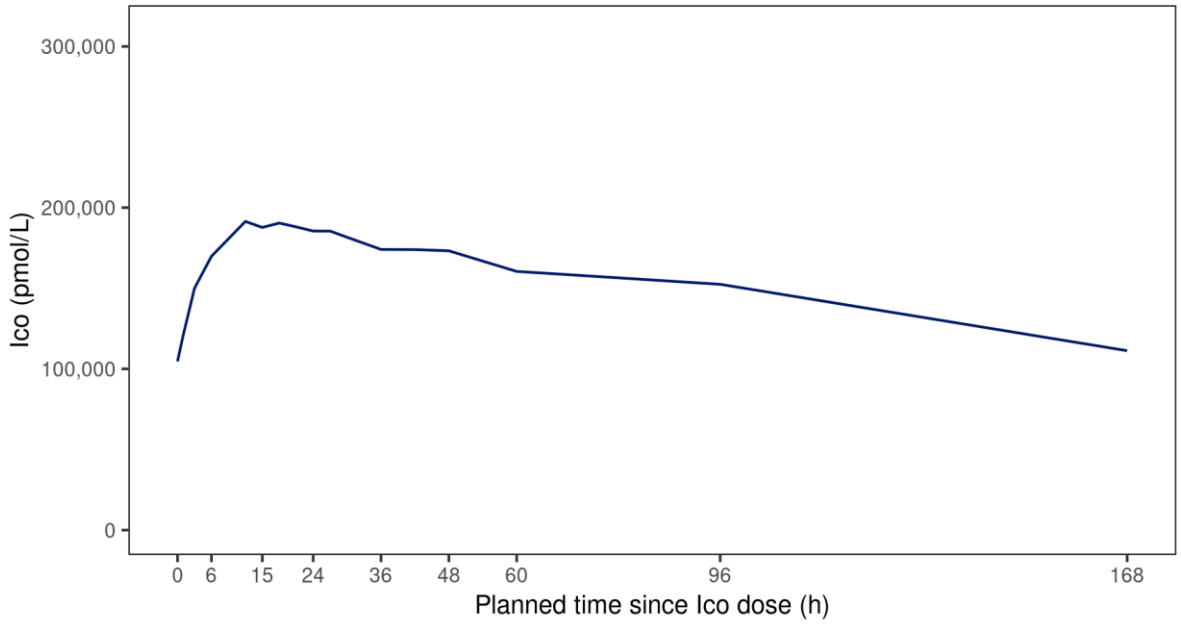


Day 50 - Ico actual dose range (U/kg): 1.53 - 5.64.

adpc.xpt; variable(s): AVAL; criteria: FASFL == "Y" & PARAM == "Ico (pmol/L)" & ANELFL == "Y" & PROFID == "Ico SS" & ATPT2N <= 168

nn1436/exploratory/pueot001_20221031_er
02NOV2022:05:53:16 - fmeantime3/fpci287meansslin4569fas2.png

5.3.28 Ico at steady state - 0-168h (one dosing interval) after Ico dose day 36 - mean profile - linear scale - full analysis set

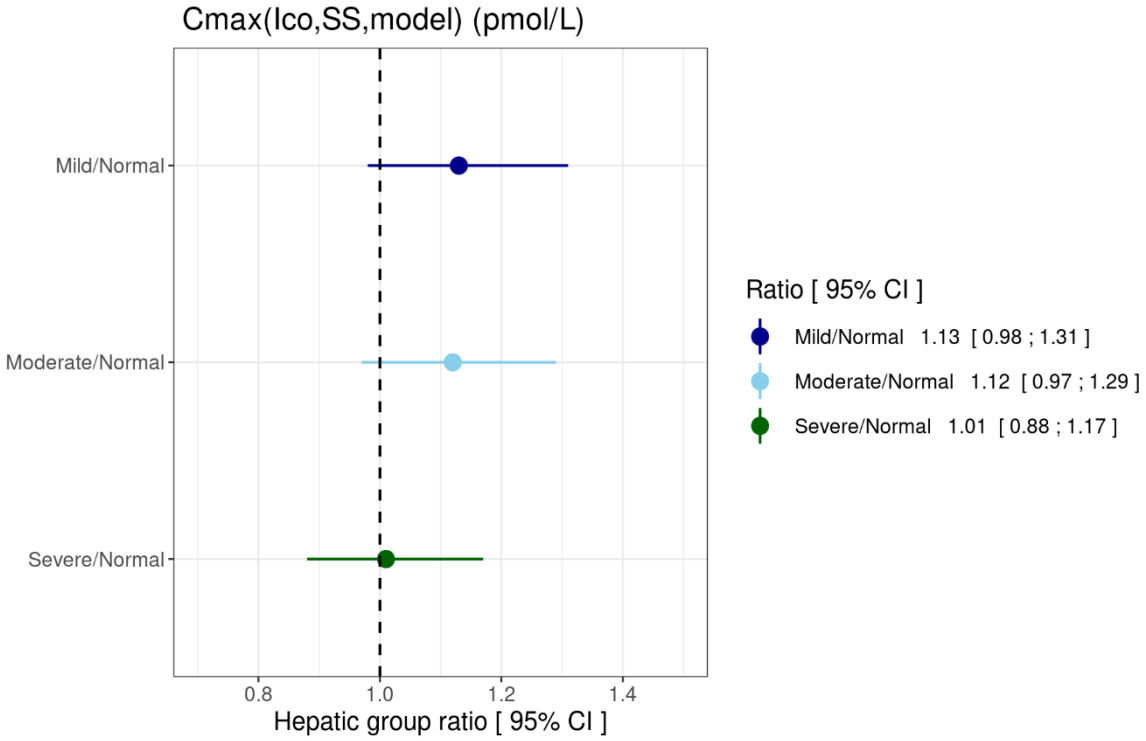


Ico actual dose range (U/kg): 1.27 - 4.92.

adpc.xpt; variable(s): AVAL; criteria: FASFL == "Y" & PARAM == "Ico (pmol/L)" & ANELFL == "Y" & PROFID == "Ico SS" & ATPT2N <= 168

nn1436/exploratory/pueot001_20221031_er
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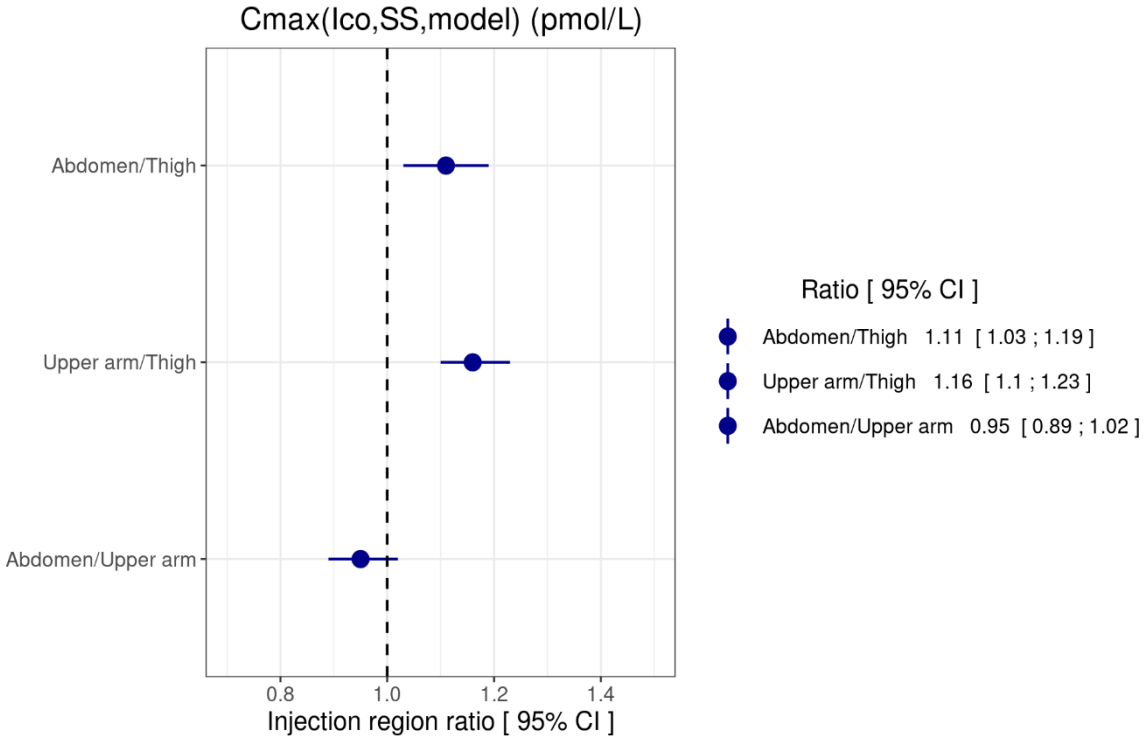
5.3.29 Insulin icodec endpoints - Cmax(Ico,SS,model) - plot of statistical analysis results - full analysis set



SS: Steady state, CI: Confidence interval.

nn1436/exploratory/pueot001_20221031_er
02NOV2022:05:53:11 - fppendptmodel/fppcmaxmodel4570fas.png

5.3.30 Insulin icodec endpoints - Cmax(Ico,SS,model) - plot of statistical analysis results - full analysis set



SS: Steady state, CI: Confidence interval.

nn1436/exploratory/pueot001_20221031_er
02NOV2022:05:53:13 - fppendptmodel/fppcmaxmodel4572fas.png

5.3.31 C(trough, Ico) - mean of within subject variability - day 22, 29 and 36 - full analysis set

Endpoint	FAS	N	Mean of within subject CV%	95% CI
C(trough,Ico) (pmol/L)	24	24	11.48	[7.88 ; 15.08]

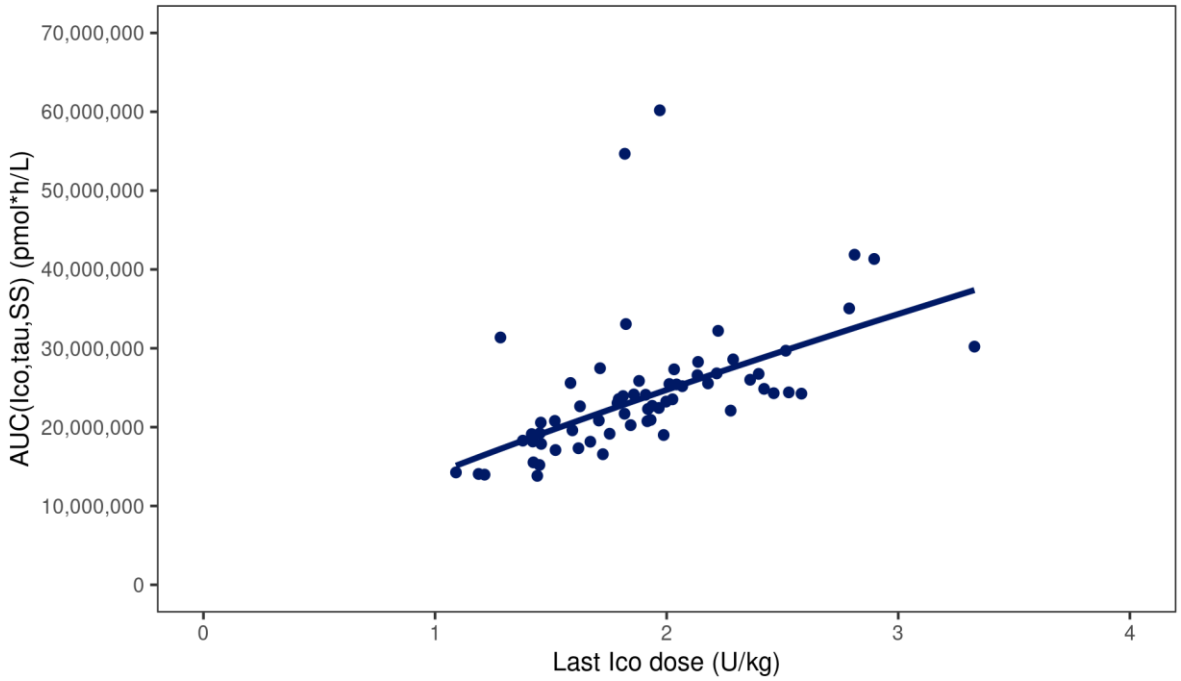
CV: Coefficient of variation, CI: Confidence interval, FAS: Full analysis set, N: Number of subjects contributing to the analysis. One subject is only contributing to the analysis with C(trough, Ico) on day 22 and 29.

5.3.32 C(trough, Ico) - mean of within subject variability - day 22, 29 and 36 - excluding subject 101016 - full analysis set

Endpoint	FAS	N	Mean of within subject CV%	95% CI
C(trough,Ico) (pmol/L)	24	23	10.78	[7.33 ; 14.24]

CV: Coefficient of variation, CI: Confidence interval, FAS: Full analysis set, N: Number of subjects contributing to the analysis. One subject is only contributing to the analysis with C(trough, Ico) on day 22 and 29. Subject 101016 is excluded.

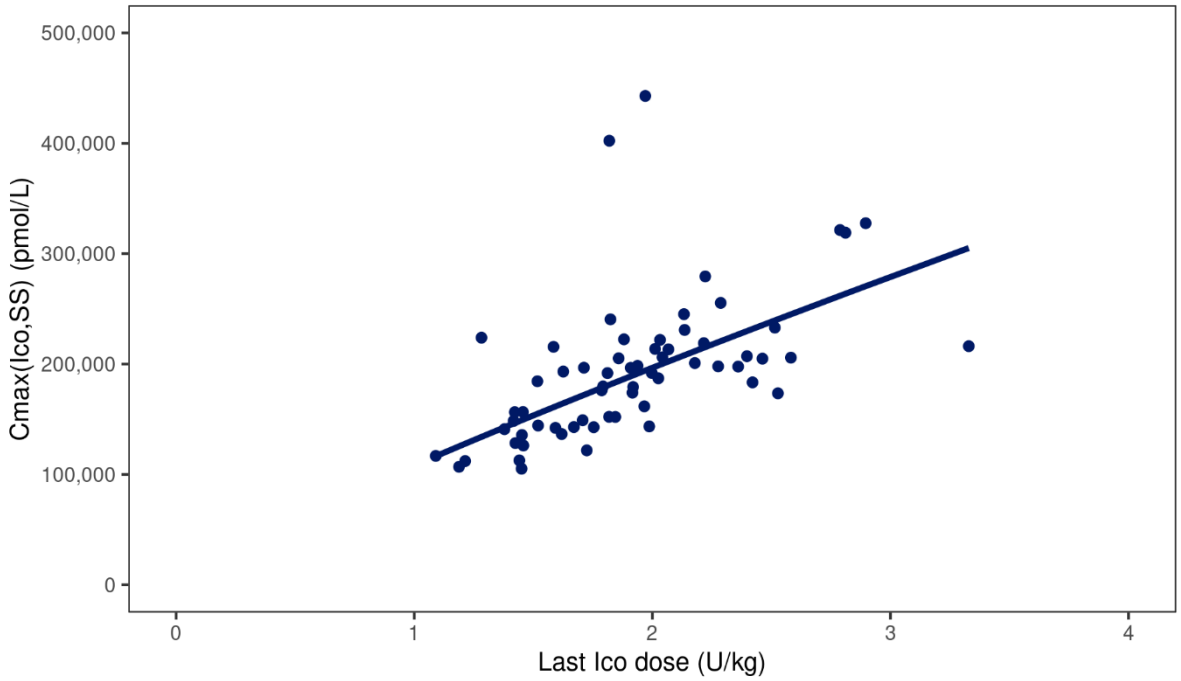
5.3.33 AUC(Ico,tau,SS) against last Ico dose - scatter plot - insulin icodec - full analysis set



SS: Steady state.
The solid represents the estimated curve based on a linear regression model with log(dose) as regressor fitted to the logarithmically transformed endpoint.

nn1436/exploratory/pueot001_20221031_er
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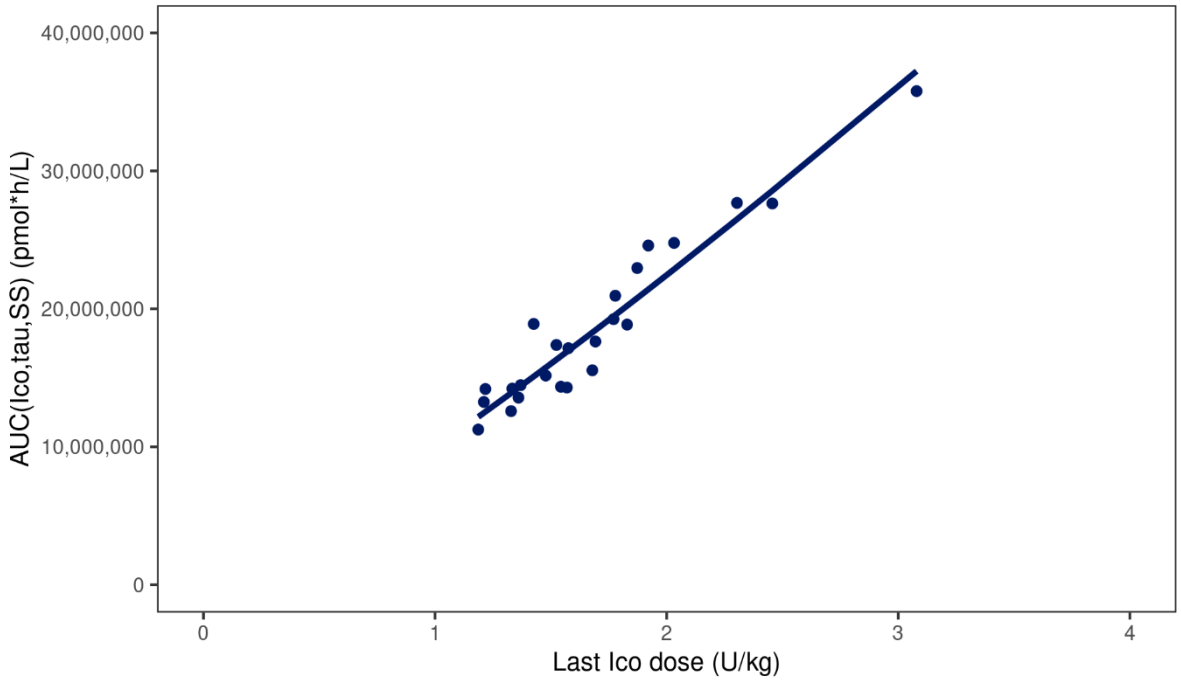
5.3.34 Cmax(Ico,SS) against last Ico dose - scatter plot - insulin icodec - full analysis set



SS: Steady state.
The solid represents the estimated curve based on a linear regression model with log(dose) as regressor fitted to the logarithmically transformed endpoint.

nn1436/exploratory/pueot001_20221031_er
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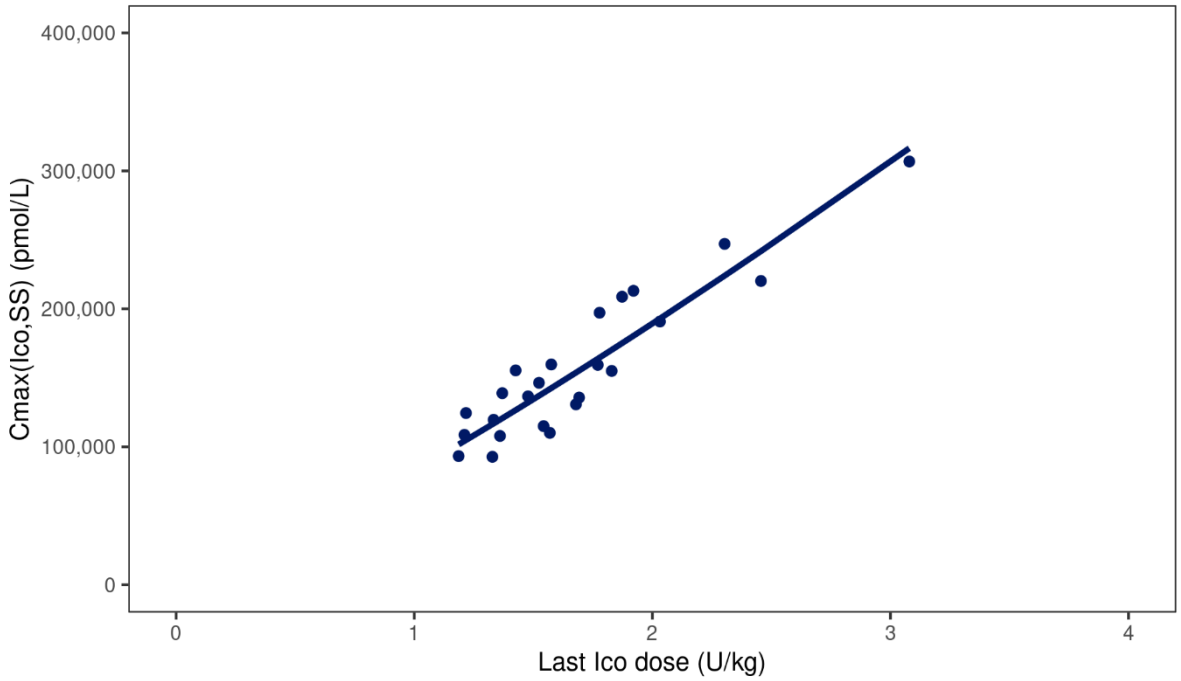
5.3.35 AUC(Ico,tau,SS) against last Ico dose - scatter plot - insulin icodec - full analysis set



SS: Steady state.
The solid represents the estimated curve based on a linear regression model with log(dose) as regressor fitted to the logarithmically transformed endpoint.

nn1436/exploratory/pueot001_20221031_er
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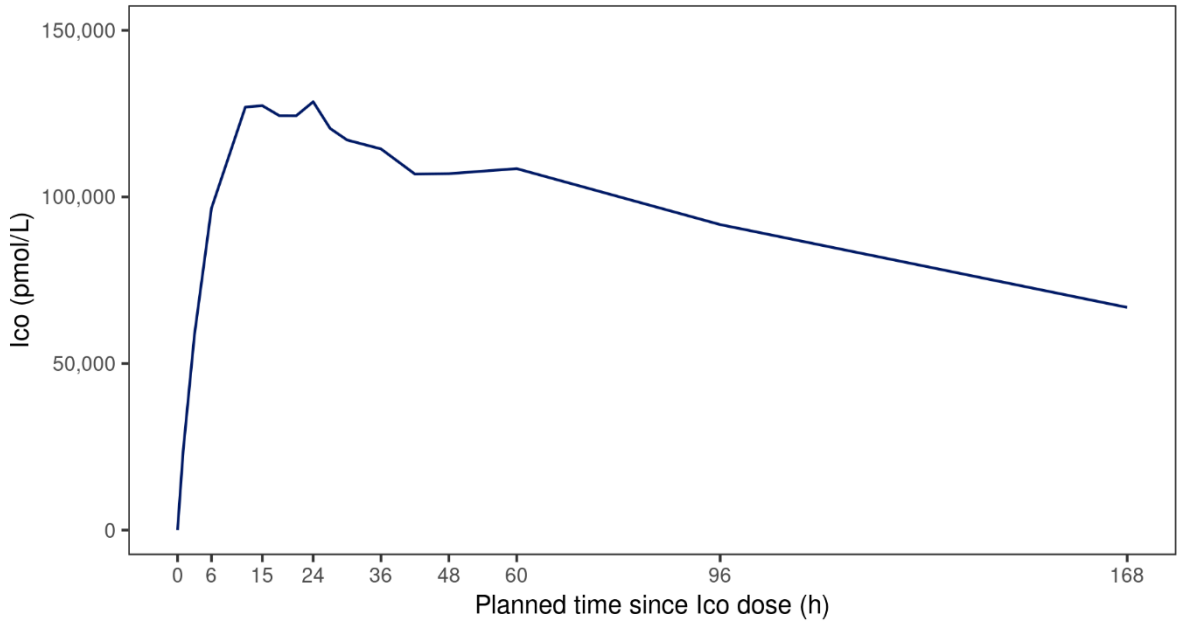
5.3.36 Cmax(Ico,SS) against last Ico dose - scatter plot - insulin icodec - full analysis set



SS: Steady state.
The solid represents the estimated curve based on a linear regression model with log(dose) as regressor fitted to the logarithmically transformed endpoint.

nn1436/exploratory/pueot001_20221031_er
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5.3.37 Ico after first dose - 0-168h (one dosing interval) after first Ico dose - mean profile - linear scale - full analysis set

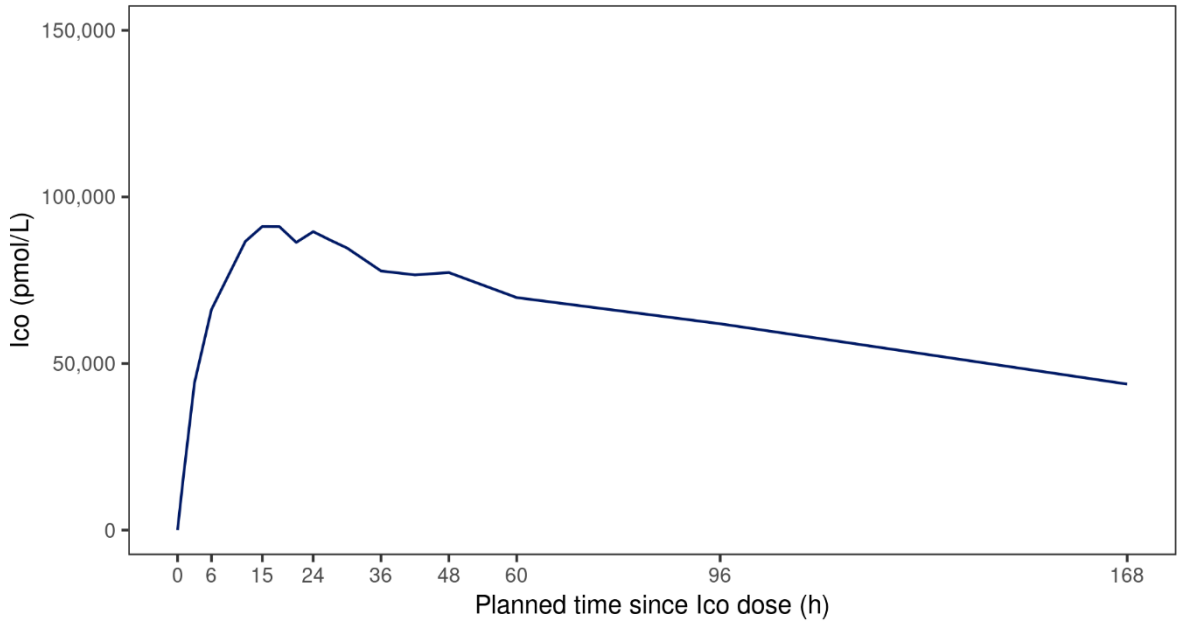


First Ico actual dose range (U/kg): 1.21 - 5.27

adpc.xpt; variable(s): AVAL; criteria: FASFL == "Y" & PARAM == "Ico (pmol/L)" & ANELFL == "Y" & PROFID == "Ico FD" & ATPT1N <= 168

nn1436/exploratory/pueot001_20221031_er
02NOV2022:05:52:46 - fmeantimefd/fpcicomeanfdlin4569fas.png

5.3.38 Ico after first dose - 0-168h (one dosing interval) after first Ico dose - mean profile - linear scale - full analysis set

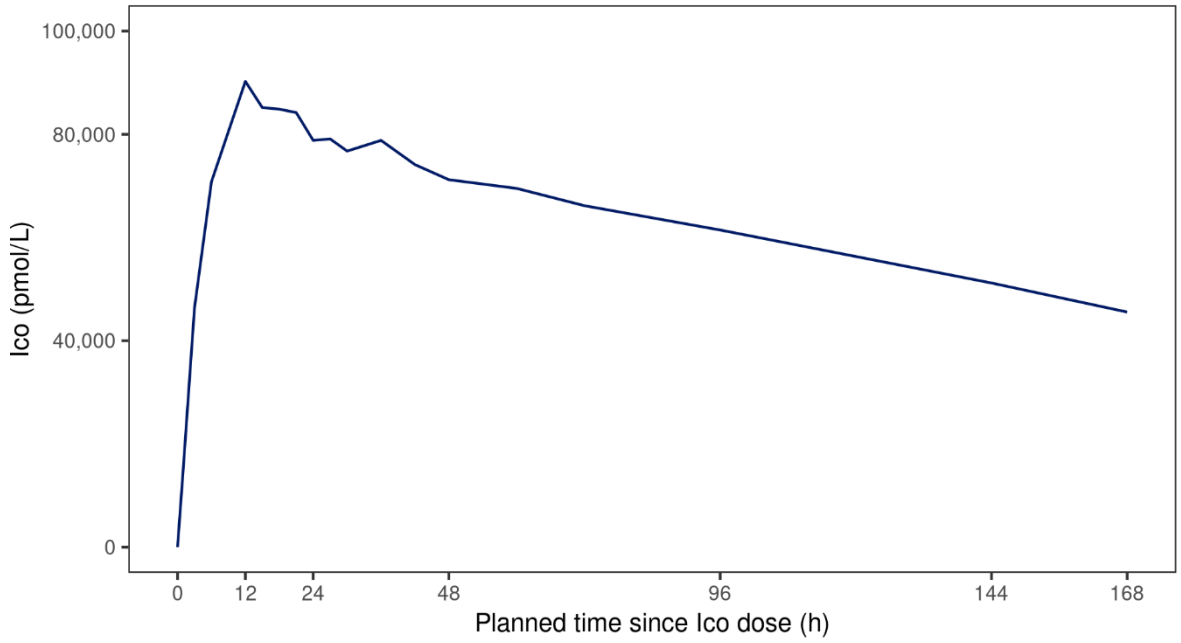


Ico actual dose range (U/kg): 1.27 - 4.92.

adpc.xpt; variable(s): AVAL; criteria: FASFL == "Y" & PARAM == "Ico (pmol/L)" & ANELFL == "Y" & PROFID == "Ico FD" & ATPT1N <= 168

nn1436/exploratory/pueot001_20221031_er
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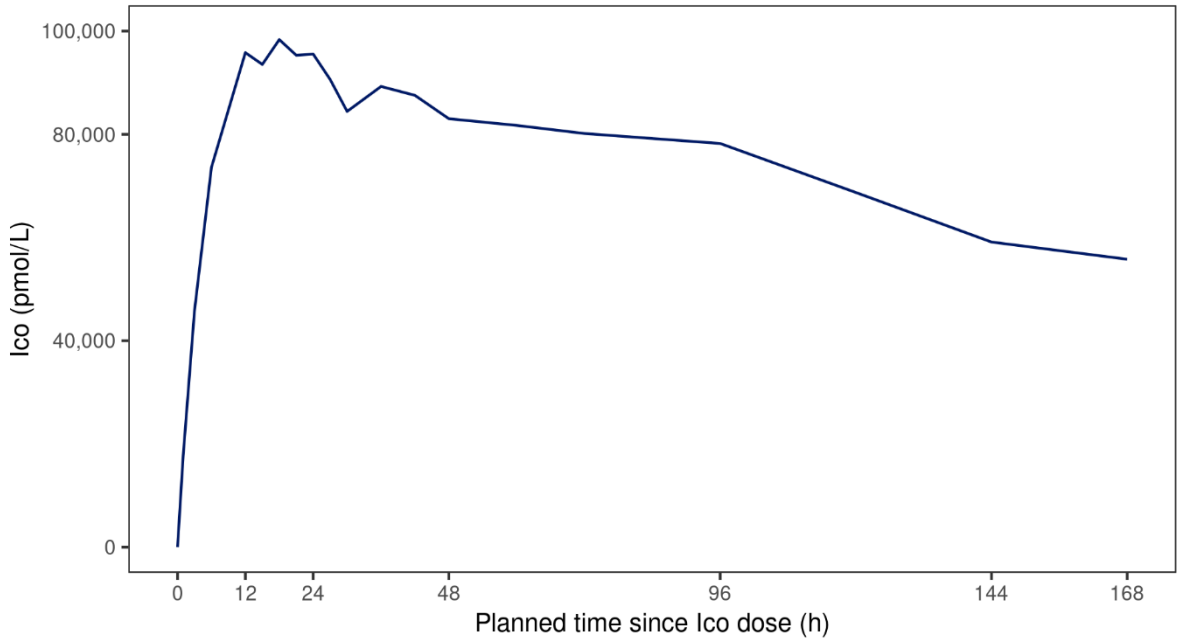
5.3.39 Ico after first dose - 0-168h (one dosing interval) after first Ico dose - mean profile - linear scale - full analysis set



adpc.xpt; variable(s): AVAL; criteria: FASFL == "Y" & PARAMCD == "INS287SR" & ANELFL == "Y" & TYPE == "FD" & TRTPN == 2 & ATPT1N <= 168

nn1436/exploratory/pueot001_20221031_er
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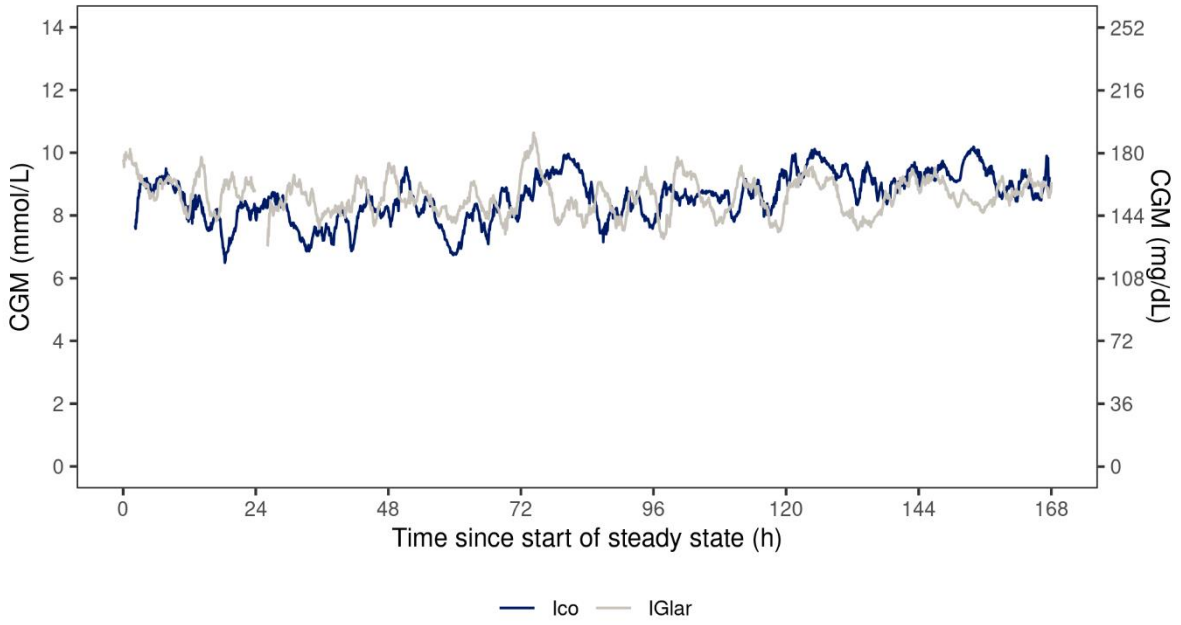
5.3.40 Ico after first dose - 0-168h (one dosing interval) after first Ico dose - mean profile - linear scale - full analysis set



adpc.xpt; variable(s): AVAL; criteria: FASFL == "Y" & PARAMCD == "INS287SR" & ANELFL == "Y" & TYPE == "FD" & TRTPN == 2 & ATPT1N <= 168

nn1436/exploratory/pueot001_20221031_er
02NOV2022:05:53:10 - fmeantimefd/fpcicomeanfdlin4225fas.png

5.3.41 CGM - during one week at steady state - treatment period - mean profiles - subjects with sufficient dose - full analysis set

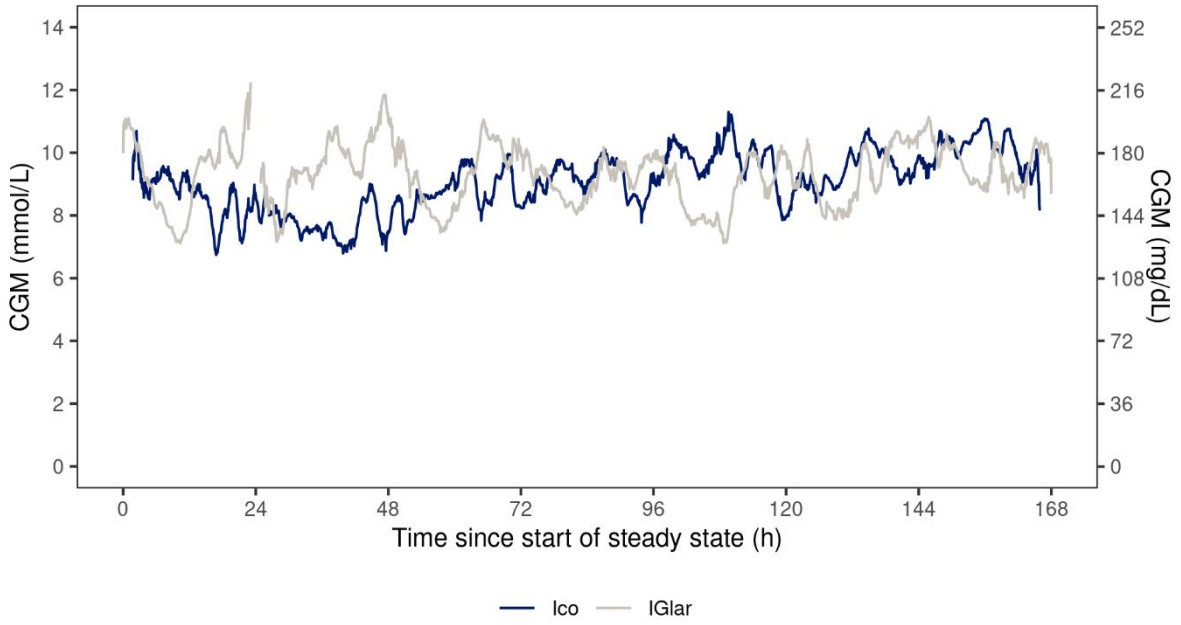


CGM: Continious glucose monitoring.
The week at steady state is from administration of the 7th Ico dose (planned at 20.00 on day 43) for Ico and from administration of the 6th IGlar dose (planned at 20.00 on day 6) for Iglar. The week at steady state ends 7 days (i.e. 168 hours) later.
The mean is calculated for timepoints with at least 17 values. No interpolation is done for timepoints with less than 17 values.

adcgm.xpt; variable(s): AVAL; criteria: FASFL == "Y" & TYPE == "SS" & ARELTM1 <= 168 & SUBGR1FL == "Y"

nn1436/exploratory/pueot001_20221031_er
02NOV2022:05:53:54 - fcgmmean/fcgmmeanssweeksuff4225fas.png

5.3.42 CGM - during one week at steady state - treatment period - mean profiles - full analysis set



CGM: Continious glucose monitoring.
The week at steady state is from administration of the 7th Ico dose (planned at 20.00 on day 43) for Ico and from administration of the 6th IGlar dose (planned at 20.00 on day 6) for Iglar. The week at steady state ends 7 days (i.e. 168 hours) later.
The mean is calculated for timepoints with at least 6 values. No interpolation is done for timepoints with less than 6 values.

adcgm.xpt; variable(s): AVAL; criteria: FASFL == "Y" & TYPE == "SS" & ARELTM1 <= 168

nn1436/exploratory/pueot001_20221031_er
02NOV2022:05:55:46 - fcgmmean/fcgmmeanssweek4422fas.png

インスリン イコデク（遺伝子組換え）

2.7.2.5 付録
4. 4462 試験に関する追加帳票

ノボ ノルディスク ファーマ株式会社

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5.4.1 Hypoglycaemia awareness - summary - subjects with symptoms or clinically significant hypoglycaemia

	Ico 2xdose N (%)	Ico 3xdose N (%)	IGlar 2xdose N (%)	IGlar 3xdose N (%)
Number of subjects	20	20	19	29
Hypo Awareness, at PG level 3.0 mmol/L				
N	17 (100.0)	20 (100.0)	15 (100.0)	28 (100.0)
Yes	9 (52.9)	5 (25.0)	2 (13.3)	8 (28.6)
No	8 (47.1)	15 (75.0)	13 (86.7)	20 (71.4)

`Number of subjects` refers to number of subjects with symptoms or clinically significant hypoglycaemia. N: Number of subjects. 2xdose refers to double dose, 3xdose refers to triple dose.

5.4.2 Counterregulatory hormones at PG decline 3.0 mmol/L for triple dose - statistical analysis - subjects with clinically significant hypoglycaemia

	N	Nobs	Estimate	95% CI	p-value
Glucagon (pg/mL), TD					
Estimated geometric means					
Ico	20	20	55.15		
IGlar	28	28	51.62		
Treatment ratio					
Ico / IGlar			1.07	[0.86 ; 1.33]	0.5278
Growth Hormone (ng/mL), TD					
Estimated geometric means					
Ico	20	20	3.70		
IGlar	28	28	2.41		
Treatment ratio					
Ico / IGlar			1.54	[0.72 ; 3.29]	0.2524

N: Number of subjects considered, Nobs: Number of subjects contributing to the analysis, CI: Confidence interval, p-value: Two-sided test for no difference, TD: Triple dose.
The endpoints are analysed using a linear mixed effects model. A multiplicative model is used, i.e. the endpoint is log-transformed before analysis. The model includes treatment and period as fixed effects and subject as a random effect.

5.4.3 Counterregulatory hormones at PG decline 3.0 mmol/L for double dose - statistical analysis - subjects with clinically significant hypoglycaemia

	N	Nobs	Estimate	95% CI	p-value
Adrenaline (pg/mL), DD					
Estimated geometric means					
Ico	17	17	87.34		
IGlar	15	15	96.78		
Treatment ratio					
Ico / IGlar			0.90	[0.54 ; 1.52]	0.6572
Cortisol (ng/mL), DD					
Estimated geometric means					
Ico	17	17	89.12		
IGlar	15	15	55.75		
Treatment ratio					
Ico / IGlar			1.60	[0.91 ; 2.80]	0.0932
Glucagon (pg/mL), DD					
Estimated geometric means					
Ico	17	17	39.61		
IGlar	15	15	47.72		
Treatment ratio					
Ico / IGlar			0.83	[0.59 ; 1.16]	0.2424
Growth Hormone (ng/mL), DD					
Estimated geometric means					
Ico	17	17	3.64		
IGlar	15	15	4.07		
Treatment ratio					
Ico / IGlar			0.89	[0.46 ; 1.75]	0.7218
Noradrenaline (pg/mL), DD					
Estimated geometric means					
Ico	17	17	161.18		
IGlar	15	15	144.31		
Treatment ratio					
Ico / IGlar			1.12	[0.83 ; 1.50]	0.4242

N: Number of subjects considered, Nobs: Number of subjects contributing to the analysis, CI: Confidence interval, p-value: Two-sided test for no difference, DD: Double dose.
The endpoints are analysed using a linear mixed effects model. A multiplicative model is used, i.e. the endpoint is log-transformed before analysis. The model includes treatment and period as fixed effects and subject as a random effect.

5.4.4 HSS - statistical analysis - full analysis set - subjects with clinically significant hypoglycaemia

	N	Nobs	Estimate	95% CI	p-value
HSS (score), PG 5.5 mmol/L-PG 3.0 mmol/L, DD					
LSMeans					
Ico	17	17	1.81		
IGlar	15	15	0.59		
Treatment contrast					
Ico - IGlar			1.23	[-1.53 ; 3.98]	0.3620
HSS (score), PG 5.5 mmol/L-PG 3.0 mmol/L, TD					
LSMeans					
Ico	20	20	2.19		
IGlar	28	28	2.58		
Treatment contrast					
Ico - IGlar			-0.39	[-2.60 ; 1.82]	0.7187

HSS: Hypoglycaemic symptoms score.
N: Number of subjects considered, Nobs: Number of subjects contributing to the analysis, CI: Confidence interval, p-value: Two-sided test for no difference, DD: Double dose, TD: Triple dose. The endpoint is analysed using a linear mixed effects model. The model includes treatment and period as fixed effects and subject as a random effect. Corresponding value at the PG concentration of 5.5 mmol/L (100 mg/dL) prior to start of hypoglycaemia induction is included in the model as a covariate.

5.4.5 Vital signs - statistical analysis - full analysis set - subjects with clinically significant hypoglycaemia

	N	Nobs	Estimate	95% CI	p-value
DBP (mmHg), PG 5.5 mmol/L-PG 3.0 mmol/L, DD					
LSMeans					
Ico	17	17	-6.09		
IGlar	15	15	-7.74		
Treatment contrast					
Ico - IGlar			1.65	[-3.12 ; 6.43]	0.4727
DBP (mmHg), PG 5.5 mmol/L-PG 3.0 mmol/L, TD					
LSMeans					
Ico	20	20	-2.42		
IGlar	28	28	-3.22		
Treatment contrast					
Ico - IGlar			0.81	[-3.36 ; 4.98]	0.6944
Pulse (beats/min), PG 5.5 mmol/L-PG 3.0 mmol/L, DD					
LSMeans					
Ico	17	17	-1.33		
IGlar	15	15	-0.48		
Treatment contrast					
Ico - IGlar			-0.86	[-7.39 ; 5.67]	0.7748
Pulse (beats/min), PG 5.5 mmol/L-PG 3.0 mmol/L, TD					
LSMeans					
Ico	20	20	3.11		
IGlar	28	28	2.36		
Treatment contrast					
Ico - IGlar			0.75	[-4.44 ; 5.94]	0.7545
SBP (mmHg), PG 5.5 mmol/L-PG 3.0 mmol/L, DD					
LSMeans					
Ico	17	17	-4.87		
IGlar	15	15	-8.57		
Treatment contrast					
Ico - IGlar			3.70	[-4.32 ; 11.71]	0.3330
SBP (mmHg), PG 5.5 mmol/L-PG 3.0 mmol/L, TD					
LSMeans					
Ico	20	20	-0.87		
IGlar	28	28	-1.59		
Treatment contrast					
Ico - IGlar			0.71	[-6.57 ; 7.99]	0.8420

DBP: Diastolic blood pressure, SBP: Systolic blood pressure.
N: Number of subjects considered, Nobs: Number of subjects contributing to the analysis, CI: Confidence interval, p-value: Two-sided test for no difference, DD: Double dose, TD: Triple dose.
The endpoints are analysed using a linear mixed effects model. The model includes treatment and period as fixed effects and subject as a random effect. Corresponding value at the PG concentration of 5.5 mmol/L (100 mg/dL) prior to start of hypoglycaemia induction is included in the model as a covariate.

5.4.6 DSST - statistical analysis - full analysis set - subjects with clinically significant hypoglycaemia

	N	Nobs	Estimate	95% CI	p-value
DSST, PG 5.5 mmol/L-PG 3.0 mmol/L, DD					
LSMeans					
Ico	17	16	-5.44		
IGlar	15	15	-6.62		
Treatment contrast					
Ico - IGlar			1.18	[-3.18 ; 5.53]	0.5716
DSST, PG 5.5 mmol/L-PG 3.0 mmol/L, TD					
LSMeans					
Ico	20	20	-5.50		
IGlar	28	28	-6.01		
Treatment contrast					
Ico - IGlar			0.50	[-3.27 ; 4.27]	0.7849

DSST: Digit symbol substitution test.
N: Number of subjects considered, Nobs: Number of subjects contributing to the analysis, CI: Confidence interval, p-value: Two-sided test for no difference, DD: Double dose, TD: Triple dose. The endpoint is analysed using a linear mixed effects model. The model includes treatment and period as fixed effects and subject as a random effect. Corresponding value at the PG concentration of 5.5 mmol/L (100 mg/dL) prior to start of hypoglycaemia induction is included in the model as a covariate.

5.4.7 4CRT (reaction time) - statistical analysis - full analysis set - subjects with clinically significant hypoglycaemia

	N	Nobs	Estimate	95% CI	p-value
4CRTreacttime (msec), PG 5.5 mmol/L-PG 3.0 mmol/L, DD					
LSMeans					
Ico	17	16	19.73		
IGlar	15	15	99.46		
Treatment contrast					
Ico - IGlar			-79.73	[-170.36 ; 10.89]	0.0808
4CRTreacttime (msec), PG 5.5 mmol/L-PG 3.0 mmol/L, TD					
LSMeans					
Ico	20	20	55.39		
IGlar	28	27	43.57		
Treatment contrast					
Ico - IGlar			11.82	[-43.97 ; 67.62]	0.6618

4CRT: Four choice reaction time.
N: Number of subjects considered, Nobs: Number of subjects contributing to the analysis, CI: Confidence interval, p-value: Two-sided test for no difference, DD: Double dose, TD: Triple dose.
The endpoint is analysed using a linear mixed effects model. The model includes treatment and period as fixed effects and subject as a random effect. Corresponding value at the PG concentration of 5.5 mmol/L (100 mg/dL) prior to start of hypoglycaemia induction is included in the model as a covariate.

5.4.8 4CRT (percentage of correct answers) - statistical analysis - full analysis set - subjects with clinically significant hypoglycaemia

	N	Nobs	Estimate	95% CI	p-value
4CRTpctcorrectanswer (%), PG 5.5 mmol/L-PG 3.0 mmol/L, DD					
LSMeans					
Ico	17	16	0.12		
IGlar	15	15	-0.07		
Treatment contrast					
Ico - IGlar			0.19	[-1.06 ; 1.44]	0.7489
4CRTpctcorrectanswer (%), PG 5.5 mmol/L-PG 3.0 mmol/L, TD					
LSMeans					
Ico	20	20	-0.25		
IGlar	28	27	-0.36		
Treatment contrast					
Ico - IGlar			0.11	[-0.70 ; 0.92]	0.7759

4CRT (%): Four choice reaction time (percentage of correct answers).
N: Number of subjects considered, Nobs: Number of subjects contributing to the analysis, CI: Confidence interval, p-value: Two-sided test for no difference, DD: Double dose, TD: Triple dose.
The endpoint is analysed using a linear mixed effects model. The model includes treatment and period as fixed effects and subject as a random effect. Corresponding value at the PG concentration of 5.5 mmol/L (100 mg/dL) prior to start of hypoglycaemia induction is included in the model as a covariate.

5.4.9 TMB - statistical analysis - full analysis set - subjects with clinically significant hypoglycaemia

	N	Nobs	Estimate	95% CI	p-value
TMB, PG 5.5 mmol/L-PG 3.0 mmol/L, DD					
LSMeans					
Ico	17	16	0.29		
IGlar	15	15	-0.07		
Treatment contrast					
Ico - IGlar			0.37	[-0.25 ; 0.98]	0.2246
TMB, PG 5.5 mmol/L-PG 3.0 mmol/L, TD					
LSMeans					
Ico	20	20	-0.01		
IGlar	28	26	0.07		
Treatment contrast					
Ico - IGlar			-0.08	[-0.36 ; 0.20]	0.5763

TMB: Trail making B.
N: Number of subjects considered, Nobs: Number of subjects contributing to the analysis, CI: Confidence interval, p-value: Two-sided test for no difference, DD: Double dose, TD: Triple dose. The endpoint is analysed using a linear mixed effects model. The model includes treatment and period as fixed effects and subject as a random effect. Corresponding value at the PG concentration of 5.5 mmol/L (100 mg/dL) prior to start of hypoglycaemia induction is included in the model as a covariate.

5.4.10 Time to decline 3.9 mmol/L - summary - subjects with symptoms or clinically significant hypoglycaemia

	Ico 2xdose	Ico 3xdose	IGlar 2xdose	IGlar 3xdose
Number of subjects	20	20	19	29
tdecline, PG 5.5 - 3.9 mmol/L (h)				
N	20	20	19	29
Mean (SD)	0.75 (0.39)	0.67 (0.24)	1.40 (1.13)	0.83 (0.46)
Median	0.65	0.60	1.10	0.63
Min ; Max	0.27 ; 1.92	0.33 ; 1.25	0.42 ; 5.50	0.28 ; 2.00

`Number of subjects` refers to number of subjects with symptoms or clinically significant hypoglycaemia.
N: Number of subjects, SD: Standard deviation, h: hour, min: minute.
2xdose refers to double dose, 3xdose refers to triple dose.

5.4.11 PGnadir below or equal to 2.5 mmol/L - statistical analysis - full analysis set

	N	Nobs	Estimate	95% CI	p-value
PG Below or equal to 2.5 mmol/L, DD					
Estimated odds					
Ico	43	43	0.04		
IGlar	42	42	0.07		
Treatment odds ratio					
Ico / IGlar			0.62	[0.09 ; 4.40]	0.6291
PG Below or equal to 2.5 mmol/L, TD					
Estimated odds					
Ico	39	38	0.02		
IGlar	40	40	0.29		
Treatment odds ratio					
Ico / IGlar			0.08	[0.01 ; 0.77]	0.0293

N: Number of subjects considered, Nobs: Number of subjects contributing to the analysis, CI: Confidence interval, p-value: Two-sided test for no difference, DD: Double dose, TD: Triple dose. The endpoint is analysed using a logistic regression mode with logit link. The model includes treatment and period as fixed effects and subject as a random effect.

5.4.12 Actual PGnadir - statistical analysis - full analysis set - subjects with symptoms or clinically significant hypoglycaemia

	N	Nobs	Estimate	95% CI	p-value
PGnadir, DD (mmol/L)					
Estimated geometric means					
Ico	20	20	2.93		
IGlar	19	19	2.89		
Treatment ratio					
Ico / IGlar			1.01	[0.96 ; 1.07]	0.5841
PGnadir, TD (mmol/L)					
Estimated geometric means					
Ico	20	20	2.86		
IGlar	29	29	2.71		
Treatment ratio					
Ico / IGlar			1.05	[1.01 ; 1.10]	0.0186

N: Number of subjects considered, Nobs: Number of subjects contributing to the analysis, CI: Confidence interval, p-value: Two-sided test for no difference, TD: Triple dose.
The endpoints are analysed using a linear mixed effects model. A multiplicative model is used, i.e. the endpoint is log-transformed before analysis. The model includes treatment and period as fixed effects and subject as a random effect.

5.4.13 Counterregulatory hormones at PG decline 3.0 mmol/L for triple dose - statistical analysis - subjects with clinically significant hypoglycaemia after both icodec and IGlar triple dose

	N	Nobs	Estimate	95% CI	p-value
Adrenaline (pg/mL), TD					
Estimated geometric means					
Ico	16	16	148.89		
IGlar	16	16	59.73		
Treatment ratio					
Ico / IGlar			2.49	[1.58 ; 3.93]	0.0007
Cortisol (ng/mL), TD					
Estimated geometric means					
Ico	16	16	70.32		
IGlar	16	16	49.05		
Treatment ratio					
Ico / IGlar			1.43	[0.99 ; 2.08]	0.0556
Glucagon (pg/mL), TD					
Estimated geometric means					
Ico	16	16	50.47		
IGlar	16	16	47.24		
Treatment ratio					
Ico / IGlar			1.07	[0.85 ; 1.34]	0.5380
Growth Hormone (ng/mL), TD					
Estimated geometric means					
Ico	16	16	3.90		
IGlar	16	16	2.18		
Treatment ratio					
Ico / IGlar			1.79	[0.82 ; 3.93]	0.1342
Noradrenaline (pg/mL), TD					
Estimated geometric means					
Ico	16	16	179.21		
IGlar	16	16	147.10		
Treatment ratio					
Ico / IGlar			1.22	[0.85 ; 1.75]	0.2632

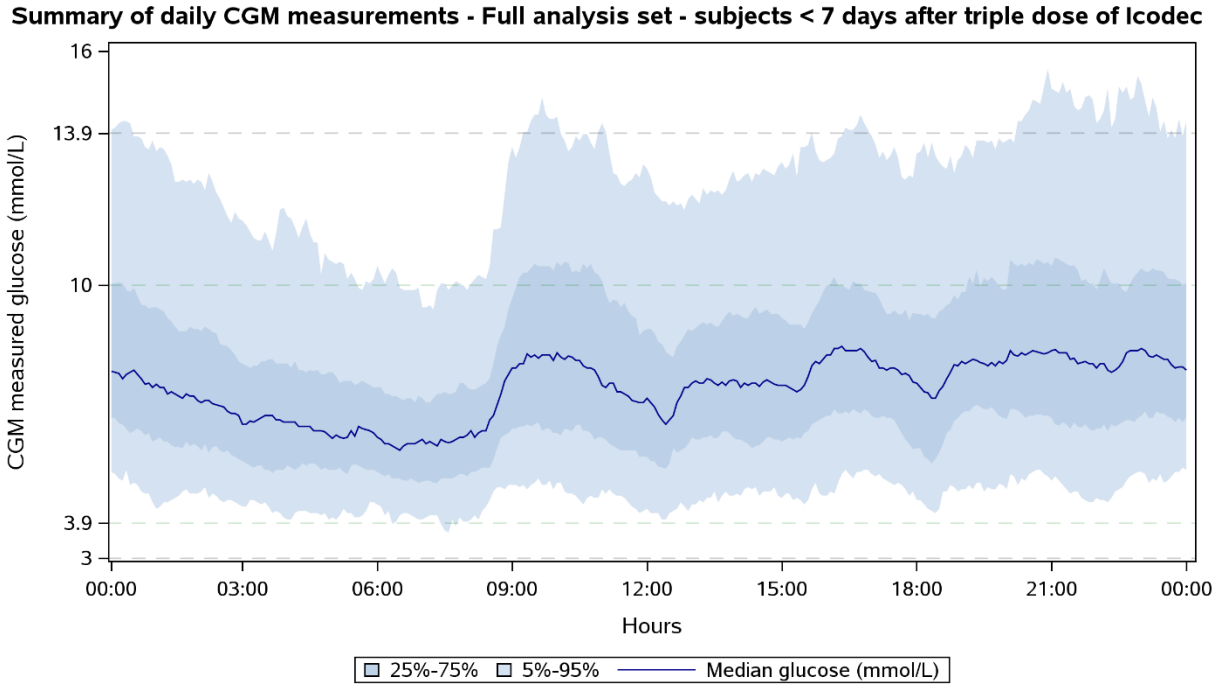
N: Number of subjects considered, Nobs: Number of subjects contributing to the analysis, CI: Confidence interval, p-value: Two-sided test for no difference, TD: Triple dose.
The endpoints are analysed using a linear mixed effects model. A multiplicative model is used, i.e. the endpoint is log-transformed before analysis. The model includes treatment and period as fixed effects and subject as a random effect.
Only subjects with measurements at PG decline 3.0 mmol/L after both icodec and IGlar triple dose are included in the analysis.

5.4.14 Counterregulatory hormones at PG Nadir for triple dose - statistical analysis - subjects with symptoms or clinically significant hypoglycemia after both icodec and IGlar triple dose

	N	Nobs	Estimate	95% CI	p-value
Adrenaline (pg/mL), TD					
Estimated geometric means					
Ico	17	17	162.69		
IGlar	17	17	151.54		
Treatment ratio					
Ico / IGlar			1.07	[0.73 ; 1.57]	0.6976
Cortisol (ng/mL), TD					
Estimated geometric means					
Ico	17	16	123.03		
IGlar	17	16	82.70		
Treatment ratio					
Ico / IGlar			1.49	[0.88 ; 2.51]	0.1267
Glucagon (pg/mL), TD					
Estimated geometric means					
Ico	17	17	55.96		
IGlar	17	17	59.39		
Treatment ratio					
Ico / IGlar			0.94	[0.69 ; 1.28]	0.6886
Growth Hormone (ng/mL), TD					
Estimated geometric means					
Ico	17	16	3.77		
IGlar	17	16	3.97		
Treatment ratio					
Ico / IGlar			0.95	[0.56 ; 1.60]	0.8379
Noradrenaline (pg/mL), TD					
Estimated geometric means					
Ico	17	17	162.59		
IGlar	17	17	161.81		
Treatment ratio					
Ico / IGlar			1.00	[0.75 ; 1.35]	0.9731

N: Number of subjects considered, Nobs: Number of subjects contributing to the analysis, CI: Confidence interval, p-value: Two-sided test for no difference, TD: Triple dose.
The endpoints are analysed using a linear mixed effects model. A multiplicative model is used, i.e. the endpoint is log-transformed before analysis. The model includes treatment and period as fixed effects and subject as a random effect.
Only subjects with measurements at PG nadir after both icodec and IGlar triple dose are included in the analysis.

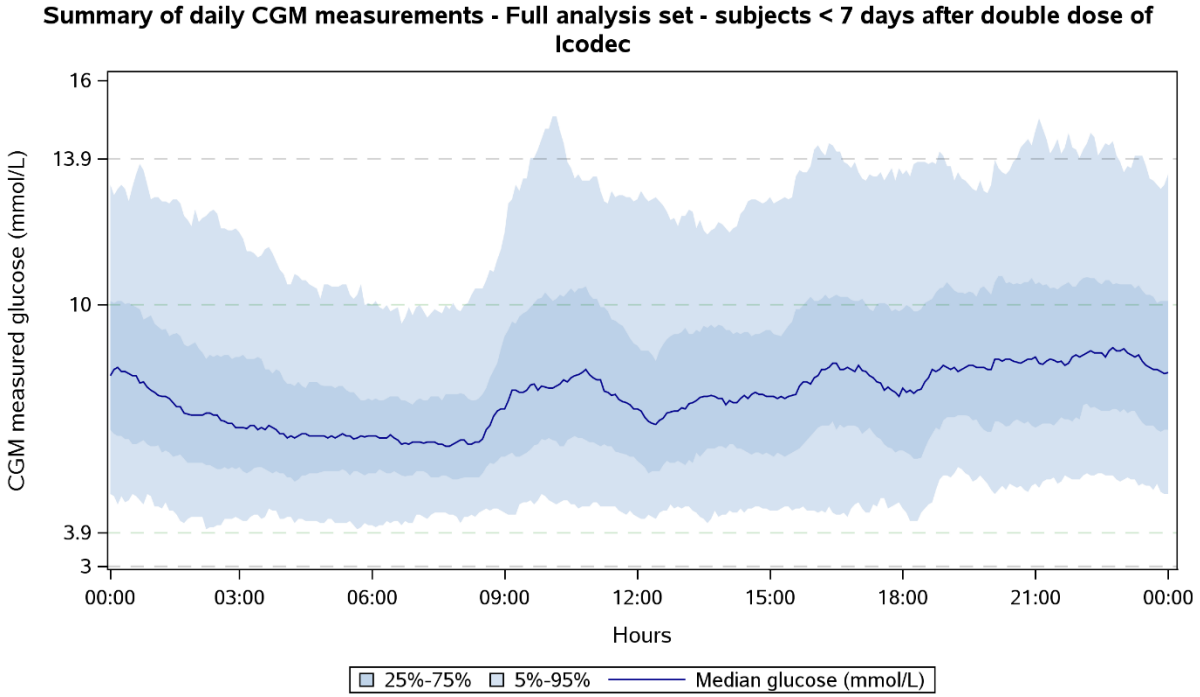
5.4.15 Summary of daily CGM measurements - Full analysis set - subjects < 7 days after triple dose of Icodec



CGM: Continuous Glucose Monitoring.
The clamp period has been excluded.
Darker blue shaded area contains 50 percent of measurements. Light blue shaded area contains 90 percent of measurements.

nn1436/exploratory/pucph002_20220930_er
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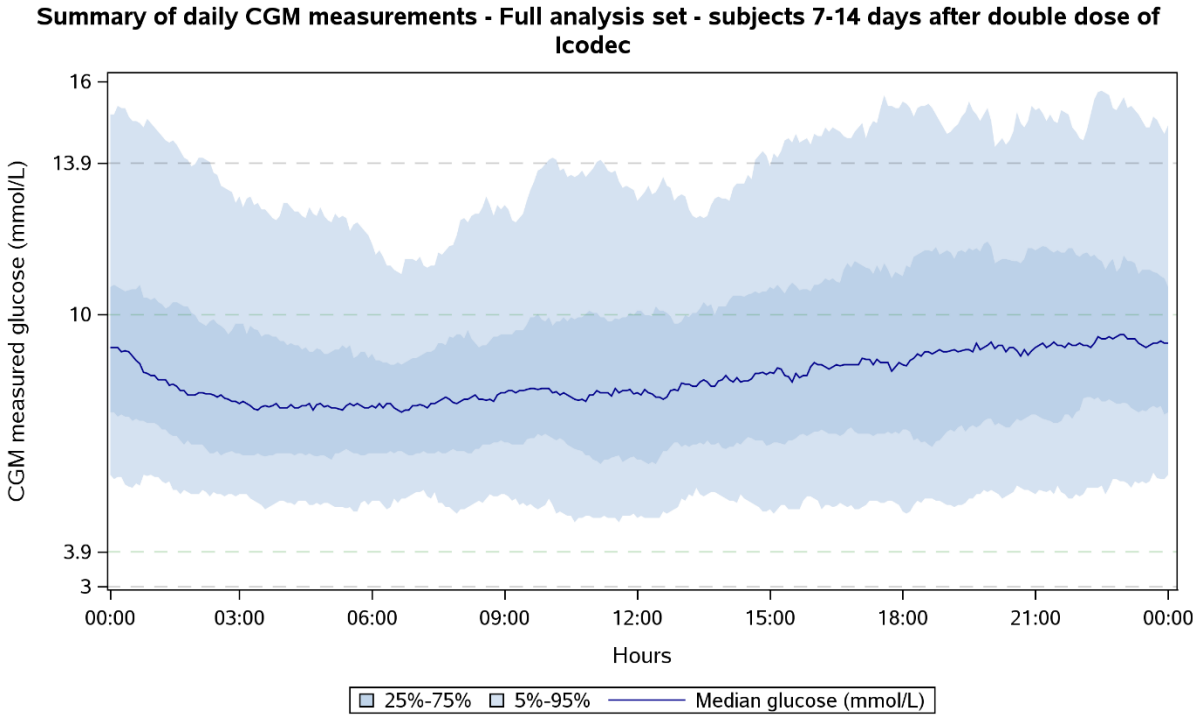
5.4.16 Summary of daily CGM measurements - Full analysis set - subjects < 7 days after double dose of Icodec



CGM: Continuous Glucose Monitoring.
The clamp period has been excluded.
Darker blue shaded area contains 50 percent of measurements. Light blue shaded area contains 90 percent of measurements.

nn1436/exploratory/pucph002_20220930_er
20OCT2022:08:26:44 - ftcgmsum.sas/fcgmsumDDdayfas.png

5.4.17 Summary of daily CGM measurements - Full analysis set - subjects 7-14 days after double dose of Icodec



CGM: Continuous Glucose Monitoring.
Darker blue shaded area contains 50 percent of measurements. Light blue shaded area contains 90 percent of measurements.

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20OCT2022:08:26:45 - ftcgmsum.sas/fcgmsumDDday7fas.png

5.4.18 Time in range for CGM measurements - Full analysis set - subjects < 7 days after triple dose of Icodec and < 14 days after double dose of Icodec

	14 days after DD	7 days after TD
Number of subjects	43	39
Time spent < 3.9 mmol/L (%)		
N	38	39
Mean (SD)	0.99 (2.12)	1.56 (3.54)
Median	0.22	0.50
Min ; Max	0.00 ; 10.75	0.00 ; 19.91
Time spent < 3.0 mmol/L (%)		
N	38	39
Mean (SD)	0.15 (0.44)	0.29 (1.24)
Median	0.00	0.00
Min ; Max	0.00 ; 2.12	0.00 ; 7.57
Time in range 3.9-10.0 mmol/L (%)		
N	38	39
Mean (SD)	74.28 (15.85)	80.10 (14.41)
Median	77.58	83.38
Min ; Max	36.20 ; 97.60	39.42 ; 99.11
Time spent > 10.0 mmol/L (%)		
N	38	39
Mean (SD)	24.73 (16.48)	18.34 (14.94)
Median	21.94	15.50
Min ; Max	0.29 ; 63.80	0.06 ; 60.58
Time spent > 13.9 mmol/L (%)		
N	38	39
Mean (SD)	4.26 (5.53)	3.09 (4.68)
Median	1.83	0.69
Min ; Max	0.00 ; 24.42	0.00 ; 18.56
Time spent between 3.0-3.8 mmol/L (%)		
N	38	39
Mean (SD)	0.83 (1.72)	1.27 (2.49)
Median	0.21	0.45
Min ; Max	0.00 ; 9.01	0.00 ; 12.34
Time spent between 10.0-13.9 mmol/L (%)		
N	38	39
Mean (SD)	20.48 (12.00)	15.25 (11.24)
Median	20.48	12.27
Min ; Max	0.29 ; 49.51	0.06 ; 47.48

Number of subjects' refers to number of subjects receiving DD or TD.
'N' refers to number of subjects with >70% of possible CGM measurements in the period.
CGM: Continuous Glucose Monitoring.
Clamp periods excluded.
Subjects with <70% of GCM measurements excluded.

5.4.19 Level 2 hypoglycaemia events during the 2-week period following a double dose of insulin icodec outside of the hypoglycaemic clamp induction period - listing

Subject ID/ Age (years)/ Sex (M/F)/ BMI(kg/m^2)	Treatment/ day	Hypo no.	Severity	Lowest plasma glucose (mg/dL)	Start/stop date and time (date:h:m)	Duration of hypo	Need help (Y/N)	Recorded as SAE (Y/N) (AE no.)	Last trial product	
									Type	Date/time (date:h:m)	Dose (U)
101004/ 6[redacted]/ F/ 2[redacted].[redacted]	Ico/21	10	CLINICALLY SIGNIFICANT HYPOGLYCAEMIA (LEVEL 2)	46	2019-07-28 06:30:00/ 2019-07-28 07:00:00	00h30m	N	N	Ico	2019-07-22 20:00:00	140
101009/ 6[redacted]/ M/ 2[redacted].[redacted]	Ico/35	6	CLINICALLY SIGNIFICANT HYPOGLYCAEMIA (LEVEL 2)	47	2019-10-11 07:50:00/ 2019-10-11 08:20:00	00h30m	N	N	Ico	2019-10-06 20:00:00	602
	Ico/36	7	CLINICALLY SIGNIFICANT HYPOGLYCAEMIA (LEVEL 2)	53	2019-10-12 05:40:00/ 2019-10-12 06:13:00	00h33m	N	N	Ico	2019-10-06 20:00:00	602
101016/ 5[redacted]/ M/ 2[redacted].[redacted]	Ico/22	5	CLINICALLY SIGNIFICANT HYPOGLYCAEMIA (LEVEL 2)	34	2019-11-12 06:08:00/ 2019-11-12 06:30:00	00h22m	N	N	Ico	2019-11-05 20:00:00	364

AE: Adverse event, BMI: Body mass index, F: Female, h: Hours, M: Male, m: Minutes, N: No, no.: Number, SAE: Serious adverse event, Y: Yes.
Day is actual day in the treatment period.
Level 1: Plasma glucose < 3.9 mmol/L (70 mg/dL) and >= 3.0 mmol/L (54 mg/dL). Level 2: Plasma glucose < 3.0 mmol/L (54 mg/dL). Level 3: Hypoglycaemia with severe cognitive impairment requiring external assistance for recovery.
Unclassifiable: Event requiring external assistance for recovery, no glucose values and unknown if symptoms were subsequently alleviated.
The clamp periods are excluded from the evaluation of hypoglycaemic episodes.

5.4.20 Individuals with out of range CGM measurements - Full analysis set - subjects < 7 days after triple dose of Icodec and < 14 days after double dose of Icodec

	14 days after DD	7 days after TD
Number of subjects	43	39
>4% of CGM measurements<3.9mmol/L		
N	38	39
Number of subjects meeting criteria	3	3
>1% of CGM measurements<3mmol/L		
N	38	39
Number of subjects meeting criteria	2	2
<70% of CGM measurements<=10mmol/L		
N	38	39
Number of subjects meeting criteria	12	7

Number of subjects' refers to number of subjects receiving DD or TD.
'N' refers to number of subjects with >70% of possible CGM measurements in the period.
CGM: Continuous Glucose Monitoring.
Clamp periods excluded.
Subjects with <70% of GCM measurements excluded.

5.4.21 Counterregulatory hormones at PG decline 3.0 mmol/L for double dose - statistical analysis - subjects with clinically significant hypoglycaemia after both icodec and IGlar double dose

	N	Nobs	Estimate	95% CI	p-value
Adrenaline (pg/mL), DD					
Estimated geometric means					
Ico	12	12	104.49		
IGlar	12	12	113.70		
Treatment ratio					
Ico / IGlar			0.92	[0.59 ; 1.44]	0.6830
Cortisol (ng/mL), DD					
Estimated geometric means					
Ico	12	12	78.57		
IGlar	12	12	73.83		
Treatment ratio					
Ico / IGlar			1.06	[0.66 ; 1.72]	0.7793
Glucagon (pg/mL), DD					
Estimated geometric means					
Ico	12	12	44.90		
IGlar	12	12	51.44		
Treatment ratio					
Ico / IGlar			0.87	[0.64 ; 1.19]	0.3551
Growth Hormone (ng/mL), DD					
Estimated geometric means					
Ico	12	12	3.28		
IGlar	12	12	3.66		
Treatment ratio					
Ico / IGlar			0.89	[0.44 ; 1.81]	0.7315
Noradrenaline (pg/mL), DD					
Estimated geometric means					
Ico	12	12	163.19		
IGlar	12	12	148.00		
Treatment ratio					
Ico / IGlar			1.10	[0.82 ; 1.49]	0.4832

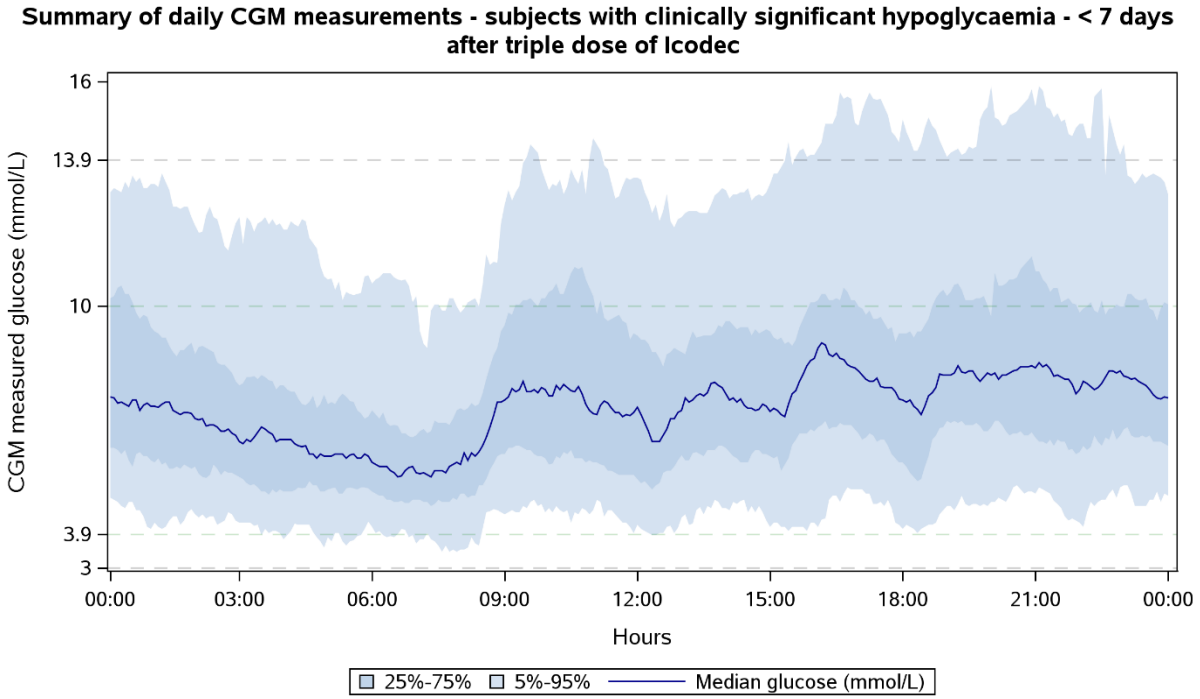
N: Number of subjects considered, Nobs: Number of subjects contributing to the analysis, CI: Confidence interval, p-value: Two-sided test for no difference, DD: Double dose.
The endpoints are analysed using a linear mixed effects model. A multiplicative model is used, i.e. the endpoint is log-transformed before analysis. The model includes treatment and period as fixed effects and subject as a random effect.
Only subjects with measurements at PG decline 3.0 mmol/L after both icodec and IGlar double dose are included in the analysis.

5.4.22 Counterregulatory hormones at PG Nadir for double dose - statistical analysis - subjects with symptoms or clinically significant hypoglycemia after both icodec and IGlar double dose

	N	Nobs	Estimate	95% CI	p-value
Adrenaline (pg/mL), DD					
Estimated geometric means					
Ico	16	16	121.09		
IGlar	16	16	130.98		
Treatment ratio					
Ico / IGlar			0.92	[0.65 ; 1.32]	0.6456
Cortisol (ng/mL), DD					
Estimated geometric means					
Ico	16	15	121.31		
IGlar	16	15	131.62		
Treatment ratio					
Ico / IGlar			0.92	[0.67 ; 1.27]	0.5918
Glucagon (pg/mL), DD					
Estimated geometric means					
Ico	16	15	51.20		
IGlar	16	15	53.96		
Treatment ratio					
Ico / IGlar			0.95	[0.71 ; 1.27]	0.7043
Growth Hormone (ng/mL), DD					
Estimated geometric means					
Ico	16	15	5.13		
IGlar	16	15	3.69		
Treatment ratio					
Ico / IGlar			1.39	[0.96 ; 2.02]	0.0772
Noradrenaline (pg/mL), DD					
Estimated geometric means					
Ico	16	16	216.48		
IGlar	16	16	176.98		
Treatment ratio					
Ico / IGlar			1.22	[0.93 ; 1.61]	0.1390

N: Number of subjects considered, Nobs: Number of subjects contributing to the analysis, CI: Confidence interval, p-value: Two-sided test for no difference, DD: Double dose.
The endpoints are analysed using a linear mixed effects model. A multiplicative model is used, i.e. the endpoint is log-transformed before analysis. The model includes treatment and period as fixed effects and subject as a random effect.
Only subjects with measurements at PG nadir after both icodec and IGlar double dose are included in the analysis.

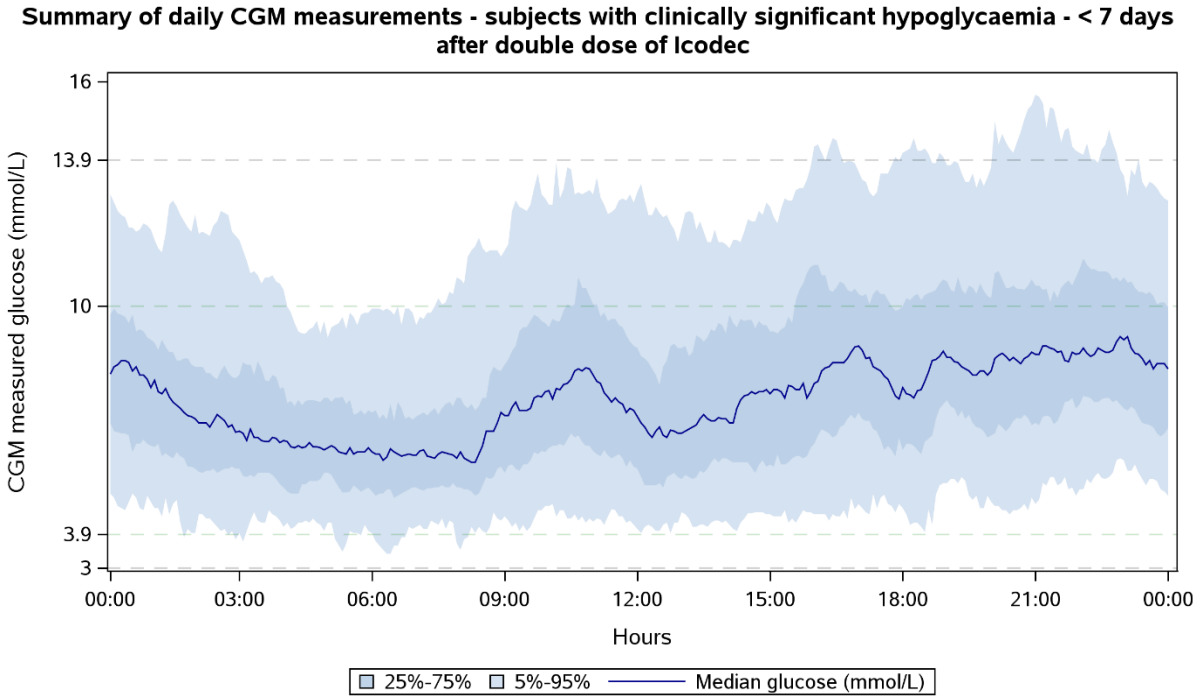
5.4.23 Summary of daily CGM measurements - subjects with clinically significant hypoglycaemia - < 7 days after triple dose of Icodec



CGM: Continuous Glucose Monitoring.
The clamp period has been excluded.
Darker blue shaded area contains 50 percent of measurements. Light blue shaded area contains 90 percent of measurements.

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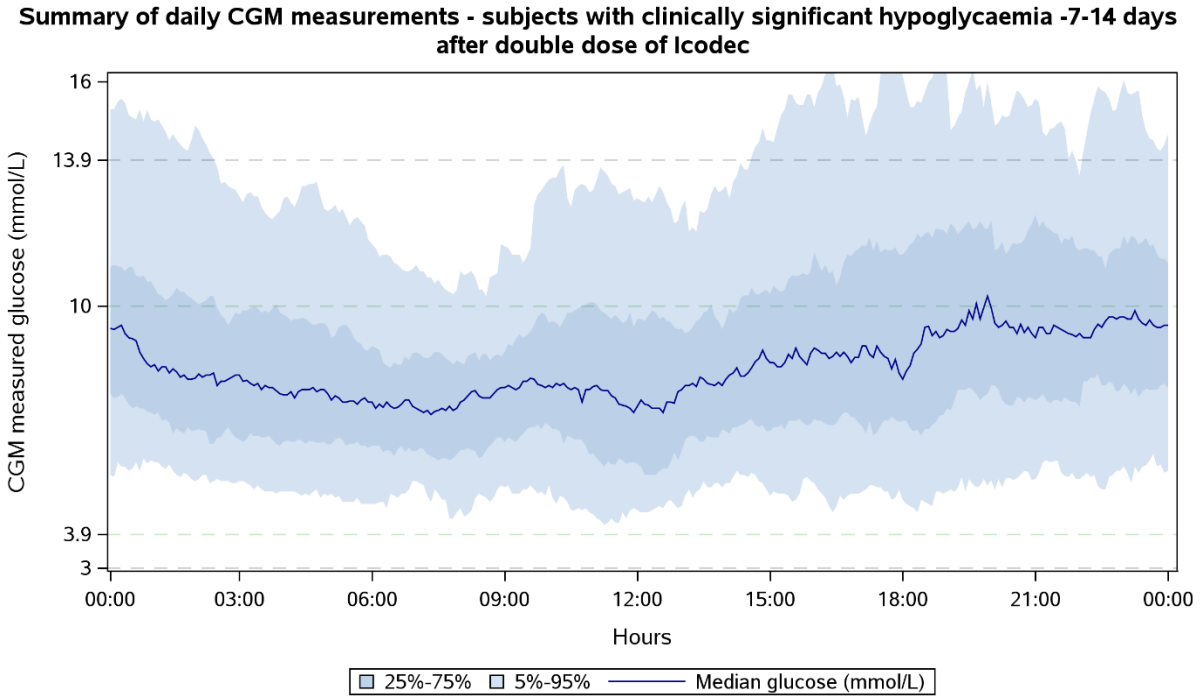
5.4.24 Summary of daily CGM measurements - subjects with clinically significant hypoglycaemia - < 7 days after double dose of Icodec



CGM: Continuous Glucose Monitoring.
The clamp period has been excluded.
Darker blue shaded area contains 50 percent of measurements. Light blue shaded area contains 90 percent of measurements.

nn1436/exploratory/pucph002_20220930_er
20OCT2022:08:27:08 - ftcgmsum30.sas/fcgmsumDD30dayfas.png

5.4.25 Summary of daily CGM measurements - subjects with clinically significant hypoglycaemia - 7-14 days after double dose of Icodec



CGM: Continuous Glucose Monitoring.
The clamp period has been excluded.
Darker blue shaded area contains 50 percent of measurements. Light blue shaded area contains 90 percent of measurements.

nn1436/exploratory/pucph002_20220930_er
20OCT2022:08:27:09 - ftcgmsum30.sas/fcgmsumDD30day7fas.png

5.4.26 Time in range for CGM measurements -subjects with clinically significant hypoglycaemia - < 7 days after triple dose of Icodec and < 14 days after double dose of Icodec

	14 days after DD	7 days after TD
Number of subjects	17	20
Time spent < 3.9 mmol/L (%)		
N	15	20
Mean (SD)	1.63 (2.75)	2.67 (4.71)
Median	0.89	1.10
Min ; Max	0.00 ; 10.75	0.00 ; 19.91
Time spent < 3.0 mmol/L (%)		
N	15	20
Mean (SD)	0.21 (0.45)	0.56 (1.70)
Median	0.03	0.03
Min ; Max	0.00 ; 1.74	0.00 ; 7.57
Time in range 3.9-10.0 mmol/L (%)		
N	15	20
Mean (SD)	74.09 (11.98)	77.89 (16.61)
Median	76.90	81.38
Min ; Max	50.79 ; 97.60	39.42 ; 97.64
Time spent > 10.0 mmol/L (%)		
N	15	20
Mean (SD)	24.28 (13.18)	19.44 (17.75)
Median	22.13	13.89
Min ; Max	0.29 ; 49.21	1.06 ; 60.58
Time spent > 13.9 mmol/L (%)		
N	15	20
Mean (SD)	4.20 (4.57)	3.42 (5.39)
Median	1.86	0.69
Min ; Max	0.00 ; 15.45	0.00 ; 18.56
Time spent between 3.0-3.8 mmol/L (%)		
N	15	20
Mean (SD)	1.42 (2.32)	2.12 (3.27)
Median	0.81	1.10
Min ; Max	0.00 ; 9.01	0.00 ; 12.34
Time spent between 10.0-13.9 mmol/L (%)		
N	15	20
Mean (SD)	20.07 (9.92)	16.02 (13.21)
Median	20.66	13.26
Min ; Max	0.29 ; 39.37	1.06 ; 47.48

'Number of subjects' refers to number of subjects receiving DD or TD and experiencing clinically significant hypoglycaemia.
'N' refers to number of subjects with >70% of possible CGM measurements in the period.
CGM: Continuous Glucose Monitoring.
Clamp periods excluded.
Subjects with <70% of GCM measurements excluded.

5.4.27 Individuals with out of range CGM measurements - subjects with clinically significant hypoglycaemia - < 7 days after triple dose of Icodec and < 14 days after double dose of Icodec

	14 days after DD	7 days after TD
Number of subjects	17	20
>4% of CGM measurements<3.9mmol/L		
N	15	20
Number of subjects meeting criteria	2	3
>1% of CGM measurements<3mmol/L		
N	15	20
Number of subjects meeting criteria	1	2
<70% of CGM measurements<=10mmol/L		
N	15	20
Number of subjects meeting criteria	5	4

'Number of subjects' refers to number of subjects receiving DD or TD and experiencing clinically significant hypoglycaemia.
'N' refers to number of subjects with >70% of possible CGM measurements in the period.
CGM: Continuous Glucose Monitoring.
Clamp periods excluded.
Subjects with <70% of GCM measurements excluded.

5.4.28 Counterregulatory hormones (adrenaline, noradrenaline and cortisol (SI units)) at PG decline 3.0 mmol/L for double dose - statistical analysis - subjects with clinically significant hypoglycaemia

	N	Nobs	Estimate	95% CI	p-value
Adrenaline (pmol/L), DD					
Estimated geometric means					
Ico	17	17	476.71		
IGlar	15	15	528.27		
Treatment ratio					
Ico / IGlar			0.90	[0.54 ; 1.52]	0.6572
Cortisol (nmol/L), DD					
Estimated geometric means					
Ico	17	17	245.88		
IGlar	15	15	153.82		
Treatment ratio					
Ico / IGlar			1.60	[0.91 ; 2.80]	0.0932
Noradrenaline (pmol/L), DD					
Estimated geometric means					
Ico	17	17	952.72		
IGlar	15	15	853.01		
Treatment ratio					
Ico / IGlar			1.12	[0.83 ; 1.50]	0.4242

N: Number of subjects considered, Nobs: Number of subjects contributing to the analysis, CI: Confidence interval, p-value: Two-sided test for no difference, DD: Double dose.
The endpoints are analysed using a linear mixed effects model. A multiplicative model is used, i.e. the endpoint is log-transformed before analysis. The model includes treatment and period as fixed effects and subject as a random effect.

5.4.29 Counterregulatory hormones (adrenaline, noradrenaline and cortisol (SI units)) at PG decline 3.0 mmol/L for triple dose - statistical analysis - subjects with clinically significant hypoglycaemia

	N	Nobs	Estimate	95% CI	p-value
Adrenaline (pmol/L), TD					
Estimated geometric means					
Ico	20	20	793.78		
IGlar	28	28	312.21		
Treatment ratio					
Ico / IGlar			2.54	[1.69 ; 3.82]	0.0001
Cortisol (nmol/L), TD					
Estimated geometric means					
Ico	20	20	201.41		
IGlar	28	28	122.92		
Treatment ratio					
Ico / IGlar			1.64	[1.13 ; 2.38]	0.0121
Noradrenaline (pmol/L), TD					
Estimated geometric means					
Ico	20	20	1058.36		
IGlar	28	28	842.98		
Treatment ratio					
Ico / IGlar			1.26	[0.89 ; 1.77]	0.1796

N: Number of subjects considered, Nobs: Number of subjects contributing to the analysis, CI: Confidence interval, p-value: Two-sided test for no difference, TD: Double dose.
The endpoints are analysed using a linear mixed effects model. A multiplicative model is used, i.e. the endpoint is log-transformed before analysis. The model includes treatment and period as fixed effects and subject as a random effect.

5.4.30 Level 2 hypoglycaemia events during the 1-week period following a triple dose of insulin icodec outside of the hypoglycaemic clamp induction period - listing

Subject ID/ Age (years)/ Sex (M/F)/ BMI(kg/m^2)	Treatment/ day	Hypo no.	Severity	Lowest plasma glucose (mg/dL)	Start/stop date and time (date:h:m)	Duration of hypo	Need help (Y/N)	Recorded as SAE (Y/N) (AE no.)	Last trial product		
									Type	Date/time (date:h:m)	Dose (U)
101009/ 6[redacted]/ M/ 2[redacted].[redacted]	Ico/56	8	CLINICALLY SIGNIFICANT HYPOGLYCAEMIA (LEVEL 2)	42	2019-11-01 07:18:00/ 2019-11-01 07:50:00	00h32m	N	N	Ico	2019-10-27 20:00:00	903
101016/ 5[redacted]/ M/ 2[redacted].[redacted]	Ico/43	7	CLINICALLY SIGNIFICANT HYPOGLYCAEMIA (LEVEL 2)	46	2019-12-03 04:36:00/ 2019-12-03 05:15:00	00h39m	N	N	Ico	2019-11-26 20:00:00	546
101027/ 5[redacted]/ M/ 3[redacted].[redacted]	Ico/42	4	CLINICALLY SIGNIFICANT HYPOGLYCAEMIA (LEVEL 2)	51	2020-01-22 07:25:00/ 2020-01-22 07:55:00	00h30m	N	N	Ico	2020-01-16 20:00:00	630
101034/ 6[redacted]/ F/ 3[redacted].[redacted]	Ico/56	7	CLINICALLY SIGNIFICANT HYPOGLYCAEMIA (LEVEL 2)	53	2020-03-06 00:48:00/ 2020-03-06 01:15:00	00h27m	N	N	Ico	2020-03-02 20:00:00	1050
101067/ 4[redacted]/ M/ 3[redacted].[redacted]	Ico/59	6	CLINICALLY SIGNIFICANT HYPOGLYCAEMIA (LEVEL 2)	53	2021-06-28 05:00:00/ 2021-06-28 05:30:00	00h30m	N	N	Ico	2021-06-24 20:00:00	1176
	Ico/59	7	CLINICALLY SIGNIFICANT HYPOGLYCAEMIA (LEVEL 2)	53	2021-06-28 07:20:00/ 2021-06-28 07:30:00	00h10m	N	N	Ico	2021-06-24 20:00:00	1176

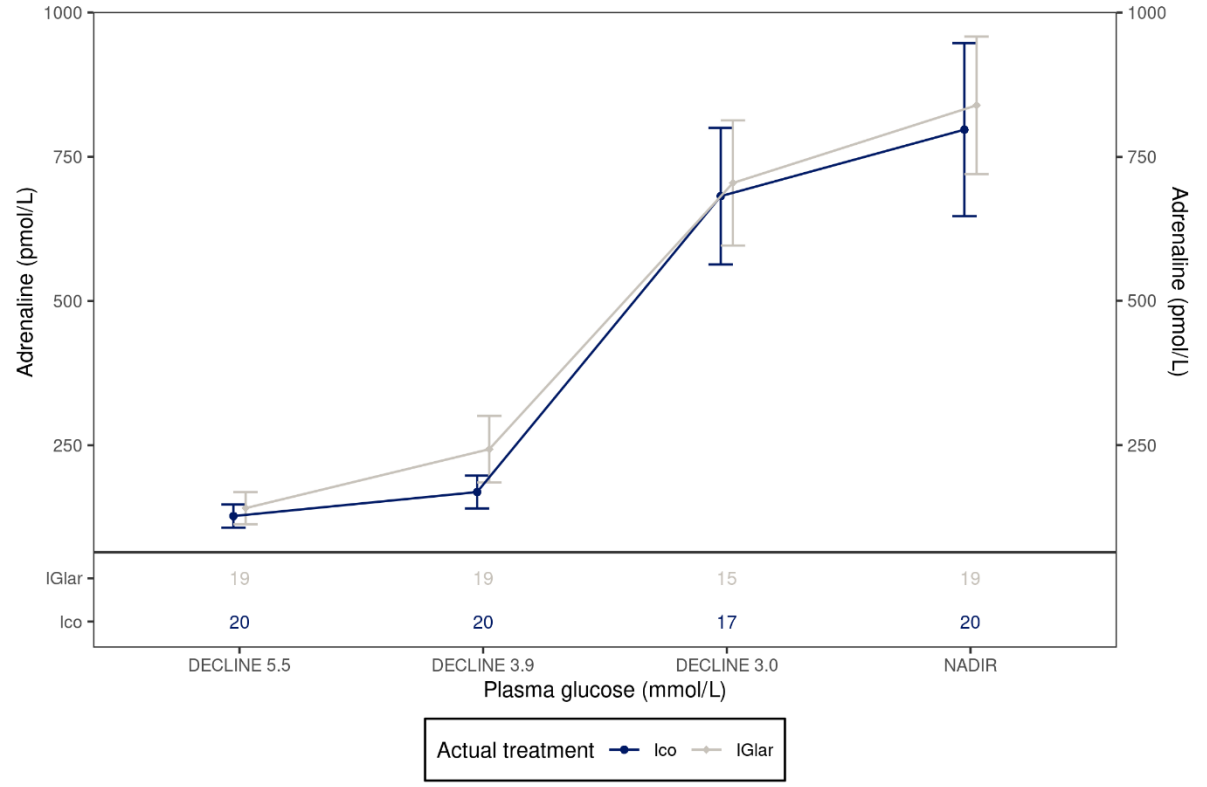
AE: Adverse event, BMI: Body mass index, F: Female, h: Hours, M: Male, m: Minutes, N: No, no.: Number, SAE: Serious adverse event, Y: Yes.
Day is actual day in the treatment period.
Level 1: Plasma glucose < 3.9 mmol/L (70 mg/dL) and >= 3.0 mmol/L (54 mg/dL). Level 2: Plasma glucose < 3.0 mmol/L (54 mg/dL). Level 3: Hypoglycaemia with severe cognitive impairment requiring external assistance for recovery.
Unclassifiable: Event requiring external assistance for recovery, no glucose values and unknown if symptoms were subsequently alleviated.
The clamp periods are excluded from the evaluation of hypoglycaemic episodes.

5.4.31 Counterregulatory hormones at PG nadir - statistical analysis - subjects with symptoms or clinically significant hypoglycaemia

	N	Nobs	Estimate	95% CI	p-value
C(adrenaline), PGnadir, DD (pmol/L)					
Estimated geometric means					
Ico	20	20	530.39		
IGlar	19	19	590.88		
Treatment ratio					
Ico / IGlar			0.90	[0.62 ; 1.30]	0.5389
C(adrenaline), PGnadir, TD (pmol/L)					
Estimated geometric means					
Ico	20	20	735.76		
IGlar	29	29	570.93		
Treatment ratio					
Ico / IGlar			1.29	[0.88 ; 1.89]	0.1795
C(cortisol), PG nadir, DD (nmol/L)					
Estimated geometric means					
Ico	20	19	295.97		
IGlar	19	19	300.30		
Treatment ratio					
Ico / IGlar			0.99	[0.67 ; 1.45]	0.9333
C(cortisol), PG nadir, TD (nmol/L)					
Estimated geometric means					
Ico	20	19	354.99		
IGlar	29	29	197.58		
Treatment ratio					
Ico / IGlar			1.80	[1.09 ; 2.97]	0.0243
C(noradrenaline), PGnadir, DD (pmol/L)					
Estimated geometric means					
Ico	20	20	1077.99		
IGlar	19	19	907.42		
Treatment ratio					
Ico / IGlar			1.19	[0.91 ; 1.55]	0.1926
C(noradrenaline), PGnadir, TD (pmol/L)					
Estimated geometric means					
Ico	20	20	934.11		
IGlar	29	29	890.48		
Treatment ratio					
Ico / IGlar			1.05	[0.79 ; 1.40]	0.7309

N: Number of subjects considered, Nobs: Number of subjects contributing to the analysis, CI: Confidence interval, p-value: Two-sided test for no difference, DD: Double dose, TD: Double dose. The endpoints are analysed using a linear mixed effects model. A multiplicative model is used, i.e. the endpoint is log-transformed before analysis. The model includes treatment and period as fixed effects and subject as a random effect.

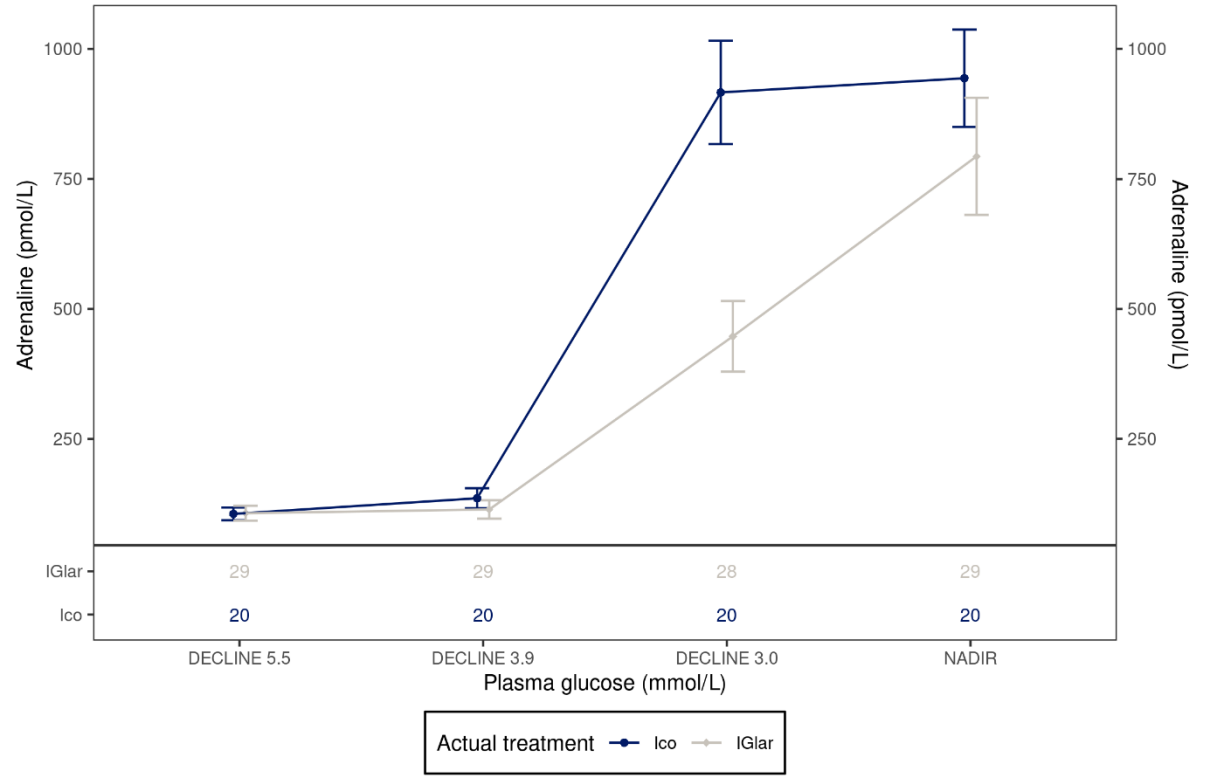
5.4.32 Adrenaline profiles during development of hypoglycaemia - double dose - mean plot - full analysis set - subjects with symptoms or clinically significant hypoglycaemia



Error bars : +/- Standard error (mean)

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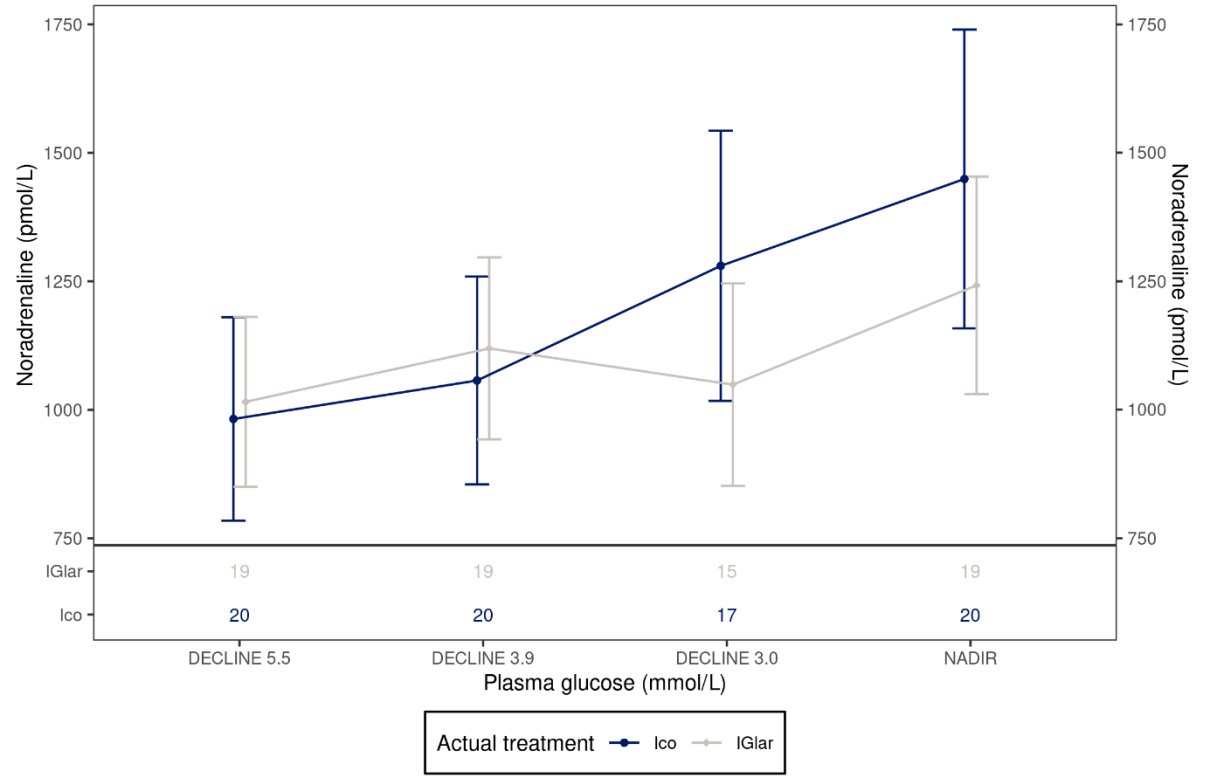
5.4.33 Adrenaline profiles during development of hypoglycaemia - triple dose - mean plot - full analysis set - subjects with symptoms or clinically significant hypoglycaemia



Error bars : +/- Standard error (mean)

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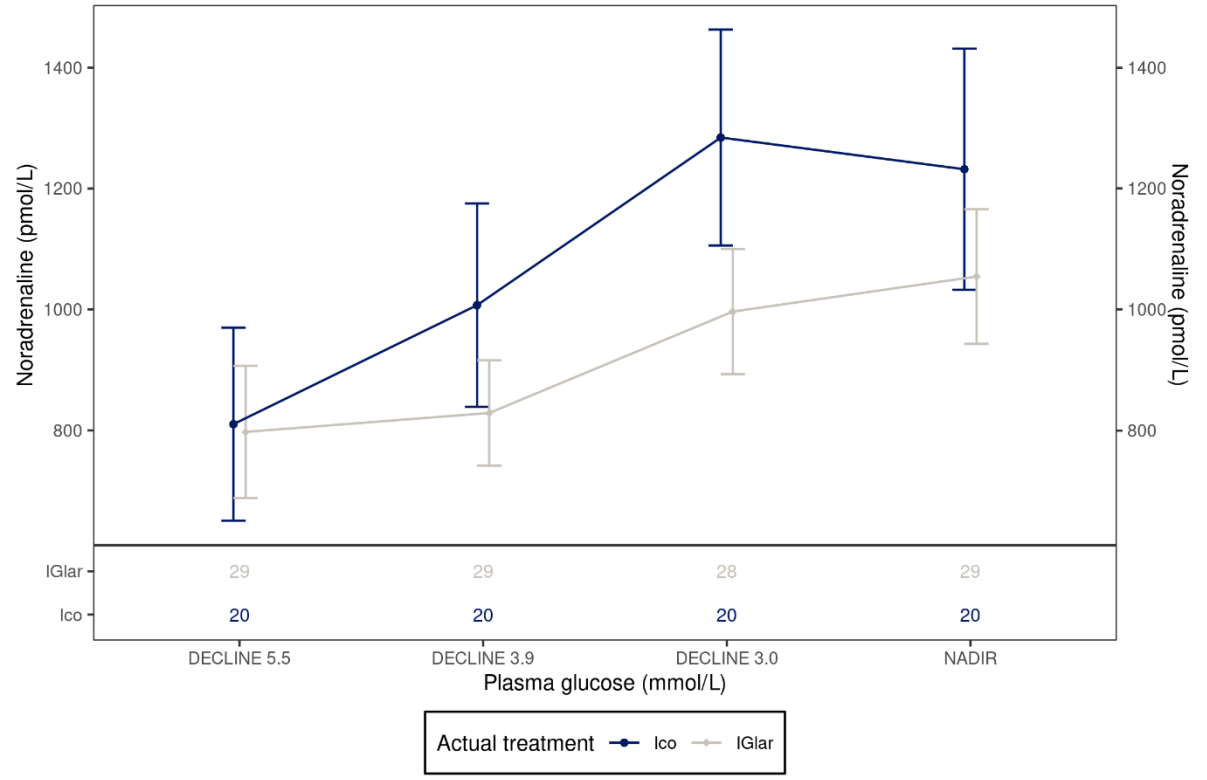
5.4.34 Noradrenaline profiles during development of hypoglycaemia - double dose - mean plot - full analysis set - subjects with symptoms or clinically significant hypoglycaemia



Error bars : +/- Standard error (mean)

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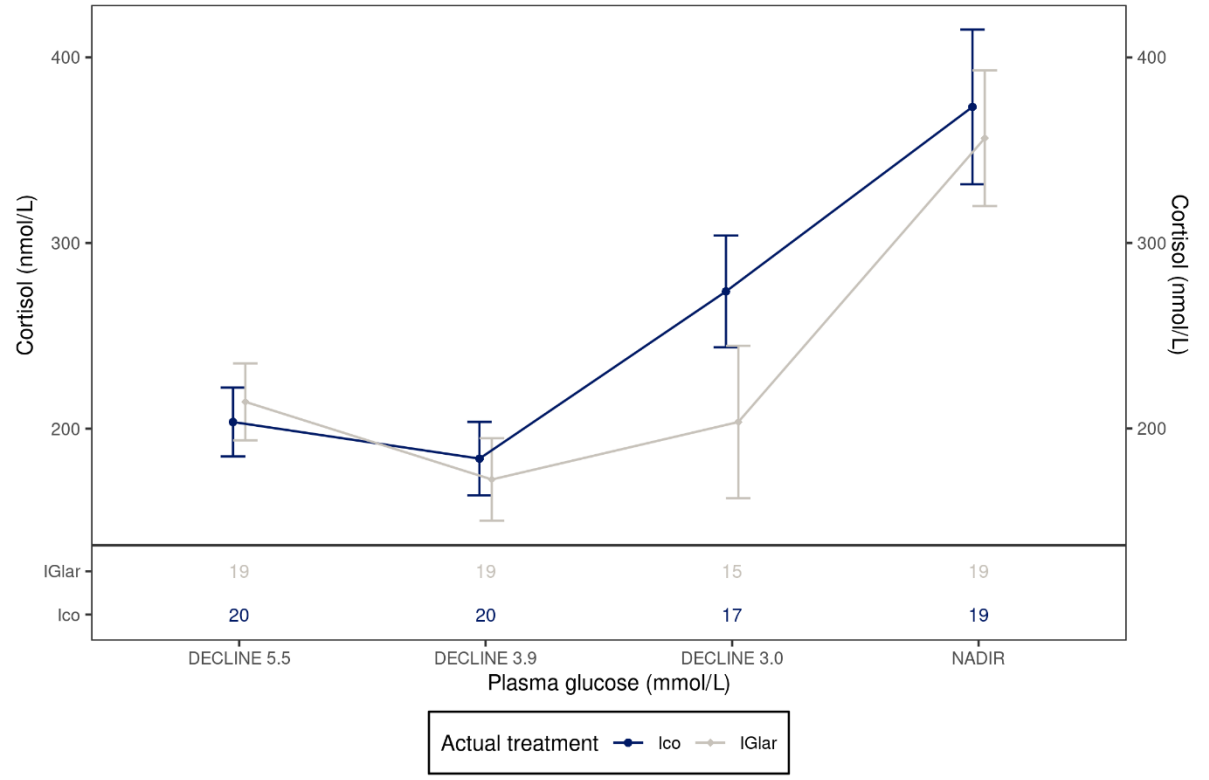
5.4.35 Noradrenaline profiles during development of hypoglycaemia - triple dose - mean plot - full analysis set - subjects with symptoms or clinically significant hypoglycaemia



Error bars : +/- Standard error (mean)

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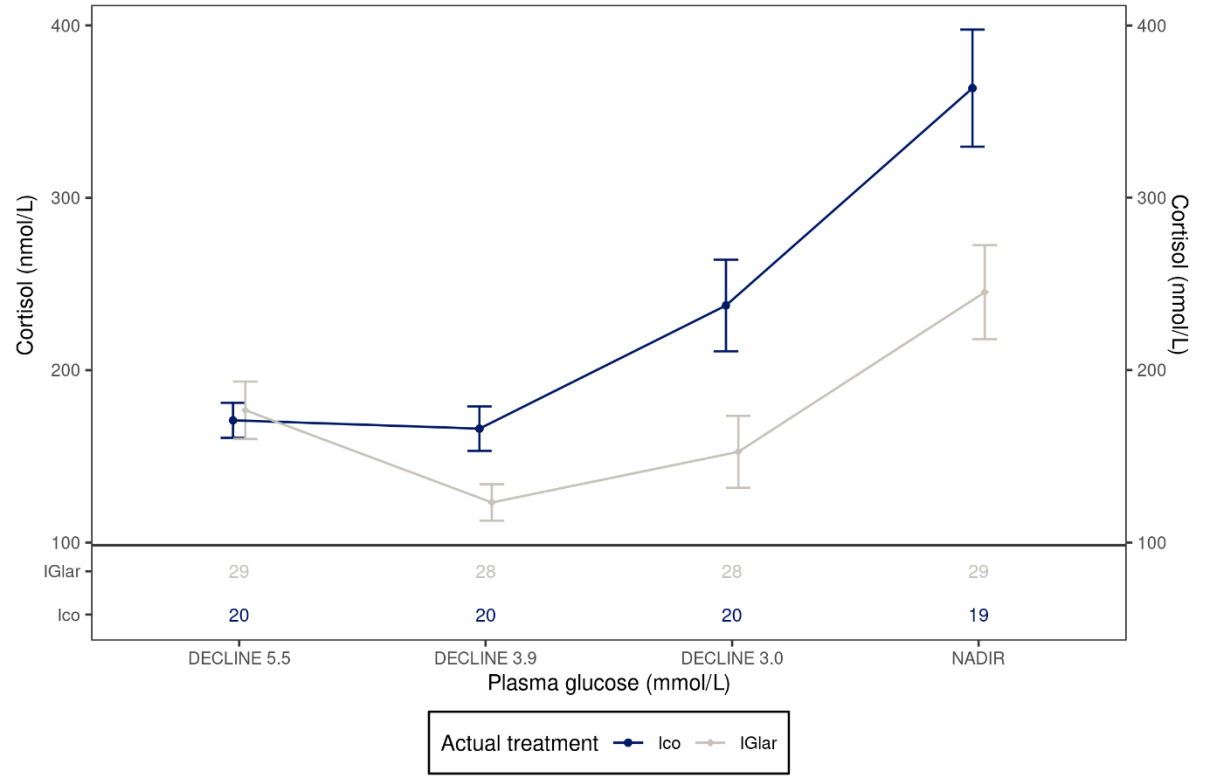
5.4.36 Cortisol profiles during development of hypoglycaemia - double dose - mean plot - full analysis set - subjects with symptoms or clinically significant hypoglycaemia



Error bars : +/- Standard error (mean)

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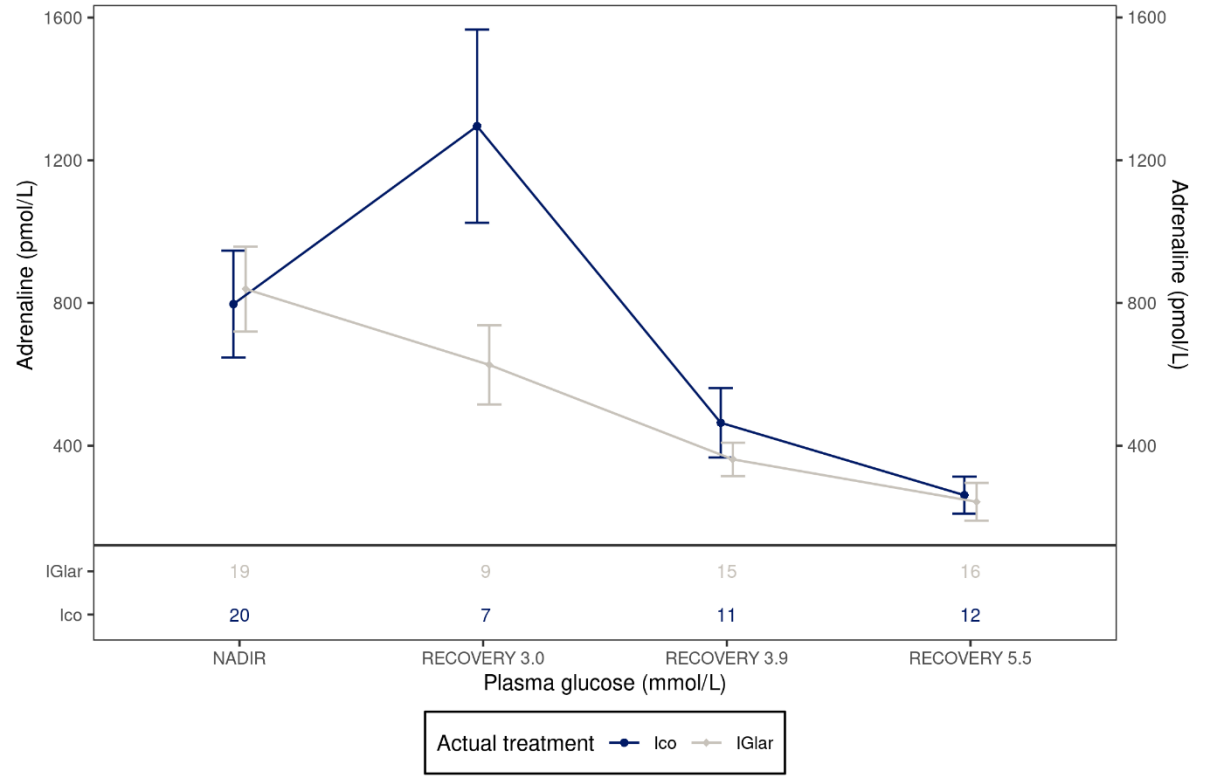
5.4.37 Cortisol profiles during development of hypoglycaemia - triple dose - mean plot - full analysis set - subjects with symptoms or clinically significant hypoglycaemia



Error bars : +/- Standard error (mean)

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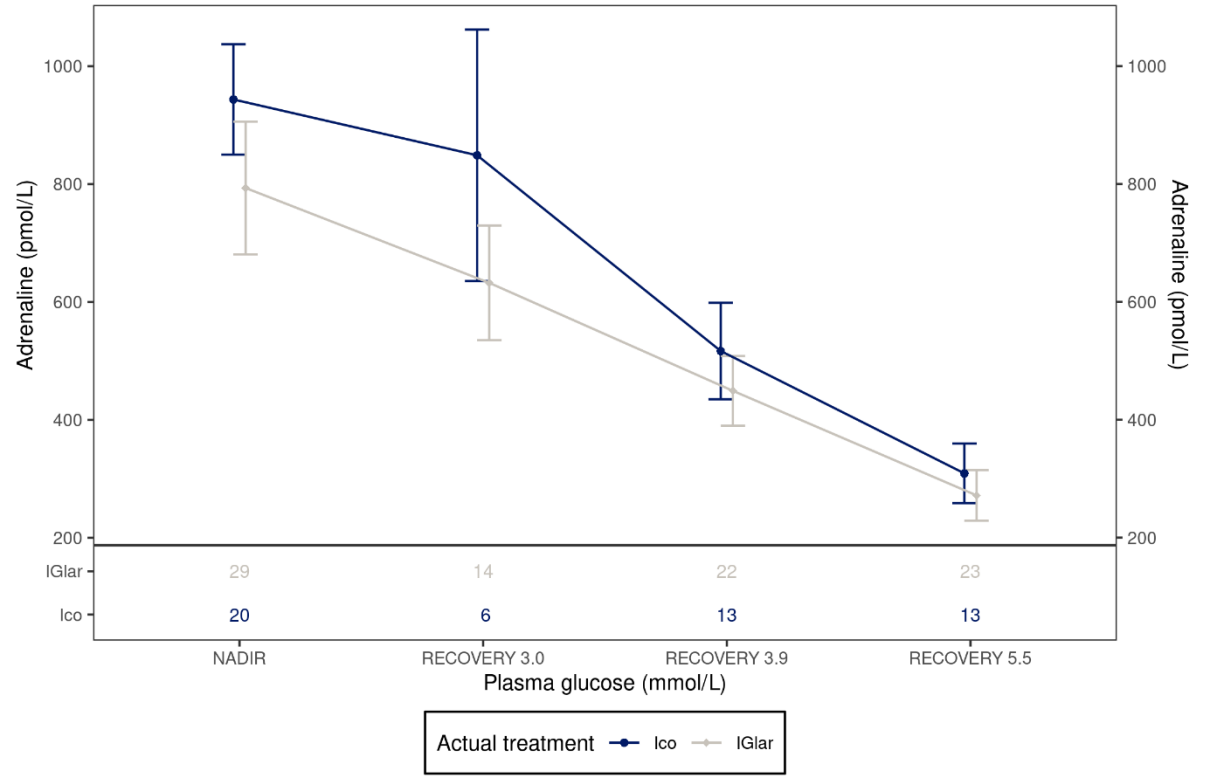
5.4.38 Adrenaline profiles during recovery from hypoglycaemia - double dose - mean plot - full analysis set - subjects with symptoms or clinically significant hypoglycaemia



Error bars : +/- Standard error (mean)

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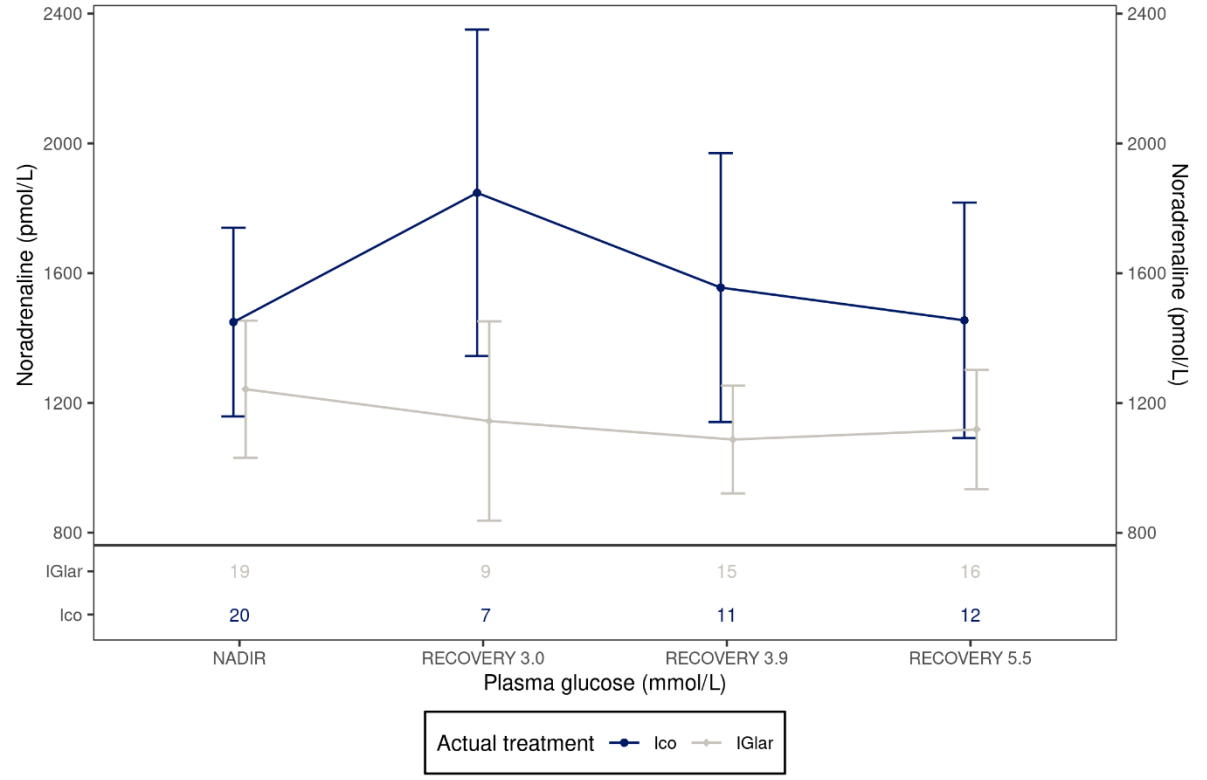
5.4.39 Adrenaline profiles during recovery from hypoglycaemia - triple dose - mean plot - full analysis set - subjects with symptoms or clinically significant hypoglycaemia



Error bars : +/- Standard error (mean)

nn1436/exploratory/pucph002_20220930_er
20OCT2022:07:59:34 - fmean/fmeanradntrlSI.png

5.4.40 Noradrenaline profiles during recovery from hypoglycaemia - double dose - mean plot - full analysis set - subjects with symptoms or clinically significant hypoglycaemia



Error bars : +/- Standard error (mean)

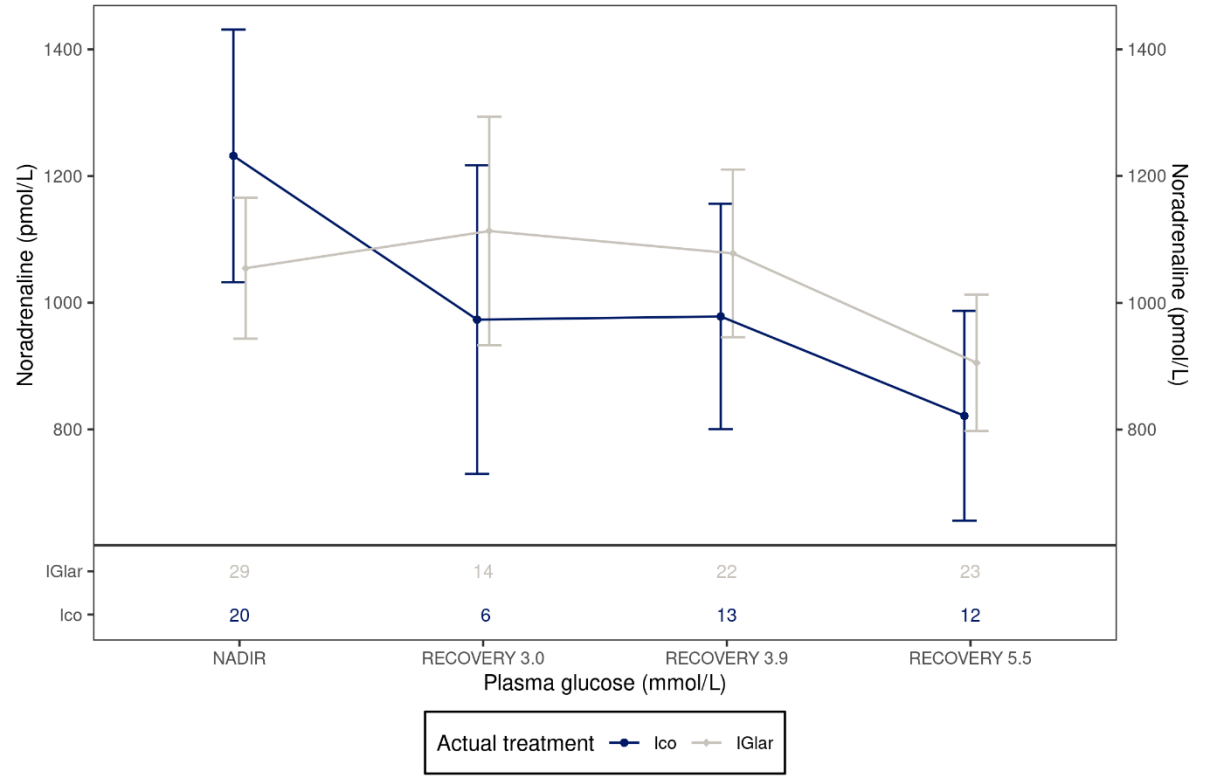
nn1436/exploratory/pucph002_20220930_er
20OCT2022:07:59:36 - fmean/fmeanrnondblSI.png

5.4.41 Actual pgnadir - summary - subjects with symptoms or clinically significant hypoglycaemia

	Ico 2xdose	Ico 3xdose	IGlar 2xdose	IGlar 3xdose
Number of subjects	20	20	19	29
Actual PGnadir (mmol/L)				
N	20	20	19	29
Geometric mean (CV%)	2.91 (8.58)	2.83 (5.56)	2.88 (10.45)	2.71 (9.71)
Median	2.97	2.83	2.86	2.75
Min ; Max	2.50 ; 3.55	2.47 ; 3.00	2.47 ; 3.69	2.25 ; 3.14

`Number of subjects` refers to number of subjects experiencing clinically significant hypoglycaemia or symptoms.
N: Number of subjects, CV: Coefficient of variation.
2xdose refers to double dose, 3xdose refers to triple dose.

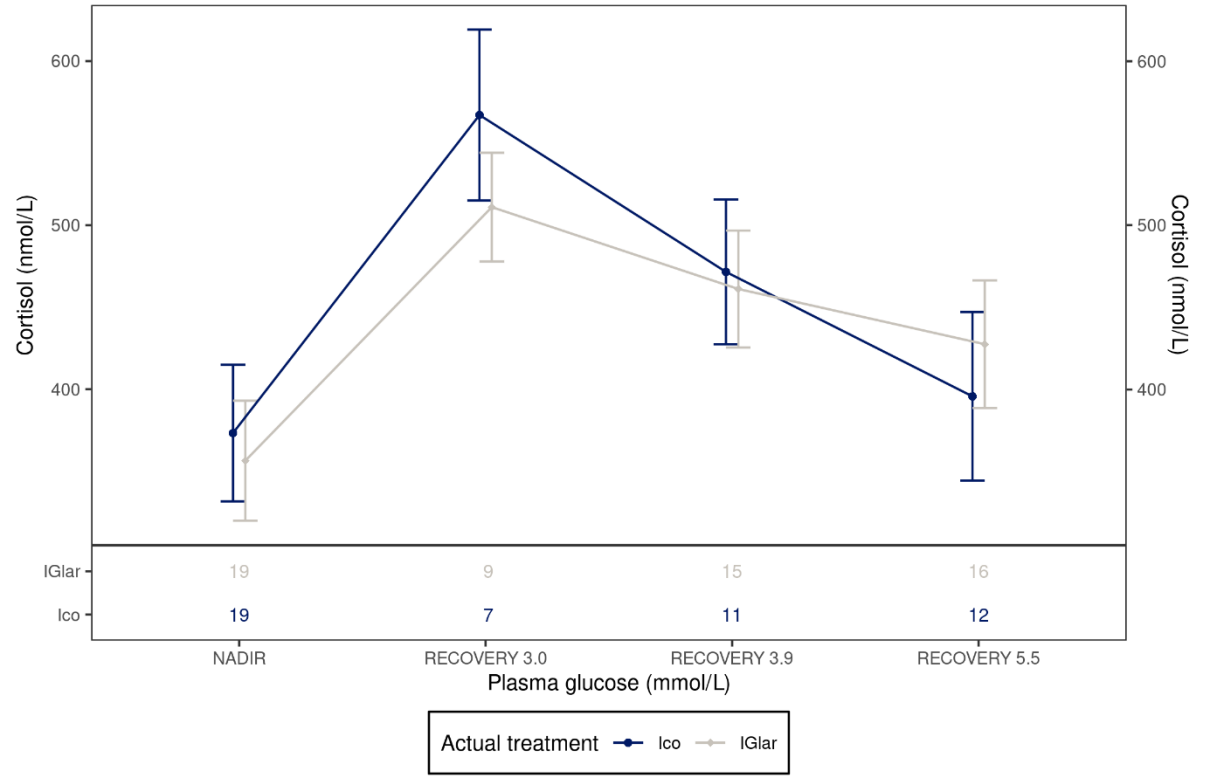
5.4.42 Noradrenaline profiles during recovery from hypoglycaemia - triple dose - mean plot - full analysis set - subjects with symptoms or clinically significant hypoglycaemia



Error bars : +/- Standard error (mean)

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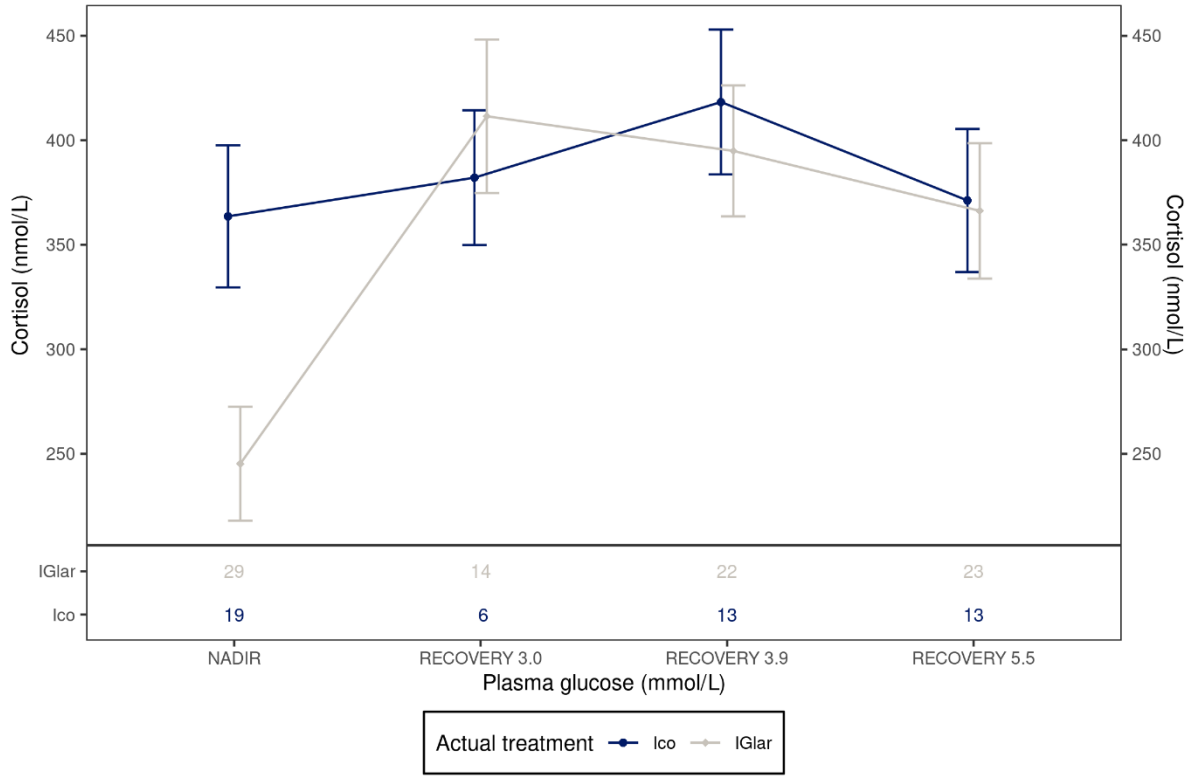
5.4.43 Cortisol profiles during recovery from hypoglycaemia - double dose - mean plot - full analysis set - subjects with symptoms or clinically significant hypoglycaemia



Error bars : +/- Standard error (mean)

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5.4.44 Cortisol profiles during recovery from hypoglycaemia - triple dose - mean plot - full analysis set - subjects with symptoms or clinically significant hypoglycaemia



Error bars : +/- Standard error (mean)

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5.4.45 Counterregulatory hormones summary - at PG Nadir - subjects with symptoms or clinically significant hypoglycaemia after both icodec and IGlar triple dose

	Ico 3xdose	IGlar 3xdose
Number of subjects	17	17
Adrenaline (pg/mL)		
N	17	17
Geometric mean (CV%)	163.41 (49.94)	150.87 (89.46)
Median	171.60	197.00
Min ; Max	53.70 ; 391.50	28.20 ; 433.20
Cortisol (ng/mL)		
N	16	16
Geometric mean (CV%)	123.77 (49.82)	82.21 (68.92)
Median	148.50	93.50
Min ; Max	54.00 ; 205.00	21.00 ; 195.00
Glucagon (pg/mL)		
N	17	17
Geometric mean (CV%)	56.27 (49.09)	59.06 (44.83)
Median	54.10	51.70
Min ; Max	30.70 ; 169.10	27.20 ; 146.20
Growth Hormone (ng/mL)		
N	16	16
Geometric mean (CV%)	3.81 (92.20)	3.92 (57.91)
Median	3.80	3.90
Min ; Max	0.91 ; 15.04	1.68 ; 12.05
Noradrenaline (pg/mL)		
N	17	17
Geometric mean (CV%)	162.71 (70.51)	161.69 (66.04)
Median	177.60	168.30
Min ; Max	55.00 ; 520.30	55.00 ; 435.30

`Number of subjects` refers to number of subjects with symptoms or clinically significant hypoglycaemia in both treatment arms.
N: Number of subjects, PG: Plasma glucose, CV: Coefficient of variation.
3xdose refers to triple dose.
Only subjects with measurements at PG nadir after both icodec and IGlar triple dose are included in the descriptive statistics.

5.4.46 Counterregulatory hormones summary - at decline 3.0 mmol/L - subjects with symptoms or clinically significant hypoglycaemia after both icodec and IGlar triple dose

	Ico 3xdose	IGlar 3xdose
Number of subjects	17	17
Adrenaline (pg/mL)		
N	16	16
Geometric mean (CV%)	151.18 (61.80)	58.83 (121.94)
Median	181.95	78.35
Min ; Max	51.10 ; 367.10	13.75 ; 214.90
Cortisol (ng/mL)		
N	16	16
Geometric mean (CV%)	69.88 (57.94)	49.36 (68.68)
Median	73.50	53.50
Min ; Max	28.00 ; 170.00	14.00 ; 170.00
Glucagon (pg/mL)		
N	16	16
Geometric mean (CV%)	50.47 (47.08)	47.25 (43.60)
Median	48.05	50.15
Min ; Max	21.30 ; 104.60	22.60 ; 80.70
Growth Hormone (ng/mL)		
N	16	16
Geometric mean (CV%)	3.82 (149.35)	2.23 (152.52)
Median	4.88	2.38
Min ; Max	0.17 ; 14.63	0.29 ; 28.17
Noradrenaline (pg/mL)		
N	16	16
Geometric mean (CV%)	180.09 (61.60)	146.38 (62.76)
Median	186.45	153.45
Min ; Max	55.00 ; 472.30	55.00 ; 321.10

`Number of subjects` refers to number of subjects with symptoms or clinically significant hypoglycaemia in both treatment arms.
N: Number of subjects, PG: Plasma glucose, CV: Coefficient of variation.
3xdose refers to triple dose.
Only subjects with measurements at PG decline 3.0 mmol/L after both icodec and IGlar triple dose are included in the descriptive statistics.

5.4.47 Baseline characteristics summary - categorical - Subjects with symptoms or clinically significant hypoglycemia - safety analysis set

	Ico 2xdose		Ico 3xdose		IGlar 2xdose		IGlar 3xdose	
	N	(%)	N	(%)	N	(%)	N	(%)
Number of subjects	20		20		19		29	
Age group								
No	20	(100.0)	20	(100.0)	19	(100.0)	29	(100.0)
18<= to <65 years	14	(70.0)	13	(65.0)	13	(68.4)	21	(72.4)
65<= to <75 years	6	(30.0)	7	(35.0)	6	(31.6)	8	(27.6)
Sex								
No	20	(100.0)	20	(100.0)	19	(100.0)	29	(100.0)
Male	10	(50.0)	15	(75.0)	12	(63.2)	19	(65.5)
Female	10	(50.0)	5	(25.0)	7	(36.8)	10	(34.5)
Ethnicity								
No	20	(100.0)	20	(100.0)	19	(100.0)	29	(100.0)
Not hispanic or latino	20	(100.0)	20	(100.0)	19	(100.0)	29	(100.0)
Race								
White	20	(100.0)	20	(100.0)	18	(94.7)	28	(96.6)
Asian indian	0		0		1	(5.3)	1	(3.4)
Country (label)								
No	20	(100.0)	20	(100.0)	19	(100.0)	29	(100.0)
Austria	20	(100.0)	20	(100.0)	19	(100.0)	29	(100.0)
OAD								
Yes	19	(95.0)	19	(95.0)	18	(94.7)	27	(93.1)
No	1	(5.0)	1	(5.0)	1	(5.3)	2	(6.9)

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

5.4.48 Baseline characteristics summary - continuous - Subjects with symptoms or clinically significant hypoglycemia - safety analysis set

	Ico 2xdose	Ico 3xdose	IGlar 2xdose	IGlar 3xdose
Number of subjects	20	20	19	29
Age (years)				
N	20	20	19	29
Mean (SD)	56.55 (10.11)	59.55 (6.69)	57.89 (8.61)	56.48 (9.85)
Median	59.50	60.50	60.00	59.00
Min ; Max	28.00 ; 67.00	46.00 ; 71.00	42.00 ; 71.00	28.00 ; 71.00
Body weight (kg)				
N	20	20	19	29
Mean (SD)	82.89 (12.84)	85.36 (12.70)	83.71 (13.37)	85.31 (13.81)
Median	82.40	82.65	81.60	85.30
Min ; Max	61.10 ; 113.00	61.10 ; 105.00	61.10 ; 113.00	61.10 ; 113.00
Height (m)				
N	20	20	19	29
Mean (SD)	1.72 (0.09)	1.73 (0.10)	1.71 (0.09)	1.74 (0.10)
Median	1.72	1.75	1.72	1.74
Min ; Max	1.56 ; 1.87	1.56 ; 1.89	1.56 ; 1.87	1.56 ; 1.91
BMI (kg/m^2)				
N	20	20	19	29
Mean (SD)	28.10 (4.08)	28.61 (4.51)	28.56 (4.22)	28.15 (4.04)
Median	28.24	28.29	28.93	27.65
Min ; Max	20.68 ; 37.89	20.68 ; 37.89	20.68 ; 37.89	20.68 ; 37.89
Basal insulin dose (U/kg)				
N	20	20	19	29
Mean (SD)	2.90 (1.28)	2.74 (1.00)	0.43 (0.17)	0.36 (0.14)
Median	2.63	2.52	0.40	0.32
Min ; Max	1.11 ; 5.73	1.37 ; 4.63	0.22 ; 0.82	0.16 ; 0.66

N: Number of subjects, SD: Standard deviation, BMI: Body mass index.

5.4.49 Baseline diabetes characteristics - summary - Subjects with symptoms or clinically significant hypoglycemia - safety analysis set

	Ico 2xdose	Ico 3xdose	IGlar 2xdose	IGlar 3xdose
Number of subjects	20	20	19	29
Duration of diabetes (years)				
N	20	20	19	29
Mean (SD)	13.87 (8.93)	15.03 (8.49)	14.80 (8.62)	14.79 (8.55)
Median	10.66	14.95	15.01	14.89
Min ; Max	0.89 ; 34.73	2.10 ; 34.73	0.89 ; 34.73	1.29 ; 34.73
HbA1c (%)				
N	20	20	19	29
Mean (SD)	7.26 (0.84)	7.39 (0.66)	7.38 (0.74)	7.23 (0.65)
Median	7.15	7.25	7.20	7.20
Min ; Max	5.70 ; 8.70	6.20 ; 8.60	6.20 ; 8.70	5.70 ; 8.60
HbA1c (mmol/mol)				
N	20	20	19	29
Mean (SD)	55.91 (9.15)	57.33 (7.20)	57.21 (8.08)	55.54 (7.13)
Median	54.65	55.74	55.20	55.20
Min ; Max	38.80 ; 71.59	44.27 ; 70.50	44.27 ; 71.59	38.80 ; 70.50
FPG (mmol/L)				
N	20	20	19	29
Mean (SD)	7.24 (1.79)	7.43 (1.69)	7.32 (1.85)	7.15 (1.55)
Median	7.24	7.27	7.27	7.21
Min ; Max	4.72 ; 11.88	4.94 ; 11.88	4.94 ; 11.88	4.72 ; 11.88
FPG (mg/dL)				
N	20	20	19	29
Mean (SD)	130.55 (32.27)	133.90 (30.50)	131.89 (33.31)	128.90 (27.89)
Median	130.50	131.00	131.00	130.00
Min ; Max	85.00 ; 214.00	89.00 ; 214.00	89.00 ; 214.00	85.00 ; 214.00
Fasting C-peptide (nmol/L)				
N	20	20	19	29
Mean (SD)	0.58 (0.32)	0.63 (0.31)	0.71 (0.83)	0.74 (0.71)
Median	0.49	0.56	0.50	0.56
Min ; Max	0.24 ; 1.62	0.24 ; 1.60	0.24 ; 4.03	0.24 ; 4.03
Fasting C-peptide (ng/mL)				
N	20	20	19	29
Mean (SD)	1.75 (0.96)	1.91 (0.94)	2.14 (2.50)	2.25 (2.16)
Median	1.48	1.69	1.51	1.68
Min ; Max	0.72 ; 4.90	0.72 ; 4.83	0.72 ; 12.17	0.72 ; 12.17

FPG: Fasting plasma glucose, HbA1c: Glycated haemoglobin, N: Number of subjects, SD: Standard deviation.
FPG measurements are performed at the trial site using Super GL2 Analyzer.

インスリン イコデク（遺伝子組換え）

2.7.2.5 付録
5. Child-Pugh スコアの一覧（4570 試験）

ノボ ノルディスク ファーマ株式会社

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5.5.1 Overview table of Child-Pugh scores

Subject ID	Encephalopathy	Ascites	Bilirubin	Albumin	Prothrombin time	Total score
MILD						
101004	1	1	1	1	1	5
101007	2	1	1	1	1	6
101008	1	1	1	1	1	5
102001	1	1	1	1	1	5
102002	1	1	1	1	1	5
102003	1	1	1	2	1	6
MODERATE						
101002	2	2	1	1	1	7
101003	1	1	1	1	3	7
101009	2	2	1	1	1	7
102004	2	1	2	2	1	8
102005	2	2	1	1	1	7
102006	2	1	2	1	1	7
SEVERE						
101010	2	3	3	2	2	12
101011	2	3	3	1	1	10
101012	2	3	2	1	3	11
101017	2	1	3	3	2	11
102007	2	2	3	1	2	10
102013	2	3	2	3	1	11
102014	2	2	3	2	1	10

5.5.2 Child-Pugh score - listing - full analysis set

Subject ID/ Age (years)/ Sex (M/F)/ BMI (kg/m^2)	Hepatic group	Parameter	Score
101002/ 4[redacted]/F/ 3[redacted]	Moderate	Encephalopathy	Grade 1 or 2
	Moderate	Ascites	Slight
	Moderate	Serum Bilirubin	<34.2
	Moderate	Serum Albumin	>35
	Moderate	Prothrombin Time	<4
	Moderate	Total Score	7
	Moderate	Grade	B
101003/ 4[redacted]/M/ 3[redacted]	Moderate	Encephalopathy	None
	Moderate	Ascites	Absent
	Moderate	Serum Bilirubin	<34.2
	Moderate	Serum Albumin	>35
	Moderate	Prothrombin Time	>6
	Moderate	Total Score	7
	Moderate	Grade	B
101004/ 6[redacted]/F/ 3[redacted]	Mild	Encephalopathy	None
	Mild	Ascites	Absent
	Mild	Serum Bilirubin	<34.2
	Mild	Serum Albumin	>35
	Mild	Prothrombin Time	<4
	Mild	Total Score	5
	Mild	Grade	A

BMI: Body mass index, F: Female, M: Male.

Child pugh score - listing - full analysis set

Subject ID/ Age (years)/ Sex (M/F)/ BMI (kg/m^2)	Hepatic group	Parameter	Score
101007/ 5[redacted]/M/ 3[redacted]	Mild	Encephalopathy	Grade 1 or 2
	Mild	Ascites	Absent
	Mild	Serum Bilirubin	<34.2
	Mild	Serum Albumin	>35
	Mild	Prothrombin Time	<4
	Mild	Total Score	6
	Mild	Grade	A
101008/ 4[redacted]/M/ 2[redacted]	Mild	Encephalopathy	None
	Mild	Ascites	Absent
	Mild	Serum Bilirubin	<34.2
	Mild	Serum Albumin	>35
	Mild	Prothrombin Time	<4
	Mild	Total Score	5
	Mild	Grade	A
101009/ 6[redacted]/F/ 2[redacted]	Moderate	Encephalopathy	Grade 1 or 2
	Moderate	Ascites	Slight
	Moderate	Serum Bilirubin	<34.2
	Moderate	Serum Albumin	>35
	Moderate	Prothrombin Time	<4
	Moderate	Total Score	7
	Moderate	Grade	B

BMI: Body mass index, F: Female, M: Male.

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Child pugh score - listing - full analysis set

Subject ID/ Age (years)/ Sex (M/F)/ BMI (kg/m^2)	Hepatic group	Parameter	Score
101010/ 6[redacted]/M/ 3[redacted]	Severe	Encephalopathy	Grade 1 or 2
	Severe	Ascites	Moderate
	Severe	Serum Bilirubin	>51.3
	Severe	Serum Albumin	28-35
	Severe	Prothrombin Time	4-6
	Severe	Total Score	12
	Severe	Grade	C
101011/ 6[redacted]/F/ 2[redacted]	Severe	Encephalopathy	Grade 1 or 2
	Severe	Ascites	Moderate
	Severe	Serum Bilirubin	>51.3
	Severe	Serum Albumin	>35
	Severe	Prothrombin Time	<4
	Severe	Total Score	10
	Severe	Grade	C
101012/ 5[redacted]/M/ 2[redacted]	Severe	Encephalopathy	Grade 1 or 2
	Severe	Ascites	Moderate
	Severe	Serum Bilirubin	34.2-51.3
	Severe	Serum Albumin	>35
	Severe	Prothrombin Time	>6
	Severe	Total Score	11
	Severe	Grade	C

BMI: Body mass index, F: Female, M: Male.

Child pugh score - listing - full analysis set

Subject ID/ Age (years)/ Sex (M/F)/ BMI (kg/m^2)	Hepatic group	Parameter	Score
101017/ 5[redacted]/F/ 3[redacted]	Severe	Encephalopathy	Grade 1 or 2
	Severe	Ascites	Absent
	Severe	Serum Bilirubin	>51.3
	Severe	Serum Albumin	<28
	Severe	Prothrombin Time	4-6
	Severe	Total Score	11
	Severe	Grade	C
102001/ 4[redacted]/F/ 2[redacted]	Mild	Encephalopathy	None
	Mild	Ascites	Absent
	Mild	Serum Bilirubin	<34.2
	Mild	Serum Albumin	>35
	Mild	Prothrombin Time	<4
	Mild	Total Score	5
	Mild	Grade	A
102002/ 6[redacted]/M/ 1[redacted]	Mild	Encephalopathy	None
	Mild	Ascites	Absent
	Mild	Serum Bilirubin	<34.2
	Mild	Serum Albumin	>35
	Mild	Prothrombin Time	<4
	Mild	Total Score	5
	Mild	Grade	A

BMI: Body mass index, F: Female, M: Male.

nn1436/exploratory/sucph002_20221207_er
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Child pugh score - listing - full analysis set

Subject ID/ Age (years)/ Sex (M/F)/ BMI (kg/m^2)	Hepatic group	Parameter	Score
102003/ 4[redacted]/M/ 2[redacted]	Mild	Encephalopathy	None
	Mild	Ascites	Absent
	Mild	Serum Bilirubin	<34.2
	Mild	Serum Albumin	28-35
	Mild	Prothrombin Time	<4
	Mild	Total Score	6
	Mild	Grade	A
102004/ 5[redacted]/F/ 2[redacted]	Moderate	Encephalopathy	Grade 1 or 2
	Moderate	Ascites	Absent
	Moderate	Serum Bilirubin	34.2-51.3
	Moderate	Serum Albumin	28-35
	Moderate	Prothrombin Time	<4
	Moderate	Total Score	8
	Moderate	Grade	B
102005/ 6[redacted]/M/ 2[redacted]	Moderate	Encephalopathy	Grade 1 or 2
	Moderate	Ascites	Slight
	Moderate	Serum Bilirubin	<34.2
	Moderate	Serum Albumin	>35
	Moderate	Prothrombin Time	<4
	Moderate	Total Score	7
	Moderate	Grade	B

BMI: Body mass index, F: Female, M: Male.

nn1436/exploratory/sucph002_20221207_er
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Child pugh score - listing - full analysis set

Subject ID/ Age (years)/ Sex (M/F)/ BMI (kg/m^2)	Hepatic group	Parameter	Score
102006/ 5[redacted]/F/ 2[redacted]	Moderate	Encephalopathy	Grade 1 or 2
	Moderate	Ascites	Absent
	Moderate	Serum Bilirubin	34.2-51.3
	Moderate	Serum Albumin	>35
	Moderate	Prothrombin Time	<4
	Moderate	Total Score	7
	Moderate	Grade	B
102007/ 3[redacted]/M/ 3[redacted]	Severe	Encephalopathy	Grade 1 or 2
	Severe	Ascites	Slight
	Severe	Serum Bilirubin	>51.3
	Severe	Serum Albumin	>35
	Severe	Prothrombin Time	4-6
	Severe	Total Score	10
	Severe	Grade	C
102013/ 4[redacted]/F/ 2[redacted]	Severe	Encephalopathy	Grade 1 or 2
	Severe	Ascites	Moderate
	Severe	Serum Bilirubin	34.2-51.3
	Severe	Serum Albumin	<28
	Severe	Prothrombin Time	<4
	Severe	Total Score	11
	Severe	Grade	C

BMI: Body mass index, F: Female, M: Male.

Child pugh score - listing - full analysis set

Subject ID/ Age (years)/ Sex (M/F)/ BMI (kg/m^2)	Hepatic group	Parameter	Score
102014/ 4[redacted]/F/ 2[redacted]	Severe	Encephalopathy	Grade 1 or 2
	Severe	Ascites	Slight
	Severe	Serum Bilirubin	>51.3
	Severe	Serum Albumin	28-35
	Severe	Prothrombin Time	<4
	Severe	Total Score	10
	Severe	Grade	C

BMI: Body mass index, F: Female, M: Male.