Statistical Analysis Plan

Study Code	D5676C00001
Edition Number	V5.0

A Phase 2b, Multicentre, Randomised, Double-blind, Placebo-controlled, and Open-Label Comparator Study of Cotadutide in Participants Who Have Chronic Kidney Disease with Type 2 Diabetes Mellitus

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AAR	Aspartate transaminase/ Alanine transaminase ratio
ABPM	Ambulatory blood pressure monitoring
ADA	Anti-drug antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
AST	Aspartate transaminase
ATC	Anatomical therapeutic chemical
BKD	Burden of Kidney Disease
BMI	Body mass index
BP	Blood pressure
BSR	Baseline scaled ratio
CGM	Continuous glucose monitoring
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease-epidemiology collaboration
COVID-19	Coronavirus disease 2019
CS	Compound symmetry covariance structures
CSH	Heterogeneous compound symmetry covariance structures
CSR	Clinical study report
CV	Coefficient of variation
DBP	Diastolic blood pressure
DDFM	Denominator degrees of freedom
BID	Twice a day
dECG	Digital electrocardiogram
DTSQ	Diabetes treatment satisfaction questionnaire
eHbA1c	Estimated HbA1c
ECG	Electrocardiogram
eCRF	Electronic case report form
E/D	Early discontinuation
eGFR	Estimated glomerular filtration rate
EKD	Effects of Kidney Disease
EQ-5D	EuroQol five-dimension scale

Abbreviation or special term	Explanation
EXP	Exponential
GLP-1	Glucagon-like peptide-1
HbA1c	Haemoglobin A1c
HDL	High density lipoprotein
HLT	High level term
IDRP	Integrated Data Review Plan
IFG	Impaired fasting glucose
IP	Investigational product
IPD	Important protocol deviation
ITT	Intention to treat
IQR	Interquartile range
IWRS	Interactive web response system
KDQOL-36	Kidney disease quality of life-36
KIM1	Kidney injury molecule 1
LDL	Low density lipoprotein
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
LOG	Logarithm
LSmeans	Least-square means
MAGE	Mean Amplitude of Glycaemic Excursions
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MEDI0382	Cotadutide
MMRM	Mixed model repeated measures
NAFLD	Non-alcoholic fatty liver disease
NC	Not calculable
NFS	NAFLD fibrosis score
NT-proBNP	N-terminal pro-brain natriuretic peptide
NQ	Not quantifiable
NR	Not reportable
NS	No sample
PCS	Physical Component Summary
PD	Protocol deviation
PDMP	Protocol deviation Management Plan
PK	Pharmacokinetic
PP	Per protocol

Abbreviation or special term	Explanation
PRO	Patient reported outcome
PT	Preferred term
Q1	First quartile
Q3	Third quartile
QD	Once daily
QRS	QRS wave
QT	QT wave
QTcB	Corrected QT Interval using Bazett's Formula
QTcF	Corrected QT Interval using Fridericia's Formula
Q-Q plot	Quantile–quantile plot
REML	Restricted maximum likelihood
RPP	Rate pressure product
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis software
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SDTM	Study data tabulation model
SGLT-2	Sodium-glucose co-transporter-2
SI	International system of units
SOC	System organ class
SP (POW)	Power spatial covariance structures
SPKD	Symptoms and Problems of Kidney Disease
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TBL	Total bilirubin
TEAE	Treatment emergent adverse event
TESAE	Treatment-emergent serious adverse event
TOEPH	Heterogeneous Toeplitz covariance structures
TID	Three times a day
UACR	Urine albumin to creatinine ratio
UK	United Kingdoms
ULN	Upper limit of normal
UN	Unstructured covariance structures

Abbreviation or special term	Explanation
UNSCH	Unscheduled
URC	Unblinded review committee
W	Week
WHO	World Health Organization
WHO-DD	WHO Drug Dictionary

AMENDMENT HISTORY

Version number	Date	Brief description of change
V1.0	15/09/2020	N/A
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Version number	Date	Brief description of change
[redacted]	[redacted]	[redacted]

1 STUDY DETAILS

This is a randomised, double-blind, placebo-controlled, and open-label comparator study to evaluate the efficacy, safety, tolerability, and PK profile of cotadutide (MEDI0382) uptitrated from 50 to 100, 300, or 600 µg administered SC once daily over 26 weeks in participants who have CKD with T2DM (eGFR ≥ 20 and < 90 mL/min/1.73 m^2 and micro- or macroalbuminuria). Placebo will be matched to cotadutide. The open-label comparator, semaglutide, will be administered SC from 0.25 to 1.0 mg once weekly over 26 weeks. Cotadutide, placebo, and semaglutide will be administered using an injection pen device.

Approximately 225 participants will be randomised at multiple sites in approximately 8 countries. Participants will be randomised in a 1:1:1:1:1 ratio to 1 of 3 blinded cotadutide arms (100, 300, or 600 µg), a blinded placebo arm, or an open-label semaglutide arm (1.0 mg). The cotadutide and placebo arms will be double-blinded. Participants randomised to the placebo arm will be further randomised in a 1:1:1 ratio to follow 1 of 3 titration regimens matched to the cotadutide arms. Participants at sites in Japan will not be randomised to the semaglutide arm. Participants in the UK with an eGFR < 30 mL/min/1.73m2 will not be randomised to the 600 ug cotadutide arm or matched placebo.

1.1 Study objectives

1.1.1 Primary objective and associated endpoint

Table 1 Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the effects of cotadutide at different dose levels compared to placebo on UACR after 14 weeks	Change and percentage change in UACR versus placebo from baseline to the end of 14 weeks of dosing

UACR = urine albumin to creatinine ratio.

1.1.2 Secondary objectives and associated endpoints

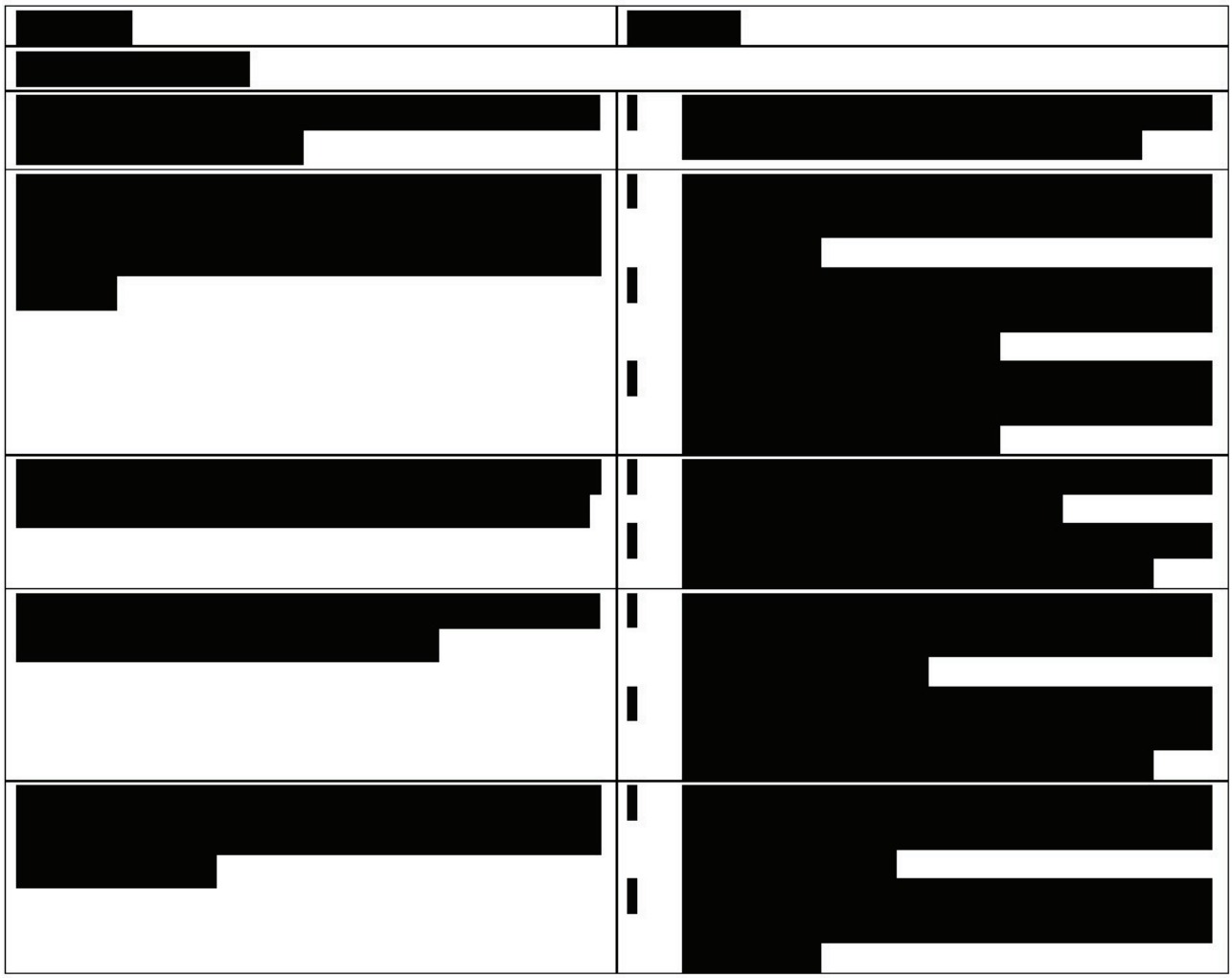
Table 2 Secondary objectives and associated endpoints

Objectives	Endpoints
Secondary	
To assess the effects of cotadutide at different dose levels compared to placebo on UACR after 26 weeks	Change and percentage change in UACR versus placebo from baseline to the end of 26 weeks of dosing
To assess the effects of cotadutide at different dose levels compared to placebo on HbA1c and fasting glucose	• Change in HbA1c versus placebo from baseline to the end of 14 and 26 weeks of dosing • Change in fasting glucose from baseline versus placebo after 14 and 26 weeks of dosing
To assess the effects of cotadutide at different dose levels compared to placebo on glucose levels as measured by CGM	• Change in 10-day average glucose levels as measured by CGM versus placebo from baseline to the end of 14 and 26 weeks of dosing • Change in percentage time spent in hyperglycaemia (> 10 mmol/L), target range (3.9 – 10 mmol/L), hypoglycaemia (< 3.9 mmol/L), and clinically significant hypoglycaemia (< 3.0 mmol/L) over 10 days as measured by CGM versus placebo from baseline to the end of 14 and 26 weeks of dosing
To assess the effects of cotadutide at different dose levels compared to placebo on body weight	• Change and percentage change in body weight versus placebo from baseline to the end of 14 and 26 weeks of dosing • Proportion of participants achieving ≥ 5% and ≥ 10% body weight loss versus placebo from baseline to the end of 14 and 26 weeks of dosing
To evaluate the immunogenicity profile of cotadutide compared to placebo	• ADAs during the titration treatment period and follow-up period
Safety	
To evaluate the safety and tolerability of cotadutide compared to placebo	• TEAEs and TESAEs • Vital signs • ECG • Clinical laboratory assessments

ADA = anti-drug antibody; BP = blood pressure; CGM = continuous glucose monitoring; ECG = electrocardiogram; HbA1c = haemoglobin A1c; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; UACR = urine albumin to creatinine ratio

1.1.3 Exploratory objectives and associated endpoints

Table 3 Tertiary/Exploratory objectives and associated endpoints



[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted] weeks (from Day 1 to Day 98)
[redacted]	[redacted]

Objectives	Endpoints
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

1.2 Study design

1.2.1 Overall design

This is a randomised, double-blind, placebo-controlled, and open-label comparator study to evaluate the efficacy, safety, tolerability, and PK profile of cotadutide uptitrated from 50 to 100, 300, or 600 µg administered SC once daily over 26 weeks in participants who have CKD with T2DM (eGFR ≥ 20 and < 90 mL/min/1.73 m2 and micro- or macroalbuminuria). Placebo will be matched to cotadutide. The open-label comparator, semaglutide, will be administered SC from 0.25 to 1.0 mg once weekly over 26 weeks.

Approximately 225 participants will be randomised at multiple sites in approximately 8 countries. Participants will be randomised in a 1:1:1:1:1 ratio to 1 of 3 blinded cotadutide arms (100, 300, or 600 µg), a blinded placebo arm, or an open-label semaglutide arm (1.0 mg). The cotadutide and placebo arms will be double-blinded. Participants randomised to the placebo arm will be further randomised in a 1:1:1 ratio to follow 1 of 3 titration regimens matched to the cotadutide arms. Participants at sites in Japan will not be randomised to the semaglutide arm. Participants in the UK with an eGFR < 30 mL/min/1.73m2 will not be randomised to the 600 ug cotadutide arm or matched placebo.

1.2.2 Stratification

The randomisation will be stratified according to whether a participant is from a site in Japan or not and on the use of sodium-glucose cotransporter 2 (SGLT2) inhibitor therapy at screening. An information will be assigned according to IWRS data. At least 40% of participants should be on an SGLT2 inhibitor that was initiated at least 4 weeks prior to screening. Up to approximately 20% of participants will be recruited in Japan.

In case of any issues with stratification assignments by IWRS, the wrong stratification factor will be kept and the participant will be analysed according to the stratification factor from the randomization assignment.

[redacted]

[redacted]

[redacted]

[redacted]

1.2.5 Schedule of Activities

Table 5 Schedule of Activities

Study Period	**Scree-ning**	**Run-in (Days -14 to -1)[a]**			**Treatment**												**E/D ± 7[b]**	**Follow-up (28 days after last dose) ± 3**	**Notes**
Study Day ± Days	**-50 to -15**	**-14**	**-5**	**-2**	**1**	**15 ± 1**	**29 ± 1**	**43 ± 1**	**57 ± 1**	**71 ± 1**	**85 ± 1**	**99 ± 1**	**113 ± 3**	**141 ± 3**	**169 ± 1**	**182**			
Week					**1**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**21**	**25**	**26**			
Visit	**1**	**2**	**3**		**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**			
Outpatient visit to clinic[t]	X	X	X	X (Optional)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Visit on Day -2 is optional for specific device training
Informed consent	X																		
[redacted]	X																		
[redacted]	X																		
Verify inclusion and exclusion criteria[c]	X			X															Assess and verify prior to randomisation
Fasting by participant 8 hours prior to outpatient visit					X							X				X			

Study Period	**Scree-ning**	**Run-in (Days -14 to -1)[a]**			**Treatment**												**E/D ± 7[b]**	**Follow-up (28 days after last dose) ± 3**	**Notes**
Study Day ± Days	**-50 to -15**	**-14**	**-5**	**-2**	**1**	**15 ± 1**	**29 ± 1**	**43 ± 1**	**57 ± 1**	**71 ± 1**	**85 ± 1**	**99 ± 1**	**113 ± 3**	**141 ± 3**	**169 ± 1**	**182**			
Week					**1**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**21**	**25**	**26**			
Visit	**1**	**2**	**3**		**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**			
Diet and exercise advice		X																	
Demographics	X																		
Medical history and comorbid conditions (until first dose)	X	X			X														
Height and BMI calculation	X																		
Concomitant medications	Collected continuously throughout the study																		
Consider insulin/antihyper-glycaemic medication dose adjustments and advise participant of any changes needed						X	X	X	X	X	X	X	X	X	X		X	X	

Study Period	**Scree-ning**	**Run-in (Days -14 to -1)[a]**			**Treatment**											**E/D ± 7[b]**	**Follow-up (28 days after last dose) ± 3**	**Notes**
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Week					**1**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**21**	**25**	**26**			
Visit	**1**	**2**	**3**		**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**			
Remote contact to advise on insulin dose adjustment prior to first dose if required[d]				X															Remote contact on Day -2 or -1, but exceptions allowed (see footnote)
Remote contact 3 days prior to visit for participant reminders[e]												X				X			
Remote contact to participants to obtain AE information, provide any reminders, and discuss insulin use, if applicable					Weekly throughout study														
Safety Assessments																			
AEs	Monitored continuously throughout the study																		
SAEs	Monitored continuously throughout the study																		
Pregnancy test (serum or urine) if applicable	X (serum only)				X			X			X			X		X	X	X	Testing for women of child-

Study Period	**Scree-ning**	**Run-in (Days -14 to -1)[a]**			**Treatment**												**E/D ± 7[b]**	**Follow-up (28 days after last dose) ± 3**	**Notes**
Study Day ± Days	**-50 to -15**	**-14**	**-5**	**-2**	**1**	**15 ± 1**	**29 ± 1**	**43 ± 1**	**57 ± 1**	**71 ± 1**	**85 ± 1**	**99 ± 1**	**113 ± 3**	**141 ± 3**	**169 ± 1**	**182**			
Week					**1**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**21**	**25**	**26**			
Visit	**1**	**2**	**3**		**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**			
																			bearing potential
Full physical examination	X																X		
Abbreviated physical examination			X		X	X	X	X	X	X	X	X	X	X	X	X		X	
Vital signs[f]	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG[g]	X				X	X	X	X	X	X		X		X		X	X	X	
Urinalysis					X			X				X		X		X	X	X	
Safety Blood Tests																			
Haematology and clinical chemistry (including eGFR calculation)	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Calcitonin	X				X							X				X	X	X[h]	
Lactate, lipase, and amylase					X							X				X	X		
C peptide[i]	X				X							X				X			
Efficacy Assessments																			
Body weight[j]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Study Period	**Scree-ning**	**Run-in (Days -14 to -1)[a]**			**Treatment**												**E/D ± 7[b]**	**Follow-up (28 days after last dose) ± 3**	**Notes**
Study Day ± Days	**-50 to -15**	**-14**	**-5**	**-2**	**1**	**15 ± 1**	**29 ± 1**	**43 ± 1**	**57 ± 1**	**71 ± 1**	**85 ± 1**	**99 ± 1**	**113 ± 3**	**141 ± 3**	**169 ± 1**	**182**			
Week					**1**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**21**	**25**	**26**			
Visit	**1**	**2**	**3**		**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**			
Efficacy Blood Tests																			
HbA1c	X				X			X				X		X		X	X	X	
Fasting glucose, lipid profile					X							X				X			
Efficacy Urine Tests																			
UACR[k]	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense urine pots for first morning void urine collection		X	X							X				X					
[redacted]																			
[redacted]					X							X				X	X	X	eGFR calculation using cystatin c
[redacted]					X							X				X			
[redacted]					X							X				X			
[redacted]																			
[redacted]					X							X				X			

Study Period	**Scree-ning**	**Run-in (Days -14 to -1)[a]**			**Treatment**												**E/D ± 7[b]**	**Follow-up (28 days after last dose) ± 3**	**Notes**
Study Day ± Days	**-50 to -15**	**-14**	**-5**	**-2**	[redacted]														
Week					[redacted]														
[redacted]	[redacted]				[redacted]														
[redacted]					[redacted]														
Pharmacokinetics and Immunogenicity																			
[redacted]					X	X	X		X	X	X			X		X	X		Not collected from participants randomised to semaglutide
[redacted]					X	X	X		X	X	X			X		X	X	X[m]	Not collected from participants randomised to semaglutide
[redacted]																			
[redacted]		X (Days -14 to -1)														X D175 - 182			
[redacted]		X (Days -14 to -1)										X				X D17			

Study Period	Scree-ning	Run-in (Days -14 to -1)[a]			Treatment											E/D ± 7[b]	Follow-up (28 days after last dose) ± 3	Notes
Study Day ± Days	-50 to -15	-14	-5	-2	1	15 ± 1	29 ± 1	43 ± 1	57 ± 1	71 ± 1	85 ± 1	99 ± 1	113 ± 3	141 ± 3	169 ± 1	182			
Week					1	3	5	7	9	11	13	15	17	21	25	26			
Visit	1	2	3		4	5	6	7	8	9	10	11	12	13	14	15			
												D 84 - 99				5-182			
[redacted]		X (Days -14 to -1)										X				X			Visit 11 and 15 ABPM assessments are for 300 and 600 µg arms only
[redacted]		X										X							Pro™ or Flash™ device as appropriate
[redacted]		X			X	X	X	X	X	X	X				X	X			
[redacted]												X	X	X					
[redacted]		X																	

Study Period	**Scree-ning**	**Run-in (Days -14 to -1)[a]**			**Treatment**												**E/D ± 7[b]**	**Follow-up (28 days after last dose) ± 3**	**Notes**
Study Day ± Days	**-50 to -15**	**-14**	**-5**	**-2**	**1**	**15 ± 1**	**29 ± 1**	**43 ± 1**	**57 ± 1**	**71 ± 1**	**85 ± 1**	**99 ± 1**	**113 ± 3**	**141 ± 3**	**169 ± 1**	**182**			
Week					**1**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**21**	**25**	**26**			
Visit	**1**	**2**	**3**		**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**			
[redacted]																			
[redacted]				X	X														At investigator's discretion and per site resources, a saline injection technique for training may be used
Study Intervention (IP) Administration and Randomisation																			
Randomisation[s]				X															
Dispense cotadutide/placebo					X	X	X	X	X	X	X	X	X	X	X				
Dispense semaglutide					X		X		X		X		X	X	X				
Cotadutide/placebo administration in clinic					X	X		X	X	X		X	X		X	X[q]			
Daily cotadutide/placebo administration					Once daily SC administration														

Study Period	Scree-ning	Run-in (Days -14 to -1)[a]			Treatment												E/D ± 7[b]	Follow-up (28 days after last dose) ± 3	Notes
Study Day ± Days	-50 to -15	-14	-5	-2	1	15 ± 1	29 ± 1	43 ± 1	57 ± 1	71 ± 1	85 ± 1	99 ± 1	113 ± 3	141 ± 3	169 ± 1	182			
Week					1	3	5	7	9	11	13	15	17	21	25	26			
Visit	1	2	3		4	5	6	7	8	9	10	11	12	13	14	15			
[redacted]						X													
[redacted]						X		X	X										
[redacted]						X		X	X	X									
[redacted]					X		X	X	X										
[redacted]					Weekly SC administration														
[redacted]							X		X										
[redacted]																			
[redacted]		X										X				X		X	

Additional details on study design are provided in the study protocol.

1.3 Number of participants

Approximately 563 participants will be screened/enrolled to achieve 225 participants randomly assigned to study intervention (IP) and 180 participants who complete study treatments.

The sample size was determined to provide 90% power to detect 40% relative reduction in UACR for cotadutide versus placebo, with two-sided type I error rate of 0.05 and standard deviation of 0.74 and an estimated treatment discontinuation rate of 20%.

Participants may be rescreened once if, in the opinion of the investigator, there is a reason to believe they may be eligible. Repeat screenings may be considered at any time prior to randomisation and in particular, although not limited to, for reasons related to the COVID-19 pandemic i.e. lack of available kits, local lockdowns and imposed quarantines.

2 ANALYSIS SETS

2.1 Definition of analysis sets

In Table 6 here below are reported all the analyses sets.

Table 6 Populations for Analysis

Population/Analysis Set	Description
All enrolled participants	All enrolled participants who have signed the informed consent form will be included in the all enrolled population and will be analysed according to the randomised treatment group. Participants who fail screening and were not rescreened will not be randomised but will also be included in all enrolled population. Rescreened participants will be analysed according to the latest enrolment code only.
As-treated population	The as-treated population includes all enrolled participants who are randomised and have received any study intervention (at least one dose of study IP). As-treated population will be analysed according to the actual treatment received. In the rare instance when the open-label active comparator semaglutide is administered in error in a participant assigned to placebo/cotadutide, the actual treatment assignment will be discussed case by case by an unblinded study team at interim safety review and the final analysis. For all other cases to determine the actual treatment for a participant, the general rule is that if a participant receives placebo as well as active

Population/Analysis Set	Description
	treatments then this participant's actual treatment will be chosen from the active treatments only. 1. If only placebo kits are delivered to the participant, then the actual arm will be set to placebo. 2. If only cotadutide kits are delivered to the participant, then: • If the maximum dose is lower or equal to 100 µg, the actual arm will be set to cotadutide 100 µg; • if the maximum dose is > 100 but ≤ 300 µg, the actual arm will be set to cotadutide 300 µg; • if the maximum dose is greater to 300 µg, the actual arm will be set to cotadutide 600 µg. 3. If the participant was provided both with cotadutide and placebo kits, then: • If the participant is received to cotadutide 100 µg, cotadutide 300 µg or cotadutide 600 µg groups, the actual arm is assigned as described in point 2 above. • If the participant is randomised to placebo group and received cotadutide kits in more than one delivery visit, the cotadutide actual arm will be evaluated case by case, looking to the reported doses and, in case needed, raising queries to the involved personnel. • If the participant is randomised to placebo group and received cotadutide kits in only one delivery visit, then – if the first dose following or on the wrong kit delivery date is lower or equal to 100 µg, the actual arm will be set to cotadutide 100 µg; – if the first dose following or on the wrong kit delivery date is > 100 but ≤ 300 µg, the actual arm will be set to cotadutide 300 µg; – if the first dose following or on the wrong kit delivery date is greater to 300 µg, the actual arm will be set to cotadutide 600 µg.
ITT population	Randomised participants included in the ITT population will be analysed according to the intervention (IP) they were randomised to.
PP population	The PP population includes all enrolled participants who are randomised and have received at least one dose of study IP except for participants who have discontinued the study IP and those with relevant IPD. Relevant IPDs are those that have the potential to affect the result of the primary efficacy results and are reported in Section 2.2. List of participants to be excluded from the PP population will be also discussed and agreed with the blinded study team in a dedicated meeting prior to database lock. PP population is analysed according to the randomised treatment group.

Population/Analysis Set	Description
PK population	Randomised participants who have at least one measurable (above LLOQ) plasma concentration time point of cotadutide will be included in the PK population. Participants will be analysed according to the treatment that they actually received. However, only samples taken from patients planned to receive cotadutide/placebo and actually received cotadutide are analysed.
Immunogenicity population	Participants in the As-treated population who have at least one serum sample for immunogenicity testing will be included in the Immunogenicity population. Immunogenicity population will be analysed according to the actual treatment received.

IPD = important protocol deviation; ITT = intent-to-treat; PP = per-protocol.

2.2 Violations and deviations

The list of important protocol deviations (IPDs) is provided in the Project Specific Protocol Deviation List. Relevant IPD that lead to participant exclusion from the PP population are a subset of all IPDs sub selected manually during IPD review meetings. Some specific groups of relevant IPDs:

- Initiation of an SGLT2 inhibitors after screening should lead to exclusion of a participant from analysis in the PP population for any UACR related endpoint.
- Participants who were randomized and consequently inclusion/exclusion criteria were identified (randomized by mistake).
- Participants who have been taking several treatments (for example placebo and cotadutide) by mistake.
- Participants who were randomised in the wrong stratification factors
- Participants having one or less UACR samples available for each separate visit: Baseline (Day -5, Day -4, Day -3, Day -2, Day 1 predose) or Week 15 (Day 97, Day 98, Day 99).
- Participants who switched permanently (i.e. the investigator was not intending to further titrate the dose) to a different dose level in comparison to what the participant was randomised to: for example, a participant who permanently switched to 0.5 mg semaglutide from 1 mg or a participant randomised to the 600 µg cota/placebo arm who was permanently switched to 300 µg.

3 BASELINE, EFFICACY AND SAFETY EVALUATION

3.1 General principles

3.1.1 Handling of missing data

Missing data are not replaced unless otherwise specified for statistical modelling. Only date of first and last dose of IP, AE start and end date and concomitant medications end date are imputed. Imputation rules are reported below.

3.1.1.1 Imputation of date of first dose of IP

Date and time of first dose of IP are mandatory eCRF fields. No Imputations are expected. In the rare cases of missing date, the date of first dose of IP will be imputed if all the following criteria are met:

- There is a completely missing or partial missing date for the first dose of IP, and
- There is at least one kit for which the amount of drug dispensed does not equal the amount of drug returned, and
- The kits for which the amount of drug dispensed does not equal the amount of drug returned have complete non-missing dispensed date

If that is the case, the date of first dose of IP is imputed with the earliest dispensed date from kits for which amount of drug dispensed does not equal the amount of drug returned. Completely missing time and time where only hour is missing is imputed to 00:00. If only minutes are missing, then it will be imputed to HH:00.

3.1.1.2 Imputation of date of last dose of IP

Last dose date and time are mandatory eCRF fields. No Imputations are expected. In the rare cases of missing date, the last dose date of study drug is imputed if all the following criteria are met:

- There is a completely missing or partial missing date for the last dose of study drug, and
- There is at least one kit for which the amount of drug dispensed does not equal the amount of drug returned, and
- The kits for which the amount of drug dispensed does not equal the amount of drug returned have complete non-missing returned date.

If that is the case, last dose date of study drug is imputed with the latest returned date from kits for which amount of drug dispensed does not equal the amount of drug returned. Missing time is not replaced.

3.1.1.3 Imputation of AE end date

Completely missing AE end dates are not imputed. Partial missing AE end dates are imputed as below:

- If the AE is ongoing, the end date is stated to missing.
- If the AE is not ongoing, and if only the day is missing: Assume the last day of the month of collection.
- If the AE is not ongoing, and both, the day and the month are missing: Assume 31-DEC of the collected year.

After applying these rules, if the imputed AE end date is after the end of study date, the AE is set to ongoing and the AE end date to missing.

3.1.1.4 Imputation of AE start date

Before to proceed with the AE start date imputation, the first dose of IP and the AE end date are imputed as described in the previous section.

Only partial AE start dates are imputed; Dates which are completely missing are not imputed. Partial dates are imputed as described below:

If the day is missing and

- If the month and/or year are different from the month and year of the first dose of IP, then assume 01-MMM-YYYY.
- If the month and year are the same as the first dose of IP month and year and
  - The end date is on or after (including ongoing / missing) the first dose of IP, then assume the date of the first dose of IP.
  - The end date is prior to the first dose of IP, then assume the end date.

If the day and the month are missing and

- If the year is different from the year of first dose of IP, then assume 01-JAN-YYYY of the collected year.
- If the year is the same as the first dose of IP year and
  - The end date is on or after (including ongoing / missing) the first dose of IP, then assume the date of the first dose of IP.
  - The end date is prior to the first dose of IP, then assume the end date.

After applying these rules, if the imputed AE start date is after a complete AE end date then assume the same date as the complete AE end date; if the end date is missing and the imputed AE start date is after the end of study date then assume the same date as the study end date.

3.1.1.5 Imputation of concomitant medication end date

Completely missing concomitant medication end dates are not imputed except for insulin where completely missing end date is replaced by end of study date. Partial missing concomitant medication end dates are imputed as below:

- If the concomitant medication is ongoing, the end date is set to missing.
- If the concomitant medication is not ongoing, and if only the day is missing: Assume the last day of the month of collection.
- If the concomitant medication is not ongoing, and both, the day and the month are missing: Assume 31-DEC of the collected year.

After applying these rules, if the imputed concomitant medication is after the end of study date, the concomitant medication is set to ongoing and the concomitant medication end date to missing.

3.1.1.6 Imputation of concomitant medication start date

Completely missing concomitant medication start date is not imputed. Partial missing concomitant medication start dates are imputed as below:

- If a medication start date has a valid year and an unknown month and day, the 1st of January will be used.

- If a medication start date has a valid year and month and an unknown day, the 1st of Month will be used.

3.1.1.7 Imputation of dates of birth

Completely missing dates of birth are not imputed. If the day of birth is missing it will be replaced with 1st. If the month of birth is missing it will be replaced with Jan. Imputed dates of birth will be used only for NFS calculation. To be noted that the age at screening is not calculated based on day of birth but reported as collected in the raw data.

3.1.2 Analysis visit windows

For the purpose of the statistical analysis, efficacy and safety variables (Sections 3.2 and 3.3), except the CGM, UACR consecutive samples (Baseline, Week 15 and Week 26), Echocardiography-determined parameters of cardiac function parameters, PK and adverse event, are allocated to the analysis visit as reported in the tables below. The allocation to analysis visit windows is performed after the imputation of date of first and last doses of IP as in Section 3.1.1. Measurements with missing or partially missing dates cannot be imputed to any analysis visit. For participants randomized not treated, the date of randomization will be used to define analysis visit windows instead of date of first dose of IP.

Table 7 Analysis visit windows

Analysis visit (AVISIT)[a]	Scheduled visit day	Visit Window (Days)
Pre-treatment	From -50 to 1	<= 1[b]
Day 1	1	1[c]
Week 3	15	13 – 17
Week 5	29	27 – 31
Week 7	43	41 – 45
Week 9	57	55 – 59
Week 11	71	69 – 73
Week 13	85	83 – 87
Week 15	99	97 – 101
Week 17	113	109 – 117
Week 21	141	137 – 145
Week 25	169	167 – 171
Week 26	182	180 – 184
Follow-up	210	206 – 214

[a] If the participant had an event of early discontinuation of study intervention before Week 26 (end of treatment CRF visit) or withdrawal from study (end of study CRF visit), all the visits (except CRF E/D and E/D Follow up visits – see Table 8) at and after this date will be marked as early discontinued. For example, if participant had an E/D event at day 120, he will have following "Early discontinuation" visits: Early discontinuation

Week 21, Early discontinuation Week 25 etc instead of regular Week X. The same rule is applicable to unscheduled analysis visits in the Table 8. These visits will not be displayed in tables and figures for analysis purposes and will be displayed in listings only.

[b] Includes all measurements collected before or on day 1 prior to first dose of IP. For height, weight, BMI, echocardiography and ADA if the measurement is collected on day 1 is always considered collected before the first dose of IP.

[c] Includes all measurements collected at day 1 on or after the first dose of IP.

After having assigned the analysis visit windows as described above, if there are measurements which have not yet the analysis visit assigned, they are labelled as reported in the table below.

[redacted]

For UACR assessments based in consecutive samples at baseline nominal visits from external vendor's data will be used, at Week 15 and Week 26 analysis visit windows will be used but prioritize nominal visit. Otherwise, only analysis visit windows will be used.

[redacted]

Table 8 Unscheduled analysis visit windows

Analysis visit (AVISIT)[a]	**Visit Window (Days)**
Early discontinuation[b]	CRF visit
E/D Follow-up[c]	CRF visit
UNSCH 1.xxx	2 – 12
UNSCH 3.xxx	18 – 26
UNSCH 5.xxx	32 – 40
UNSCH 7.xxx	46 – 54
UNSCH 9.xxx	60 – 68
UNSCH 11.xxx	74 – 82
UNSCH 13.xxx	88 – 96
UNSCH 15.xxx	102 – 108
UNSCH 17.xxx	118 – 136
UNSCH 21.xxx	146 – 166
UNSCH 25.xxx	172 – 179
UNSCH 26.xxx	185 – 205

Analysis visit (AVISIT)[a]	Visit Window (Days)
UNSCH Follow-up xxx	>214

[a] If the participant had an event of early discontinuation of study intervention before Week 26 (end of treatment CRF visit) or withdrawal from study (end of study CRF visit), all the visits (except CRF E/D and E/D Follow up visits) at and after this date will be marked as early discontinued. For example, if participant had an E/D event at day 110, he will have following "Early discontinuation" visits: Early discontinuation UNSCH 17.001, Early discontinuation UNSCH 21.001 etc instead of UNSCH X.Y. These visits will not be displayed in tables and figures for analysis purposes and will be displayed in listings only.

[b] Early discontinuation is used only for participants who discontinue the study IP before visit at Week 26 or withdrawn from study. If a measurement falls within the Early discontinuation analysis visit, then cannot be assigned to any other analysis visit.

[c] Early discontinuation follow-up analysis visit (E/D Follow-up) is used only for participants who discontinue the study before Week 26 or withdrawn from study. If a measurement falls within the E/D Follow-up analysis visit, then cannot be assigned to any other unscheduled analysis visit.

The unscheduled analysis visits will be numbered sequentially with an increment of 0.001. For example, if two measurements are done during the unscheduled analysis visits that occur between visit Week 5 and visit Week 7, then these unscheduled analysis visits will be numbered UNSCH 5.001 and UNSCH 5.002 in the order they occurred. The unscheduled analysis visits are not summarised in tables but only presented in listings. Unscheduled measurements will however be used to derive overall ADAs as well as Laboratory evaluations and vital signs maximum/minimum values on treatment, ECG last observation on treatment and QTcF any observation on treatment.

In general, for efficacy endpoints the last observed measurement prior to randomisation will be considered the baseline measurement. However, if an evaluable assessment is only available after randomisation but before the first dose of randomised treatment then this assessment will be used as baseline. Same definition will be used for baseline variables. For CGM baseline derivations see Section 3.3.1.3.

For safety endpoints and immunogenicity the last observation before the first dose of study treatment will be considered the baseline measurement unless otherwise specified.

For assessments on the day of first dose where time is not captured, a nominal predose indicator, if available, will serve as sufficient evidence that the assessment occurred prior to the first dose. Assessments on the day of the first dose where neither time nor a nominal predose indicator are captured will be considered prior to the first dose if such procedures are required by the protocol to be conducted before the first dose. This means that for height, weight, BMI, Echocardiography-determined parameters of cardiac function parameters and ADA if the measurement is collected on day 1 is always considered collected before the first dose of IP.

In the scenarios where there are two nominal predose assessments on the Day 1, one with time recorded and the other without time recorded, the one with time recorded would be selected as baseline. If multiple visits are equally eligible to assess patient status at baseline (e.g., screening and baseline assessments both on the same date prior to first dose/administration with no

washout or other intervention in the screening period), the average (the arithmetic mean for variables assumed to be normally distributed, the geometric mean for variables assumed to be distributed log-normally and the median for non-parametric distributed variables) can be taken as a baseline value. For geometric mean calculation, variable records with zero value will be imputed by half of the minimum of the non-zero records prior to the log transformation (see section 4.1 for imputation rule details). For non-numeric laboratory tests (e.g., some of urinalysis parameters) where taking an average is not possible then the best value would be taken as baseline as this is the most conservative. For example, for ECGs, if there is a tie in the overall ECG evaluation results at baseline, the baseline value will be the best value. If no value exists before the first dose/administration, then the baseline value will be treated as missing.

All other equally eligible measurements will also be presented in listings as baseline but not for analysis purpose.

For all the other analysis visit windows if more than one measurement of the variable (with no regard for the value being measured during a scheduled or an unscheduled CRF visit) falls in the same analysis visit window but in different days, the nearest to the scheduled visit day will be taken. If several measurements are collected within the same distance from the scheduled visit day, the data of the latest visit after the scheduled visit day within that window will be used. If several measurements are collected during the selected day the analysed value will be:

- the arithmetic mean for variables assumed to be normally distributed,
- the geometric mean for variables assumed to be log-normally distributed. For geometric mean calculation, variable records with zero value will be imputed by half of the minimum of the non-zero records prior to the log transformation (see section 4.1for imputation rule details).
- the median for the variables assumed with non-parametric distribution,
- the worst case for categorical values. If there are several categorical values corresponding to the worst case, then the last measurement registered in CRF/by external vendor will be taken.

This rule will apply to all data, except vital signs, ECG, PK and UACR. For vital signs, ECG, and PK, analyses are performed by visit and timepoint separately (predose and 4 hours postdose). For all predose measurements, if time of IP intake and time of measurement are captured and indicates that measurement was not done as per protocol (i.e after dosing) the measurement will be presented in a separate row of post-dose to differentiate from protocol-compliance measurements. For three consecutive urine samples related to UACR see the rules in Section 3.3.1.1. Time points will be assigned according to external vendor data if available.

All other measurement falling in the same analysis visit window will also be presented in listings as baseline but not for analysis purpose.

3.1.3 Study phase windows

For the purpose of the statistical analysis, efficacy and safety variables (Sections 3.2 and 3.3) are allocated to the study phase in which they are collected as reported below. The allocation to the study phases (Table 9) is performed after the imputation of date of first and last doses of IP as in Section 3.1.1. The allocation of the AEs to the study phases is performed after the imputation of AE start and AE end dates as described in Section 3.1.1.

Table 9 Study phases

Study phase	Phase Window for Analysis (Days)
Pre-treatment	before first dose of study IP (day ≤ 1[a])
On-treatment	from day 1[b] to day[c] of last dose of IP (included)
Follow-up	> day[c] of last dose of IP (not included)

[a] Includes all measurements collected before first dose of IP. If the measurement is collected on the day of first dose of IP but the time of collection (or the planned time point) cannot determine if the measurement was before or after first dose of IP, then it will be considered as collected after first dose of IP except for height, weight, BMI, ADA and Echocardiography, where any Day 1 measurements are always considered pre-dose.

[b] Includes all measurements collected on the day of first dose of IP (day andtime of IP intake when time is collected) and after.

[c] Daytime when time is collected.

3.2 Baseline assessments and other participant-specific characteristics

Demographic and participant characteristics and medical history are collected pre-treatment as per Section 1.2.5.

3.2.1 Demographic and participant characteristics

Demographic and participant characteristics include:

- Age (years), age group (< 50; >= 50 – < 65; >= 65 years);
- Sex, race, ethnicity, country;
- Height (cm), weight (kg), weight group (< 70; >= 70 – < 90; >= 90 kg);
- BMI (kg/m2), BMI group (<= 35 kg/m2; > 35 kg/m2);
- Participant at sites in Japan/ Participant at sites not in Japan;
- Use of sodium-glucose cotransporter-2 (SGLT-2) inhibitor therapy at screening

Age is the age at screening as reported in the eCRF. BMI (kg/m2) is calculated as: weight (kg) divided by the square of height (cm/100).

Height, weight and BMI are allocated to the concerning analysis visits as per Section 3.1.2. For weight, if the measurement is collected on day (and potentially could have predose or 4 hours post-dose time point), only one measurement with no time point and any available date should

be kept. Evaluations with missing or partially missing dates cannot be imputed to any analysis visit. Only baseline values are included in the demographic and participant characteristics.

3.2.2 Medical history

Medical history includes all medical history (allowed and disallowed), CKD diagnosis and diabetes history. All medical history and diabetes history are coded in Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or higher.

CKD diagnosis includes the following terms:

- Cystic Kidney Disease
- Ischaemic/Hypertensive Nephropathy
- Chronic Glomerulonephritis:
    - IgA Nephropathy
    - Focal Segmental Glomerulosclerosis (FSGS)
    - Membranous Nephropathy
    - Minimal Change
    - Lupus Nephritis
    - Other Primary or Secondary Glomerulonephritis
- Renal Artery Stenosis
- Chronic Pyelonephritis (Infectious)
- Chronic Interstitial Nephritis
- Obstructive Nephropathy
- Diabetic Kidney Disease
- Unknown
- Other

Collection of diabetes history for Type II diabetes mellitus also includes the date of first diagnosis of diabetes mellitus (duration in years will be based on this date) and any complications observed:

- Retinopathy
- Neuropathy autonomic
- Neuropathy peripheral
- Nephropathy
- Angiopathy
- Other

3.3 Efficacy and safety variables

The primary efficacy objective and some of the secondary and exploratory efficacy objectives of the study refer to the UACR for cotadutide compared to placebo.

Other secondary and exploratory efficacy objectives of the study refer to the following variables:

- HbA1c and fasting glucose;
- Glucose level as measured by continuous glucose monitoring (CGM);
- Body weight;
- Immunogenicity profile.

Safety objectives are on the following variables:

- AEs;
- Clinical laboratory assessment;
- Vital signs (temperature, RR);
- ECG.

Both, efficacy and safety endpoints are collected as reported in Section 1.2.5. Most of assessments will be tested in centralised external laboratories. Body weight, vital signs, ECG, AEs and insulin dose will be collected by investigators at sites and entered in eCRF.

3.3.1 Efficacy endpoints

Efficacy endpoints are:

- UACR (including UACR, urine albumin and creatinine);
- HbA1c and fasting glucose;
- Glucose level as measured by CGM;
- Body weight;
- Immunogenicity profile;
- Pharmacokinetic parameters;
- Vital signs (blood pressure, pulse rate, RPP);

In the following section are reported all the details related to the efficacy endpoints.

3.3.1.1 UACR

Urine albumin to creatinine ratio (UACR), urinary creatinine and urine albumin are collected as per Section 1.2.5. Urine albumin to creatinine ratio (UACR), urinary creatinine and urine albumin are allocated to the concerning analysis visits as per Section 3.1.2. Evaluations with missing or partially missing dates cannot be imputed to any analysis visit.

Urine albumin to creatinine ratio (milligrams of albumin per grams of creatinine) will be assessed by a central laboratory. Urine samples collected for assessment of UACR and exploratory biomarkers must not be confused with urinalysis samples collected at the study site during visits for assessment of safety parameters and pregnancy testing.

Statistical analyses of albuminuria data will be conducted using log transformed UACR values, taking the log-normal distribution of albuminuria into account.

First morning void urine samples are preferable for all collections and are essential for collections undertaken at baseline (Days -5 to -3 and Day 1 predose or Days -4 to -2 and Day 1 predose), Days 97 to 99, and Days 180 to 182 – nominal external vendor's visits will be used.

For baseline, average will be calculated using following records in order of preference:
1) Day -5,-4,-3
2) Day -4,-3,-2
3) Day -5, -3,-2 or Day -5, -4, -2
4) Day -5, -4, 1 or -5,-3, 1, Day -5,-2, 1
5) Day -5, 1 (or any other combination of 2 baseline samples)
6) Day -5, or -4, or -3 or -2 or 1 (or any other combination of a single baseline sample)

The treatment effect will be calculated based on single, the geometric mean of two or the three urine samples for albuminuria measurements collected before each follow-up visit. In the absence of results from 3 consecutive urine samples, the UACR for a time point will be calculated based on the available results. If a participant has forgotten to collect 1 or more of the samples before a visit, then the samples should be collected up to 3 consecutive days following the visit instead (with exception for the predose urine samples, which must be collected before investigational product is received). At all other visits, a single sample may be taken at the site or may be brought from home.

Urinary creatinine and urine albumin below the LLOQ for which the exact value cannot be determined, will be replaced with the LLOQ divided by the squared root of 2.

After the LLOQ replacement on every single sample result (prior to parameter derivation), change from baseline and percent change from baseline are calculated as described in Section 4.1.

3.3.1.2 HbA1c and fasting glucose

HbA1c (%) and fasting glucose (mmol/L) are collected as per Section 1.2.5. HbA1c and fasting glucose are allocated to the concerning analysis visits as per Section 3.1.2. Evaluations with missing or partially missing dates cannot be imputed to any analysis visit.

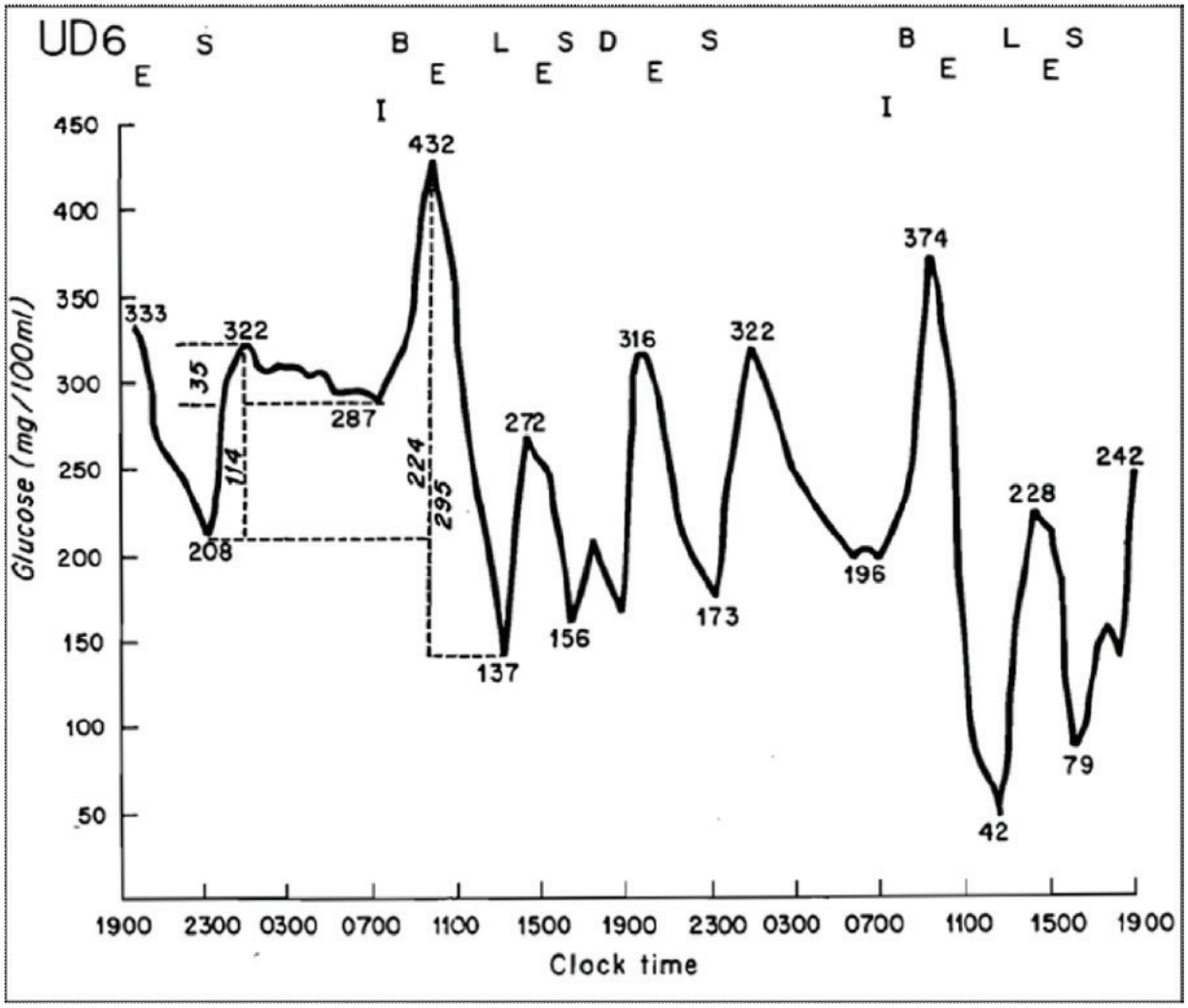
Values below the LLOQ for which the exact value cannot be determined, will be replaced with the LLOQ divided by the squared root of 2.

After the LLOQ replacement, change from baseline and percent change from baseline are defined as described in Section 4.1.

[redacted]

Week 26 (Days 172-181) values.

[redacted]



[redacted]

[redacted]

[redacted]

3.3.1.4 Body weight

Weight (kg) is collected as per Section 1.2.5 and assigned to analysis visits as described in Section 3.1.2. Measurements with missing or partial missing dates are not assigned to any analysis visit.

On day 57 or day 71 weight measurement was done once but have repeated identical values at predose or 4 hours post-dose time point, only one measurement with no time point and any available date should be kept.

Change from baseline and percent change from baseline are calculated as described in Section 4.1.

[redacted]

3.3.1.6 Pharmacokinetic parameters

PK plasma concentration are collected as per Section 1.2.5 for participants randomized to cotadutide/placebo and actually taken cotadutide only.

3.3.1.7 Vital signs (blood pressure, pulse rate)

Vital signs parameters are collected as per Section 1.2.5 and assigned to analysis visits as described in Section 3.1.2. Measurements with missing or partial missing dates are not assigned to any analysis visit.

Vital signs (seated or semi-supine) parameters are:

- SBP (mmHg);
- DBP (mmHg);
- Pulse rate (bpm);
- RPP (mmHg*bpm) – derived variable.

Other vital signs (temperature, RR) will be analysed in safety section.

The RPP is calculated as pulse rate * systolic blood pressure.

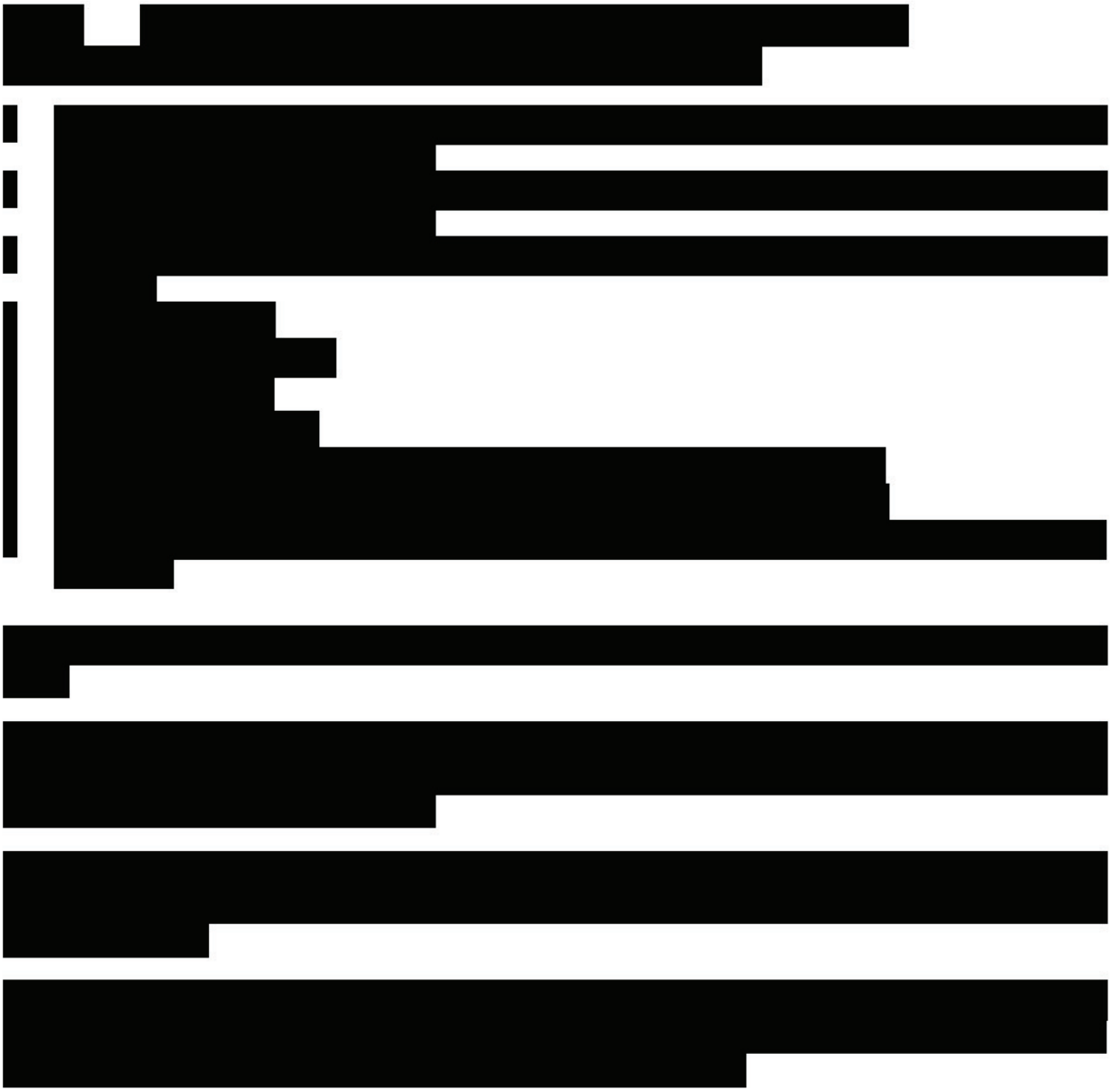
On Days 1, 57, and 71, vital signs should be performed predose and 4 hours post-dose (± 15 minutes). On all other visits only predose visit will be performed.

Change from baseline and percent change from baseline are calculated as described in Section 4.1.

Additionally, vital signs values will be classified as normal (if value is within normal reference range), low (if value is below the normal reference range), and high (if value is above the normal reference range) according to the normal reference ranges (Table 10):

Table 10 Vital signs normal reference ranges

Parameter	Normal Reference Ranges
Systolic blood pressure	80 – 130 mmHg
Diastolic blood pressure	50 – 80 mmHg
Pulse rate	50 – 100 bpm



After the UACR allocation to the concerning analysis visits and LLOQ replacement as per Section 3.3.1.1:

- If UACR at baseline is between 30 and 300 mg/g (including) and at the evaluated visit became greater than 300 mg/g, then the variable worsening microalbuminuria to macroalbuminuria will be Yes
- If UACR at baseline is between 30 and 300 mg/g (including) and at the evaluated visit became lower than 30 mg/g, then the variable improving microalbuminuria to normoalbuminuria will be Yes
- If UACR at baseline is greater than 300 mg/g and at the evaluated visit became lower or equal to 300 mg/g, then the variable improving macroalbuminuria to microalbuminuria or to normoalbuminuria will be Yes

3.3.1.9 Insulin dose adjustment

Insulin intake will be collected by local lab on regular basis. The following parameters will be derived for analysis:

- Total daily insulin dose (units) – calculated by multiplying total dose in units by frequency (eg, dose of 2 units 3 times per day will be resulting in 6 units total daily dose) and adding doses of different insulin preparations (e.g. 6 units of lantus once daily, Novorapid 2 units three times daily will result in a total daily dose of 6 + 2 * 3 = 12 units)
- Total daily insulin dose (units/kg), dividing the total daily dose by the participant's body weight at screening.

Following rules will apply:
If the concomitant medication start date and end date of insulin are on the same day:

- if the frequency is QD use the old dose value. For example, if participant taken 35 units Mane QD with end date 18-Mar-2021 and 30 units with start date 18-Mar-2021 the total daily dose on 17/18/19-Mar-2021 will be 35/35/30 units.
- if the frequency is BID use half of the insulin dose value. For example, if participant taken 18 units Novorapid BID with end date 15-Apr-2021 and 22.5 units Novorapid BID with start date 15-Apr-2021 the total daily dose on 15-Apr-2021 will be 18+22.5 units.
- if the frequency is TID use the old dose value 1 time and the new one 2 times. For example, if participant taken 28 units Mane TID with end date 04-Aug-2021 and 23 units with start date 04-Aug-2021 the total daily dose on 04-Aug-2021 will be 28+23+23 units.

Set the insulin dose to zero on the day after an end date has been entered for an insulin dose if there is no entry for the same type of insulin e.g. Novorapid, Humalog etc at the frequency. For example, If a dose of insulin Listpro 10 units BID has an end date of 28-Apr-2021 and the next insulin listpro has a start date on 14-Sep-2021 with 10 units QD the dose insulin Listpro dose from 29-Apr-2021 to 13-Sep-2021 will be set to zero.

Change from baseline and percent change from baseline are calculated as described in Section 4.1.

3.3.1.10 Markers of liver health (AST, ALT and NFS)

ALT and AST (U/L) are collected as per clinical chemistry Section 1.2.5 and assigned to analysis visits as described in Section 3.1.2. Measurements with missing or partial missing dates are not assigned to any analysis visit.

Values below the LLOQ for which the exact value cannot be determined, will be replaced with the LLOQ divided by the squared root of 2.

ALT and AST will be analysed in both safety and efficacy sections as of different purpose of analysis. However, the values for analyses will be taken from the same clinical chemistry samples.

NFS will be derived using formula:

$$-1.675 + 0.037 * \text{age (years)} + 0.094 * \text{BMI (kg/m2)} + 1.13 * \text{IFG or T2DM (yes = 1, no = 0)} + 0.99 * \text{AAR} - 0.013 * \text{platelets } (10^9/\text{L}) - 0.66 * \text{albumin (g/dL)},$$

where AAR is the AST/ALT ratio, IFG is the impaired fasting glucose and T2DM is the type 2 diabetes mellitus. If IFG and T2DM are not recorded in medical history, if baseline HbA1c is greater than 6.5% or if baseline fasting glucose = 100 – 125 mg/dL then impaired fasting glucose/diabetes should be considered equal Yes, otherwise should be considered equal No. Albumin is taken from Serum.

Age (years) for NFS is calculated as Age at baseline ((date inform consent signed – date of birth + 1)/365.25) and then rounded to 2 decimal places. If only year or month and year will be available, day will be replaced by 1 and month by January.

BMI are allocated to the concerning analysis visits as per Section 3.1.2. The AST, ALT, platelet, albumin and BMI will be taken at the corresponding visit, in case of any missing value, LOCF imputation (a missing endpoint will be replaced with the last available scheduled post-baseline measurement prior to the missing endpoint) will be applied by parameter.

Change from baseline and percent change from baseline are calculated as described in Section 4.1.

3.3.1.11 Fasting lipid profile

Lipid profile parameters are collected as per Section 1.2.5 and assigned to analysis visits as described in Section 3.1.2. Measurements with missing or partial missing dates are not assigned to any analysis visit.

Values below the LLOQ for which the exact value cannot be determined, will be replaced with the LLOQ divided by the squared root of 2.

Lipid profile parameters are:

- Total cholesterol (mmol/L);
- HDL (mmol/L);
- LDL (mmol/L);
- total cholesterol to HDL ratio – derived variable;
- triglyceride levels (mmol/L).

Change from baseline and percent change from baseline are calculated as described Section 4.1.

[redacted]

Table 11 ABPM acceptable ranges

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

(washing or dressing), moderate problems with doing usual activities, severe pain or discomfort and extreme anxiety or depression.

Change from baseline and percent change from baseline are calculated as described Section 4.1.

3.3.2 Safety endpoints

3.3.2.1 Adverse events

An AE is the development of any untoward medical occurrence in a participant or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered. SAEs will be collected from time of signature of informed consent, throughout the treatment period and including the follow-up period. All non-serious AEs will be recorded from time of first dose of IP, throughout the treatment period and including the follow-up period. AEs will be coded with MedDRA version 24.0 or later. For any additional details on AE reporting please refer to the study protocol.

The AEs are assigned to the study phases described in Section 3.1.3, based on the AE start date and time as follows:

If both the start date and start time of an AE are known, then:

- If the AE start datetime is before the first dose of IP datetime, then the AE is assigned to the pre-treatment phase.
- If the AE start datetime is on or after the first dose of IP datetime through the last dose of IP date (inclusive), then the AE is assigned to the on-treatment phase,
- If the AE start date is after the last dose of IP date, then the AE is assigned to the follow-up phase.

If only the start date of an AE is known, and the start time of the AE is unknown, then:

- If the AE start date is before the first dose of IP date, then the AE is assigned to the pre-treatment phase,
- If the AE start date is on or after the first dose of IP date through the last dose of IP date (inclusive), then the AE is assigned to the on-treatment phase,
- If the AE start date if after the last dose of IP date, then the AE is assigned to the follow-up phase.

If the start date of an AE is completely missing, the AE is assigned as follow:

- If the AE end date is known and is before the first dose of IP date, then the AE is assigned to the pre-treatment phase,
- If the AE end date is completely missing or if the AE end date is on or after the first dose of IP date no assignation can be done.

The study day of start of the AE is calculated as the start date of the AE minus date of the first dose of IP +1 for AE started on or after day 1 and as the start date of the AE minus date of the first dose of IP for AE started before day 1. Study day of start of AE is calculated for complete date only. Imputed dates should not be used. If one of the dates is missing or partially missing, the study day of start of the AE is missing.

All the AEs in the on-treatment phase are considered treatment emergent adverse events (TEAEs).

The duration of AE in days is calculated as the end date of the AE minus start date of the AE +1. Duration is calculated for complete date only. Imputed dates should not be used. If one of the dates is missing or partially missing, the duration is missing.

3.3.2.2 Laboratory evaluations

Clinical laboratory safety parameters are collected as per Section 1.2.5. Measurements with missing or partial missing dates are not assigned to any analysis visit.

Clinical laboratory safety tests are performed in a central clinical laboratory.

Table 13 Laboratory safety variables

Haematology (Whole Blood)	**Clinical Chemistry (Serum or Plasma)**	**Urinalysis** (dipstick)
B-Haemoglobin	S/P-Bilirubin, total (TBL)	U-Hb/Erythrocytes/Blood (qualitative)
B-Leukocyte count	S/P-Alkaline phosphatase (ALP)	U-Glucose (qualitative)
B-Leukocyte absolute count: neutrophils, lymphocytes, monocytes, eosinophils, basophils	S/P-Aspartate transaminase (AST)	U-pH (quantitative)
B-Platelet count	S/P-Alanine transaminase (ALT)	U-Bilirubin (qualitative)
B-Haematocrit	S/P-Albumin	U-Ketones (qualitative)
B- Red blood cell	S/P-Potassium	U-Urobilinogen (qualitative)
B-Mean corpuscular volume	S/P-Calcium, total	U-Nitrite (qualitative)
B-Mean corpuscular haemoglobin concentration	S/P-Sodium	U-Leukocyte esterase (qualitative)
	S/P Glucose	U-Protein (qualitative)
	S/P-Bicarbonate	U-Specific gravity (quantitative)
	S/P- Blood urea nitrogen	U-Color (qualitative)
	S/P-Phosphate	U-Appearance (qualitative)
	S/P-Creatinine	U-Microscopy (casts only)
	S/P-Magnesium	
	S/P-Beta-hydroxybutyrate	

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; Hb = haemoglobin; TBL = total bilirubin; U = urinalysis; WBC = white blood cell

ALT and AST will be analysed in both safety and efficacy sections as of different purpose of analysis. However, the values for analyses will be taken from the same clinical chemistry samples.

Additionally the following other safety assessments will be collected as per Section 1.2.5:

- Calcitonin;
- Lactate;
- Lipase;
- Amylase;
- C peptide levels.

Laboratory data are assigned to the analysis visits and the study phases as described in Section 3.1.2 and Section 3.1.3 respectively. Evaluations with missing or partially missing dates cannot be imputed to any study phase and analysis visit.

Quantitative parameters for laboratory test results below the lower limit of quantification (LLOQ) for which the exact value cannot be determined, will be replaced with the LLOQ divided by the squared root of 2.

After the LLOQ replacement, change from baseline to each post-baseline visit for quantitative parameters is defined as the post-baseline visit value minus the baseline visit value.

After the LLOQ replacement, quantitative parameters will also be classified as normal (if value is within normal reference range), low (if value is below the normal reference range), and high (if value is above the normal reference range) based on the reference range indicator.

After the LLOQ replacement, AST, ALT, and total bilirubin will also be classified as below:

AST and ALT:

- < 3xULN (or below the LLOQ)
- ≥ 3 – < 5xULN
- ≥ 5 – < 8xULN
- ≥ 8xULN

Total bilirubin:

- < 2xULN (or below the LLOQ)
- ≥ 2xULN

Occurrences of AST or ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN might be reported as SAE (Potential Hy´s law) as described in the study protocol.

3.3.2.3 Vital signs

Vital signs parameters are collected as per Section 1.2.5 and assigned to analysis visits as described in Section 3.1.2. Measurements with missing or partial missing dates are not assigned to any analysis visit.

Vital signs include:

- Systolic blood pressure (mmHg);
- Diastolic blood pressure (mmHg);
- Pulse rate (bpm);
- RPP (mmHg*bpm) – derived variable;
- Respiratory rate (breaths per minute);
- Temperature (C).

On Days 1, 57, and 71, vital signs should be performed predose and 4 hours postdose (± 15 minutes). On all other visits only predose visit will be performed.

Change from baseline is defined as the post-baseline visit value minus the baseline value.

Additionally, vital signs values will be classified as normal (if value is within normal reference range), low (if value is below the normal reference range), and high (if value is above the normal reference range) according to the normal reference ranges (Table 14):

Table 14 Vital signs normal reference ranges

Parameter	Normal Reference Ranges
Systolic blood pressure	80 – 130 mmHg
Diastolic blood pressure	50 – 80 mmHg
Pulse rate	50 – 100 bpm
Respiratory rate	12 – 24 breaths per minute
Temperature	<= 37°C

3.3.2.4 dECGs

dECG evaluation includes:

- PR interval (msec)
- QRS duration (msec)
- QT interval (msec)
- Heart rate (beats/min)
- QTcB interval (msec)
- QTcF interval (msec)
- Overall evaluation (normal, abnormal – only data from external vendor will be used)

dECG parameters are collected as per Section 1.2.5 and assigned to analysis visits and study phases as described in Section 3.1.2 and Section 3.1.3 respectively. Evaluations with missing or partially missing dates cannot be imputed to any study phase and analysis visit.

On Days 1, 57, and 71, dECG should be performed predose and 4 hours postdose (± 15 minutes). On all other visits only predose visit will be performed.

dECG last observation on treatment is defined as last available value among those in the on-treatment study phase.

Change from baseline is defined as the post-baseline visit value minus the baseline value.

Additionally, dECG values will be classified as normal (if value is within normal reference range), low (if value is below the normal reference range), and high (if value is above the normal reference range) according to the below normal reference ranges:

Table 15 dECG normal reference ranges

Parameter	Normal Reference Ranges
PR interval	110 – 220 msec
QRS duration	75 – 115 msec
QT interval	320 – 450 msec
Heart rate	50 – 100 beats/min
QTcB interval	320 – 450 msec
QTcF interval	320 – 450 msec

QTcF intervals will also be classified as:

- > 450 msec
- > 480 msec
- > 500 msec

QTcF increases with respect to baseline will be classified as:

- > 30 msec
- > 60 msec
- > 90 msec

3.3.2.5 Ambulatory blood pressure monitoring (ABPM)

ABPM parameters (complete, night and day: SBP (mmHg), DBP (mmHg), heart rate (bpm) and RPP) are collected as per Section 1.2.5 using the ABPM device and assigned to analysis visits as described in Section 3.1.2. Measurements with missing or partial missing dates are not assigned to any analysis visit.

ABPM parameter calculation are described in section 3.3.1.12.

3.4 Exposure and treatment compliance

As per study protocol, participants start the SC injections of the study IP at day 1.

The following visits are assigned for administration in clinic:

- Cotadutide/placebo: Week 1, Week 3, Week 7, Week 9, Week 11, Week 15, Week 17, Week 25, Week 26.
- Semaglutide: Week 1, Week 5, Week 7, Week 9.

From day 1 to day 7 (included) the injections are performed at the study site. Starting from day 8, study IP is dispensed to the participant for self-administration at home. Dispensation visits will be performed on demand.

At the dispensation visits the site provide the participant with the number of pens required from the current visit (included) and up to the next visits (excluded) considering that the participants should self-inject the required dose per day. Prefilled pens contain 3000 uL and thus can dispense multiple doses and will be discarded when empty. Participants must return any unused investigational product, and the sharps bin, at their next visit to the clinical site. Number of dispensed pens and number of returned pens are collected in CRF at each dispensation visits.

Each dosing interval will be recorded in CRF. Therefore, all dose changes and interruptions will be recorded.

3.4.1 Exposure

Exposure over time (days) is calculated only for participants in the as-treated population as the total number of days on study drug (i.e., gaps in dosing due to study drug interruption will not be taken-out from the calculation). Exposure is calculated as the study drug dose last date minus study drug dose first date plus one. If any of the first or last dates are missing or partially missing, then imputed dates will not be used, and study drug exposure is set to missing.

Actual exposure over time (days) is calculated as the total number of days of effective study drug intake (i.e., gaps in dosing due to study drug interruption will be taken-out from the calculation). In this way, the participant's dosing can be reduced to a series of unbroken intervals within each, the exposure is calculated as study drug dose stop date minus the study drug dose start date plus one. If any record of actual exposure for semaglutide exists and any of start or end dates of an interval is missing (but not both), the dose will be assumed as been taken and counted in total exposure. If any of the start or stop dates are missing or partially missing for an interval (except of the semaglutide as mentioned above), study drug exposure for that interval is set to missing. Actual exposure is then derived as the sum over only the intervals where drug exposure was not set to missing.

Cumulative exposure and cumulative actual exposure (days) are also computed based on exposure, using the following duration (days) categories:

- 0 - 14
- >= 15
- >= 29
- >= 43
- >= 57
- >= 71
- >= 85
- >= 99

- >= 113
- >= 141
- >= 169

3.4.2 Compliance

Overall compliance to the IP is calculated only for participants in the as-treated population.

The percent compliance is defined as the total dose consumed divided by the total dose that should have been taken and multiplied by 100%.

When participants are dosed at the site, they will self-administer the study intervention (IP) under medical supervision from the investigator or designee. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and eCRF.

Each dosing interval will be entered into CRF including dose, start and stop date. If any dose changes or interruptions will be detected, this data will be entered as a separate dosing interval.

Total dose consumed will be calculated as sum of actual doses at intervals multiplied by duration of corresponding dosing intervals in days: Dose at the interval * (Interval stop date minus interval start date + 1). This data will be based on the actual dosing intervals recorded in CRF.

The dose that should have been taken will be based on the dosing regimens including up-titrations. For the semaglutide dose that should have been taken we assume that participants will take the first dose on Day 1 and thereafter every 7 days. Thus, if Day 1 is Monday, Day 8 will be Monday too and so forth. Thus, if participants stopped dosing in Week 3 on Sunday, they would have taken 3 doses of semaglutide; if they stop in Week 4 Monday, they would have taken 4 doses of semaglutide.

No replacement of missing data will be performed. Therefore, if one of the dose or date is missing the resulting compliance is missing.

Compliance will also be categorized as:

- < 80%
- ≥ 80% to < 120%
- ≥ 120%

3.5 Concomitant medications and concomitant procedures

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as restricted and prohibited as listed in the study protocol and detailed (coding and indication wherever applicable) in the in the Integrated Data Review Plan (IDRP).

The WHO-DD March 2019 B3 Global or higher is used to classify medications by WHO Anatomical Therapeutic Chemical (ATC) classification of ingredients.

The imputation method described in Section 3.1.1.5 and Section 3.1.1.6 is used in case of medication stop date partially missing. Completely missing stop date and start dates are not imputed except for insulin where a completely missing stop date is imputed by end of study date.

After the end date imputation, concomitant medication is defined as any medication with a stop date on or after the first dose of study drug (including ongoing medications), or any medication taken prior to study drug and that is ongoing. Medications with completely missing stop date are classified as concomitant.

Disallowed (Prohibited) concomitant medications are firstly selected by ATC4 code as mentioned in IDRP and then confirmed and flagged by the study physician in accordance with the study protocol.

Concomitant procedures are also recorded. All concomitant procedures are coded in MedDRA version 24.0 or higher. Imputation rules for concomitant procedure are the same as for concomitant medication listed in 3.1.1.

4 ANALYSIS METHODS

4.1 General principles

Data will be summarised using descriptive statistics, by treatment group which consist of the groups listed below.

Demographic, baseline, concomitant medication, and other participant-specific characteristics:

- Cotadutide 100 µg
- Cotadutide 300 µg
- Cotadutide 600 µg
- Cotadutide total
- Placebo
- Semaglutide 1mg
- Total

Efficacy evaluation data:

- Cotadutide 100 µg
- Cotadutide 300 µg
- Cotadutide 600 µg
- Placebo
- Semaglutide 1 mg

Safety evaluation data:

- Cotadutide 100 µg
- Cotadutide 300 µg
- Cotadutide 600 µg
- Cotadutide total
- Placebo
- Semaglutide 1 mg

Placebo group includes the 3 doses of 100 µg, 300 µg and 600 µg of placebo. Cotadutide total group includes the 3 doses of 100 µg, 300 µg and 600 µg of cotadutide. Total group will include all corresponding groups.

If not stated otherwise, comparison to placebo and semaglutide will be displayed within one output.

Data will be summarised at each visit.

Two analyses will be performed with the similar scope of tables:

- A primary analysis after the completion of 14 weeks of dosing for all participants
- A final analysis for all participants after the completion of 26 weeks of dosing and safety follow-up for all participants

These two analyses will be delivered at the end of the trial.

A subpopulation analysis for only participants at sites in Japan after the completion of 26 weeks of dosing and safety follow-up will also be conducted.

All efficacy and safety endpoints will be summarised by treatment group and at each visit as appropriate using descriptive statistics. Except otherwise specified, unscheduled visits will be only listed.

For the endpoints, the following assessments will be used:

- first assessment of Week 15 for “end of 14 weeks of dosing” endpoint;
- last assessment of Week 26 for “end of 26 weeks of dosing” endpoint.

Change from baseline is defined as the post-baseline visit value minus the baseline value; percent change from baseline is calculated as the visit value minus the baseline value divided by the baseline value * 100.

For any endpoint subjected to log transformation, the change from baseline calculated and summarized on the log scale will be back-transformed and presented as a baseline scaled ratio (BSR). Percentage change (mentioned in objectives) or percent change (used in the current SAP) will be then calculated as (BSR-1)*100.

Efficacy continuous variables will be summarised for the observed values, the change from baseline and the percent change from baseline. For continuous variables, descriptive statistics will include the number of participants (n), mean, SD, median, minimum and maximum. Geometric mean and geometric CV will be additionally included for percent change.

Additionally, if the variable is log-normally distributed, Q1 and Q3 will be reported. Geometric mean and geometric CV will also be reported for the observed value and percent change. For geomean and geometric CV calculation, in case of zero records, regardless of treatment group assignment in all subjects at either baseline or post-baseline, impute half of the minimum of the non-zero records prior to log transformation and determine the lowest value present at either baseline or post-baseline and apply the same imputation for timepoints for a given variable. To assess the change from baseline to post-baseline (i.e.week 14, week 26), use the difference of the logs between the timepoints.

For categorical variables and unless otherwise specified, the number and percentages of participants by categories will be tabulated. Percentages will be calculated based on the number of participants with no missing data, i.e., will add up to 100%. Categories with count of zero will not be displayed.

Changes from baseline in certain categorical variables will be summarised using shift tables. The number and percent of participants within each treatment group will be generated for each category post-baseline by baseline category.

If not otherwise specified, all the analyses will include the post IP-discontinuation data for those participants who discontinue from study treatments but are still followed up for their scheduled visits.

The following statistical models will be used to compare active groups versus placebo/semaglutide for some of the study endpoints:

4.1.1 Statistical Hypotheses

Primary Hypothesis

Administration of cotadutide once daily titrated up to a dose level of either 100, 300, or 600 µg will result in a superior reduction in UACR versus placebo after 14 weeks of treatment in participants who have CKD with T2DM.

From analysis perspectives two-sided test with significance level of 0.05 will be used; one-sided test with 0.025 alpha is assumed as of having the same results in terms of programming procedures calculation.

Secondary Hypotheses

Administration of cotadutide once daily titrated up to a dose level of 600 µg will result in superior reduction in UACR versus placebo after 26 weeks of treatment in participants who have CKD with T2DM.

Administration of cotadutide once daily titrated up to a maximum of 600 µg across 26 weeks will be well tolerated in participants who have CKD with T2DM.

Administration of cotadutide once daily titrated up to a maximum of 600 µg will result in superior weight loss versus placebo after 26 weeks of treatment in participants who have CKD with T2DM.

From analysis perspectives two-sided test with significance level of 0.05 will be used although one-sided test with 0.025 alpha is assumed as of having the same results in terms of programming procedures calculation.

4.1.2 Analysis of covariance (ANCOVA) on normally distributed variables

The below ANCOVA model will be used to fit change or percent change at each concerning visit for some of the efficacy endpoints. Data used in the model are data from baseline and the respective scheduled visit:

- first assessment of Week 15 for “end of 14 weeks of dosing” endpoint;
- last assessment of Week 26 for “end of 26 weeks of dosing” endpoint.

The variable fitted in the model will be the change or percent change from baseline. The model will include treatment as fixed effect and the baseline value as well as the stratification factors (whether a participant is from site in Japan and whether a participant is using SGLT2 inhibitor therapy at screening or not) as covariates.

Comparisons between active groups versus placebo or versus semaglutide will be assessed within the same model (participants from all 5 arms will be included within same model). However, two separate models will be used for Week 15 and Week 26 endpoints. The restricted maximum likelihood (REML) approach will be used for the estimation of the variance and covariance parameters of the linear mixed model; two-sided tests for differences with alpha level at 5% will be used for the comparisons and for the t-type confidence interval (CI) calculation.

Unless otherwise specified, LOCF method will be applied to handle missing data, that is, a missing endpoint will be replaced with the last available scheduled post-baseline measurement prior to the missing endpoint.

Following results from the model will be reported:

- The least-square means (LSmeans) and their standard errors for each treatment group

- The difference between active treatment groups and placebo/semaglutide (LSmean difference) together with its 95% CI
- The p-value for the difference between active groups and placebo/semaglutide.

4.1.3 Analysis of covariance (ANCOVA) on log-normally distributed variables

The below ANCOVA model will be used to fit percent change at each concerning visit for some of the efficacy endpoints. Data used in the model are data from baseline and the respective scheduled visit:

- first assessment of Week 15 for "end of 14 weeks of dosing" endpoint;
- last assessment of Week 26 for "end of 26 weeks of dosing" endpoint.

The variable fitted in the model will be the percent change from baseline in logarithmical scale. Change from baseline in logarithmical scale is defined as the log-transformation of the post-baseline visit value minus the log-transformation of the baseline value. Variable records with zero value will be imputed by half of the minimum of the non-zero records prior to the log transformation (see section 4.1 for imputation rule details).

The model will include treatment as fixed effect and the baseline value (in logarithmic transformation) as well as the stratification factors (whether a participant is from site in Japan and whether a participant is using SGLT2 inhibitor therapy at screening or not) as covariates.

Comparisons between active groups versus placebo or versus semaglutide will be assessed within the same model (participants from all 5 arms will be included within same model). However, two separate models will be used for Week 15 and Week 26 endpoints. The restricted maximum likelihood (REML) approach will be used for the estimation of the variance and covariance parameters of the linear mixed model; two-sided difference test, with alpha level at 5% will be used for the comparisons and for the t-type CI calculation.

Unless otherwise specified, LOCF method will be applied to handle missing data, that is, a missing endpoint will be replaced with the last available scheduled post-baseline measurement prior to the missing endpoint.

Following results from the model will be reported:

- Back transformed LSmeans for each treatment group, which correspond to the estimated percent change from baseline; back transformed LSmeans is derived as [EXP(LSMean)-1]*100,
- 95% CI of the back transformed LSmeans for each treatment group; 95% CI of the back transformed LSmeans is derived as [EXP(Lower)-1]*100; [EXP(Upper)-1]*100.
- The ratio between active treatment groups and placebo/semaglutide; the ratio is calculated as EXP(LSMean difference)
- The 95% CI of the ratio; the 95% CI of the ratio is calculated as [EXP(Lower)]; [EXP(Upper)].
- P-value

It should be noted that a ratio lower than 1 means that the active treatment group shows a higher decrease (or a lower increase) compared to the placebo/semaglutide group. On the other hand, a ratio greater than 1 means that the active treatment group shows a lower decrease (or a higher increase) compared to the placebo/semaglutide group.

4.1.4 Non-parametric analysis

In case of non-parametric distribution non-parametric methods as outlined below. Data used in the model are data from baseline and the respective scheduled visit:

- first assessment of Week 15 for "end of 14 weeks of dosing" endpoint;
- last assessment of Week 26 for "end of 26 weeks of dosing" endpoint.

The variable fitted in the model will be the change from baseline.

Comparisons between active groups versus placebo or versus semaglutide will be assessed within the same model (participants from all 5 arms will be included within same model). However, two separate models will be used for Week 15 and Week 26 endpoints. A Wilcoxon rank sum test will be performed. The Hodges-Lehman estimator for the difference in the medians and the distribution-free 95% CIs based on the Wilcoxon rank sum test will also be presented. Exact method will be used, if an error/warning appears in the SAS log or results cannot be computed with exact method the normal approximation will be used instead.

Unless otherwise specified, LOCF method will be applied to handle missing data, that is, a missing endpoint will be replaced with the last available scheduled post-baseline measurement prior to the missing endpoint.

Following results from the model will be reported:

- Median change from baseline for each treatment group,
- The Hodges-Lehman estimator for the difference in the medians and the distribution-free 95% CIs based on the Wilcoxon rank sum test,
- P-value of Wilcoxon rank sum test.

[redacted]

[redacted]

4.1.6 Logistic regression

The logistic regression will be used to fit proportions of participants with a specific event at scheduled visits:

- first assessment of Week 15 for "end of 14 weeks of dosing" endpoint;
- last assessment of Week 26 for "end of 26 weeks of dosing" endpoint.

Data used in the model are data from baseline and the respective scheduled visit. The model will include treatment as fixed effect and the baseline value as well as the stratification factors (whether a participant is from Japan and whether a participant is using SGLT2 inhibitor therapy at screening or not) as covariates.

Comparisons between active treatment groups versus placebo or versus semaglutide will be assessed within the same model (participants from all 5 arms will be included within same model). However, two separate models will be used for Week 15 and Week 26 endpoints. Two-sided difference tests with alpha level at 5% will be used for the comparisons and for the exact CI calculation. If the error/warning appears in the SAS log file, Wald option will be used instead.

If both of Wald and Exact methods ran into SAS error/warning, descriptive statistics will be presented instead..

Unless otherwise specified, LOCF method will be applied to handle missing data, that is, a missing endpoint will be replaced with the last available scheduled post-baseline measurement prior to the missing endpoint.

Following results from the model will be reported:

- The odds ratio between active treatment groups and placebo/semaglutide together with its 95% CI, calculated by means of the Exact method (if SAS error/warning appears, use Wald instead)
- The p-value for the odds ratio between active treatment groups and placebo/semaglutide.

4.1.7 Sensitivity Analysis 1 – the mixed model repeated measures (MMRM)

The Sensitivity Analysis 1 will be used only for UACR and will consist on fitting a MMRM to percent change from baseline. This MMRM model will be calculated for following endpoint visits:

- first assessment of Week 15 for "end of 14 weeks of dosing" endpoint;
- last assessment of Week 26 for "end of 26 weeks of dosing" endpoint.

Data used in the model come from all available scheduled previous visits. The variable fitted in the model will be the change from baseline in logarithmical scale. Change from baseline in logarithmical scale is defined as the log-transformation of the post-baseline visit value minus the log-transformation of the baseline value.

Fixed factors of the model will be treatment, visit and treatment * visit interaction. The baseline UACR (in logarithmic transformation) as well as the stratification factors (whether a participant is from Japan and whether a participant is using SGLT2 inhibitor therapy at screening or not) will be used as covariates. Visit within participant will be considered as repeated measurements.

Comparisons between active groups versus placebo or versus semaglutide will be assessed within the same model (participants from all 5 arms will be included within same model). However, two separate models will be used for Week 15 and Week 26 endpoints. The restricted maximum likelihood (REML) approach will be used for the estimation of the variance and covariance parameters of the linear mixed model two-sided test for difference, with alpha level at 5% will be used for the comparisons and for the t-type CI calculation.

The model will use the SP (POW) structure for unequally spaced data variance-covariance matrix as default. Visit will be expressed as planned days to accomplish the variance-covariance matrix estimation. No data imputation will be applied.

In case the model will not converge for any reasons, the following back-up solutions will be adopted sequentially:

1. The compound symmetry (CS) will be used instead of the SP (POW)
2. The unstructured (UN) will be used instead of the CS

In case of SP(POW) or CS matrix of variance covariance will be used, the DDFM will be computed using the BETWITHIN(SAS) method. If the unstructured covariance structure will be used, the DDFM will be computed using the Kenward-Roger method. In case model does not converge, the BETWITHIN (SAS) option will be used for the denominator degrees of freedom.

The reportable results from the model will be:

- Back transformed LSmeans for each treatment group, which corresponds to the estimated percent change from baseline; back transformed LSmeans is derived as [EXP(LSMean)-1]*100,
- 95% CI of the back transformed LSmeans for each treatment group; 95% CI of the back transformed LSmeans is derived as [EXP(Lower)-1]*100; [EXP(Upper)-1]*100.
- The ratio between active groups and placebo/semaglutide; the ratio is calculated as EXP(LSMean difference)
- The 95% CI of the ratio; the 95% CI of the ratio is calculated as [EXP(Lower)]; [EXP(Upper)].
- P-value

It should be noted that a ratio lower than 1 means that the active treatment group shows a higher decrease (or a lower increase) compared to the placebo/semaglutide group. On the other hand, a ratio greater than 1 means that the active treatment group shows a lower decrease (or a higher increase) compared to the placebo/semaglutide group.

4.1.8 Sensitivity Analysis 2

The Sensitivity Analysis 2 will consist of repeating the Sensitivity Analysis 1 and the MMRM model on the same population but including body weight loss impact.

The difference from Sensitivity Analysis 1 is that the full model will be the following:

Fixed factors of the model will be treatment, visit, body weight, treatment*body weight interaction and treatment * visit interaction. The baseline UACR (in logarithmic transformation) as well as the stratification factors (whether a participant is from Japan and whether a participant is using SGLT2 inhibitor therapy at screening or not) will be used as covariates. Visit within participant will be considered as repeated measurements.

4.1.9 Sensitivity Analysis 3

The Sensitivity Analysis 3 will consist of repeating the Sensitivity 2 but without treatment*visit interaction.

The model will include interaction between treatment and body weight loss as follows:

Fixed factors of the model will be treatment, visit, body weight, treatment*body weight interaction. The baseline UACR (in logarithmic transformation) as well as the stratification factors (whether a participant is from Japan and whether a participant is using SGLT2 inhibitor therapy at screening or not) will be used as covariates. Visit within participant will be considered as repeated measurements.

4.1.10 Sensitivity Analysis 4

The Sensitivity Analysis 4 will consist of repeating the descriptive analysis and the ANCOVA model on the same population used for the main analysis but including only data in the on-treatment phase. LOCF will not be applied for this analysis.

4.1.11 Sensitivity Analysis 5

The Sensitivity Analysis 5 will consist of repeating the descriptive analysis and the ANCOVA model on the PP population.

4.1.12 Sensitivity Analysis 6

The Sensitivity Analysis 6 will use the below ANCOVA model with SGLT-2 inhibitor therapy at screening and treatment interaction to fit percent change at each concerning visit for UACR. Data used in the model are data from baseline and the respective scheduled visit:

- first assessment of Week 15 for “end of 14 weeks of dosing” endpoint;
- last assessment of Week 26 for “end of 26 weeks of dosing” endpoint.

The variable fitted in the model will be the change from baseline in logarithmical scale. Change from baseline in logarithmical scale is defined as the log-transformation of the post-baseline visit value minus the log-transformation of the baseline value.

The model will include treatment as fixed effect and SGLT-2 use at screening * treatment interaction, the baseline value (in logarithmic transformation) and the stratification factors (whether a participant is from site in Japan and whether a participant is using SGLT2 inhibitor therapy at screening or not) as covariates.

For the interaction between treatment group and SGLT-2 only p-values for corresponding models will be displayed. Separate models for each interaction (Cotadutide 100 ug / Cotadutide 300 ug / Cotadutide 600 ug vs Placebo and then vs Semaglutide at Week 15 and then at Week 26: 12 models overall) will be used.

The restricted maximum likelihood (REML) approach will be used for the estimation of the variance and covariance parameters of the linear mixed model.

Unless otherwise specified, LOCF method will be applied to handle missing data, that is, a missing endpoint will be replaced with the last available scheduled post-baseline measurement prior to the missing endpoint.

4.1.13 Interim Analyses

Further details on the conduct of the interim analyses will be delineated in Section 5.

4.2 Analysis of variables

4.2.1 Disposition of participants

The number and percentage of participants enrolled, participants randomised, participants who received at least one dose of study IP, participants who completed the treatment and participants who completed the study will be presented in a summary table for each treatment group and overall (including COVID-19 pandemic sub-selection for discontinuation from study). A listing including all standardized disposition terms will also be provided for all discontinued participants. Both, the table, and the listing will be based on all enrolled participants population.

The number of participants belonging to each analysis population will be presented in a summary table for each treatment group. The summary for all populations will be based on all enrolled participants population. An exception here will be for participants included in as-treated population which will be displayed according to actual arm. Listing of all participants excluded from the ITT, as-treated, PP,immunogenicity and PK population will also be provided. The listing will include reason for exclusion from respective population and will be based on all enrolled participants population.

A listing of randomisation codes for each participant as well as the treatment group they were randomised to, and a separate listing with lot number (kit number) will be provided for ITT population.

4.2.2 Important protocol deviations

The number and percentage of participants with at least one IPD will be summarised for ITT population following the PDMP categories, for each treatment group and overall (including COVID-19 pandemic sub selection).

All IPDs will also be listed for all participants included in the ITT population.

4.2.3 Baseline assessment and other participant-specific characteristics

4.2.3.1 Demographic and participant-specific characteristics

All demographic and participant-specific characteristics reported in Section 3.2.1 will be presented in summary tables for each treatment group and overall; age at screening, height, weight and BMI will be summarised descriptively as continuous variable with n, mean, median, SD, minimum, and maximum; all the other demographic (age group, sex, race, ethnic group, country) participant-specific characteristics (weight group, BMI group, stratification factors), participant recruitment by region ("Asia", "Europe", "North America", "Rest of the World"), country and site will be summarised as categorical variables with the number and percentages of participants by categories. Only the baseline measurement for height, weight and BMI will be considered.

All demographic and participant-specific characteristics will also be provided in listings.

The tables and the listings will be based on the ITT population. Baseline and post-baseline definitions are detailed in Section 3.1.2.

4.2.3.2 Medical history

All medical history as described in Section 3.2.2 will be presented in summary tables as number and percentages of participants by System Organ Class (SOC) and Preferred Term (PT) for each treatment group and overall. Participants with multiple events in the same SOC/PT will be counted only once in that SOC/PT. Participants with events in more than one SOC/PT will be counted once in each of those SOC/PT. Tables will be sorted alphabetically by SOC and PT.

CKD diagnosis as described in Section 3.2.2 will be presented in summary tables by treatment and overall as number and percentages of participants by most likely aetiology of CKD and type of disease.

Diabetes history as described in Section 3.2.2 will be presented in summary tables by treatment and overall as number and percentages of participants by diabetes mellitus complications. In addition, diabetes duration will be summarised descriptively as continuous variable with n, mean, median, SD, minimum, and maximum.

Retinopathy at baseline will be presented in summary table for each treatment group and overall.

Medical history, CKD diagnosis, diabetes history and retinopathy at baseline will also be provided in listings.

All the tables and the listings will be based on the ITT population.

4.2.4 Primary/Secondary efficacy endpoints

4.2.4.1 UACR

UACR is described in Section 3.3.1.1. Baseline and post-baseline definitions are detailed in Section 3.1.2. Tables, figures and listings will be based on the ITT population and presented for each treatment group. The exception is only for Sensitivity Analysis 4 which will be based on PP population.

UACR will be summarised descriptively as log-normally distributed continuous variable as described in Section 4.1.

An ANCOVA model for log-normally distributed variables as described in Section 4.1.3 for percent change from baseline, at the end of 14 and 26 weeks of dosing will also be presented.

Observed value and percent change of UACR will also be presented in figure with geometric mean and 95% CI.

Sensitivity Analyses 1, 2, 3, 4, 5 and 6 as described in Section 4.1 will also be performed with the aim to consolidate the results obtained with the previous ANCOVA model.

For subgroup analysis see Section 4.3.1.

UACR will also be listed.

4.2.5 Secondary efficacy endpoints

4.2.5.1 HbA1c and fasting glucose

HbA1c and fasting glucose are described in Section 3.3.1.2. Baseline and post-baseline definitions are detailed in Section 3.1.2. Tables, figures and listings will be based on the ITT population and presented for each treatment group.

HbA1c and fasting glucose will be summarised descriptively as normally distributed continuous variables as described in Section 4.1.

An ANCOVA model for normally distributed variables as described in Section 4.1.2 for change from baseline, at the end of 14 and 26 weeks of dosing will also be presented.

Mean and standard error of the change from baseline value for HbA1c only will also be visualised by means of graphical presentations.

HbA1c and fasting glucose will also be listed.

[redacted]

4.3.

4.2.5.3 Body weight

Body weight is described in Section 3.3.1.4. Baseline and post-baseline definitions are detailed in Section 3.1.2. Tables and listings will be based on the ITT population and presented for each treatment group.

Body weight will be summarised descriptively as normally distributed continuous variable as described in Section 4.1.

An ANCOVA model for normally distributed variables as described in Section 4.1.2 for change and percent change from baseline, at the end of 14 and 26 weeks of dosing will also be presented.

Body weight loss >= 5% and >= 10% will be summarised as categorical variables with the number and percentages of participants by categories at each analysis visit. Percentages will be calculated based on the number of participants with no missing data, i.e., will add up to 100%.

A logistic model as described in Section 4.1.6 for Body weight loss >= 5% and >= 10%, at the end of 14 and 26 weeks of dosing will also be presented.

Mean and standard error of the change from baseline value will also be visualised by means of graphical presentations.

Body weight will also be listed.

[redacted]

4.2.6.5 Urine albumin and urinary creatinine

Urine albumin and urinary creatinine are described in Section 3.3.1.1. Baseline and post-baseline definitions are detailed in Section 3.1.2. Tables and listings will be based on the ITT population and presented for each treatment group.

Urine albumin and urinary creatinine will be firstly evaluated for normality (normality will be evaluated in a separate document using Q-Q plots and test for normality). Then both variables will be summarised descriptively as continuous variables according to the distribution as described in Section 4.1.

If the distribution appears to be normal, an ANCOVA model for normally distributed variables as described in Section 4.1.2 for change from baseline, at the end of 14 and 26 weeks of dosing will also be presented.

If the distribution appears to be log-normal and parameter can take only positive value, an ANCOVA model for log-normally distributed variables as described in Section 4.1.3 for percent change from baseline, at the end of 14 and 26 weeks of dosing will also be presented.

If the distribution appears to be non-parametric, a non-parametric analysis as described in Section 4.1.4. for percent change from baseline, at the end of 14 and 26 weeks of dosing will also be presented.

Urine albumin and urinary creatinine will also be listed.

4.2.6.6 Vital signs

Vital signs (SBP, DBP, PR and RPP) are described in Section 3.3.1.7. Baseline and post-baseline definitions are detailed in Section 3.1.2. Tables, figures and listings will be based on the ITT population and presented for each treatment group.

Other vital signs (temperature, RR) will be analysed in safety section.

The vital signs (SBP, DBP, PR and RPP) will be summarised descriptively as normally distributed continuous variables as described in Section 4.1.

An ANCOVA model for normally distributed variables as described in Section 4.1.2 for change from baseline, at the end of 14 and 26 weeks of dosing will also be presented.

The number of all participants in SBP change categories with maximum pulse rate absolute change from baseline > 20 bpm at concurrent visit will also be summarised. Only measurements done predose will be considered (using scheduled and unscheduled).

Mean and standard error of the observed values and change from baseline will also be visualised by means of graphical presentations.

The vital signs (SBP, DBP, PR and RPP) will also be listed. The listing will include reference ranges and classification of vital signs as normal, low and high.

[redacted]

[redacted]

4.2.6.9 Insulin dose adjustment

Total daily insulin (in units and units/kg) is described in Section 3.3.1.9. Baseline and post-baseline definitions are detailed in Section 3.1.2. Tables and listings will be based on the ITT population and presented for each treatment group.

Total daily insulin (in units and units/kg) will be summarised by analysis visit descriptively as normally distributed continuous variable as described in Section 4.1.

An ANCOVA model for total daily dose as described in Section 4.1.2 for change and percent change from baseline, at the end of 14 and 26 weeks of dosing will also be presented. In addition, an ANCOVA model for total daily dose in units/kg for change from baseline, at the end of 14 and 26 weeks of dosing, will also be presented.

Mean and standard error of the change from baseline value of total daily dose (in units and units/kg) will also be visualised by visit by means of graphical presentations.

Mean change from baseline of total daily insulin dose (in units and units/kg) over all the study including on-treatment and off-treatment period will also be visualised by week by line graph.

Bar graph of change from baseline in total daily insulin dose (in units only) comparing each treatment dose of cotadutide versus placebo and semaglutide will be represented by week lastly.

Total daily insulin (in units and units/kg) will also be listed for all daily assessments.

4.2.6.10 Markers of liver health (AST, ALT and NFS)

All markers of liver health are described in Section 3.3.1.10. Baseline and post-baseline definitions are detailed in Section 3.1.2. Tables and listings will be based on the ITT population and presented for each treatment group and following subsets:

- all participants;
- subset with BMI ≤ 35 kg/m2;
- subset with BMI > 35 kg/m2.

All parameters (AST, ALT and NFS) will be firstly evaluated for normality (normality will be evaluated in a separate document using Q-Q plots and test for normality). Then both variables will be summarised descriptively as continuous variables according to the distribution as described in Section 4.1.

If the distribution appears to be normal, an ANCOVA model for normally distributed variables as described in Section 4.1.2 for change from baseline, at the end of 14 and 26 weeks of dosing will also be presented.

If the distribution appears to be log-normal and parameter can take only positive value, an ANCOVA model for log-normally distributed variables as described in Section 4.1.3 for percent change from baseline, at the end of 14 and 26 weeks of dosing will also be presented.

If the distribution appears to be non-parametric, a non-parametric analysis as described in Section 4.1.4 for percent change from baseline, at the end of 14 and 26 weeks of dosing will also be presented.

All markers of liver health will also be listed.

4.2.6.11 Fasting lipid profile

Fasting lipid profile contains the following assessments:

- Total cholesterol;
- HDL;
- LDL;
- total cholesterol to HDL ratio;
- triglyceride levels.

All lipid profile assessments are described in Section 3.3.1.11. Baseline and post-baseline definitions are detailed in Section 3.1.2. Tables and listings will be based on the ITT population and presented for each treatment group.

All parameters will be firstly evaluated for normality (normality will be evaluated in a separate document using Q-Q plots and test for normality). Then both variables will be summarised descriptively as continuous variables according to the distribution as described in Section 4.1.2.

If the distribution appears to be normal, an ANCOVA model for normally distributed variables as described in Section 4.1.2 for change from baseline, at the end of 14 and 26 weeks of dosing will also be presented.

If the distribution appears to be log-normal and parameter can take only positive value, an ANCOVA model for log-normally distributed variables as described in Section 4.1.3 for percent change from baseline, at the end of 14 and 26 weeks of dosing will also be presented.

If the distribution appears to be non-parametric, a non-parametric analysis as described in Section 4.1.4 for percent change from baseline, at the end of 14 and 26 weeks of dosing will also be presented.

All lipid profile parameters will also be listed.

[redacted]

4.2.7 Safety endpoints

4.2.7.1 Adverse events

After having assigned the AEs to the corresponding study phase as described in Section 3.1.3, the AEs will be summarised for each treatment group. If not stated otherwise, the AEs tables will be based on the as-treated population.

Derivation rules in Section 3.3.2.1 will be used to assign AEs to study phase. All summary tables will be displayed for the following phases:

- on-treatment phase
- follow-up phase.

Summary tables are listed below.

An overview table containing:

- Number and percentage of participants with any AEs
- Number and percentage of participants with any AEs with outcome of death
- Number and percentage of participants with any SAEs
- Number and percentage of participants with any AEs leading to discontinuation of IP (only on-treatment phase AEs)
- Number and percentage of participants with any AEs leading to withdrawal from study

The following summary tables will be presented by SOC and PT:

- The number and percentage of participants with any AEs
- The number of AEs

- The number and percentage of participants with AEs, assessed by investigator as possibly related to IP
- Number of participants with AEs by maximum reported intensity occurring in greater than 5% of participants in any treatment group
- The number and percentage of participants with any AEs by maximum reported intensity.
- The number and percentage of participants with any AEs and investigator's causality assessment. If a participant has multiple events in the same PT, the event with the strongest relationship will be counted.

- The number and percentage of participants with AEs with outcome of death,
- The number and percentage of participants with SAEs
- The number of SAEs
- The number and percentage of participants with AEs leading to discontinuation of IP

The following summary tables will be presented by PT:

- The number and percentage of participants with most common AEs (frequency of > 5% in any treatment group).

Where number of participants with AEs are summarised by system organ class (SOC) and/or preferred term (PT), participants with multiple events in the same SOC/PT are counted only once in that SOC/PT. Participants with events in more than 1 SOC/PT are counted once in each of those SOCs/PTs.

Additionally, the following tables will be presented:

- the number and percentage of participants with non-serious AEs occurring with a frequency > 5% in any treatment group for each SOC and PT. This table will be produced as a separate pdf output to meet clinical trial transparency requirements and not for inclusion in the clinical study report (CSR). It will be delivered at the same time as the CSR outputs.
- the number of participants with injection site reactions by high level term (HLT) and PT.
- the number of participants with adjudicated events by category and outcome of adjudication.
- event rates for AEs and SAEs of hypoglycaemia, overall and separately for participants taking/not taking insulin at baseline.

The event rate for hypoglycaemia based on person-years will be calculated as:

Total number of events when participants are on study IP multiplied by 100 divided by the total person-years of exposure to study IP for the whole relevant arm (number of events * 100 / person-years). Total number of events means to consider all incidences separately even if multiple events occurred. The total person-years of exposure is the sum of all the actual exposures, in years (sum of actual days of exposure divided by 365.25), of all the participants who are ever exposed to study IP, in the relevant arm.

For numerator calculation during on-treatment period, if an event is onset at day 1 and ends at day 3, then it will be counted as one event for this period. Only on-treatment days (from first

dose to last dose of IP) will be included in the denominator calculation of exposure (person-years); consequently, only events on those on-treatment days will be included in the numerator calculation.

A lists of key participant information for participants with AEs with outcome of death, participants with SAEs, and participants with AEs leading to discontinuation of IP will be provided. The durations reported in these tables, will be derived only for fully completed dates as below:

- Time from first dose of IP to AE (in days) will be calculated as the AE start date minus date of dose +1.
- Time from first dose to death (in days) will be calculated as the date of death minus date of dose +1.
- The same approach will be used for deriving time from start of treatment to AE becoming serious or discontinuation.
- Time from last dose prior to AE start and last dose prior to death will be calculated as the date of AE/death minus the date of last dose prior to AE/death +1.

Lastly, specific outputs will be provided for nausea and vomiting:

- table presenting the event rate by period;
- corresponding bar-charts for each treatment group.

The event rate for nausea and vomiting based on person-days will be calculated as:

Total number of events when participants are on study IP in the selected period divided by the total person-days of exposure to study IP for the whole relevant arm in the selected period. Total number of events means to consider all incidences separately even if multiple events occurred during same period. The total person-days of exposure is the sum of all the exposures, in days, of all the participants who are ever exposed to study IP within the specific period, in the relevant arm, for the selected period.

For numerator calculation during a period (e.g. the first 1-week analysis), if an event is onset at day 1 and ends at day 3, then it will be counted as one event for this period. For numerator calculation, if an event is onset at day 1 and ends at day 9, then this event will be counted as an event for both Week 1 analysis and Week 2 analysis. Only on-treatment days (from first dose to last dose of IP) will be included in the denominator calculation of exposure (person-days); consequently, only events on those on-treatment days will be included in the numerator calculation. In the rare case in which there is a gap in dosing of more than 7 days, the inclusion of the AE which started during the gap period and the exposure days calculation should be evaluated case by case.

No other significant adverse events (OAEs) are planned to be defined for this study.

All the AEs and adjudicated events regardless of the study phases will also be listed for all participants included in the as-treated population for all treatment groups.

4.2.7.2 Laboratory evaluation

Laboratory evaluations are described in Section 3.3.2.2. Baseline and post-baseline definitions are detailed in Section 3.1.2. All tables and listings for laboratory data will be based on the as-treated population and presented for each treatment group.

Laboratory test results for haematology, clinical chemistry, urinalysis (except microscopy panel) and other safety quantitative parameters will be summarised in SI units with n, mean, SD, median, minimum, and maximum at each visit and for change from baseline. Same summary table will be presented using conventional units (for parameters with a conventional unit different from SI unit). Shifts from baseline to maximum and minimum value during the on-treatment phase (using scheduled and unscheduled measurements) will also be presented using low, normal and high categories.

Shifts from baseline to maximum value during the on-treatment phase (using scheduled and unscheduled measurements) will be presented for urinalysis qualitative macro parameters.

The maximum on-treatment ALT and AST by maximum total bilirubin will be presented for assessing Hy's law criteria using the following categories:

Bilirubin

< 2xULN (baseline can be only < 2xULN as to exclusion criteria)

≥ 2xULN

ALT, AST

< 3xULN (baseline can be only <3xULN as to exclusion criteria)

≥ 3 – < 5xULN

≥ 5 – < 8xULN

≥ 8xULN

In addition to the tables above also the following will be presented:

- the eDISh plot for total bilirubin by maximum ALT;
- a list of key participant information for participants with potential Hy's law as described in the study protocol (AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN at any point during the study following the start of investigational product).

All clinical laboratory data (including urinalysis microscopy casts) will be presented in listings and within each listing, quantitative laboratory values outside the normal ranges will be flagged.

4.2.7.3 Vital signs

Vital signs (BP, pulse rate, RPP, temperature and RR) are described in Section 3.3.2.3. Baseline and post-baseline definitions are detailed in Section 3.1.2. Vital signs tables and listings will be based on the as-treated population and presented for each treatment group.

BP, pulse rate, RPP will be additionally analysed in efficacy section.

Vital signs will be summarized descriptively as continuous variables with n, mean, median, SD, minimum, and maximum, at each visit and time point within visit and for change from baseline.

Shifts from baseline to maximum value during the on-treatment phase will be presented for the vital signs categories (low, normal, high). Shifts from baseline to maximum value during the on-treatment phase will be presented for the vital signs (SBP, DBP, pulse rate and temperature) categories (low, normal, high).

The number of participants in SBP change categories with maximum pulse rate absolute change from baseline > 20 bpm at concurrent visit will also be summarised. Only measurements done predose will be considered (using scheduled and unscheduled).

Temperature and RR data will be listed for all treatment groups. The listing will include reference ranges and classification of vital signs as normal, low and high. Other vital signs will be listed in efficacy section.

4.2.7.4 dECG

dECG evaluation includes:

- PR interval (msec)
- QRS duration (msec)
- QT interval (msec)
- Heart rate (beats/min)
- QTcB interval (msec)
- QTcF interval (msec)
- Overall evaluation (normal, abnormal – only data from external vendor will be used)

dECG parameters are described in Section 3.3.2.4. Baseline and post-baseline definitions are detailed in Section 3.1.2. dECG tables and listings will be based on the as-treated population and presented for each treatment group.

dECG parameters (except for the overall evaluation) will be summarised in SI units with n, mean, median, SD, minimum, and maximum, at each visit and for change from baseline.

Number and percentage of participants within each QTcF intervals classes at any time during the on-treatment phase will also be reported together with number and percentage of participants within QTcF increase classes at any time during the on-treatment phase using scheduled or unscheduled measurements. QTcF (corrected using Fridericia's formula) and QTcF intervals at any observation on treatment will be classified as follows:

QTcF value above 450 ms at any time during treatment:

- > 450 (ms)

- > 480 (ms)
- > 500 (ms)

QTcF increase by more than 30 ms at any time during treatment

- > 30 (ms)
- > 60 (ms)
- > 90 (ms)

QTcF value above 450 ms and QTcF increase by more than 30 ms at any time during treatment

- Value > 450 (ms) and Increase > 30 (ms) at the same time
- Value > 500 (ms) and Increase > 60 (ms) at the same time

Overall evaluation will be analysed as shift from baseline to last value in the on-treatment phase.

dECG parameters will also be listed for all participants. Overall evaluation will be listed for participants with at least one abnormality.

[redacted]

4.2.8 Treatment compliance

Exposure and compliance are calculated as described in Section 3.4.

4.2.8.1 Exposure

Exposure and actual exposure, duration and cumulative over time (days) as described in Section 3.4.1 will be presented in a summary table for each treatment group. Actual exposure will be summarised descriptively as continuous variable with n, mean, SD, min, Q1, median, Q3, max. The table will be based on the as-treated population.

Exposure and actual exposure will be listed for the as-treated population.

4.2.8.2 Compliance

Both, overall compliance, and compliance categories will be presented in a summary table for each treatment group and overall. The overall compliance will be summarised descriptively as continuous variable with n, mean, median, SD, minimum, and maximum; compliance categories as stated in Section 3.4.2 will be summarised as categorical variable with the number and percentages of participants by categories.

Compliance will also be listed together with the exposure. Both table and listing will be based on the as-treated population.

4.2.9 Concomitant medications and concomitant procedures

Concomitant medications and procedures are described in Section 3.5.

The number and percentage of participants with at least one concomitant medication and the number and percentage of participants by ATC level 4 (therapeutic subgroup) and product name will be provided using the ITT population. Additionally, the same table for disallowed medication will be provided.

Concomitant procedures will be presented in summary tables as number and percentages of participants by System Organ Class (SOC) and Preferred Term (PT) for each treatment group and overall. Participants with multiple events in the same SOC/PT will be counted only once in that SOC/PT. Participants with events in more than one SOC/PT will be counted once in each of those SOC/PT. Tables will be sorted alphabetically by SOC and PT. The table will be based on the ITT population.

All concomitant medications, disallowed concomitant medications and concomitant procedure will also be listed based on the ITT population.

4.2.10 COVID-19 analysis

Additional analyses will be performed to explore the impact of COVID-19 and implemented contingency measures. All outputs will be based on the ITT population if not stated otherwise. The number and percentage will be provided for the following categories:

- participants discontinued from study or study treatment due to COVID-19 (for all enrolled participants)
- protocol deviations related to COVID-19
- summary of COVID-19 study disruptions.

In addition, the following listings will be provided for:

- participants affected by the COVID-19 related study disruption
- participants with reported issues in the Risk and Issues Management due to COVID-19 pandemic.

4.3 Subgroup analysis

Several groups of analysis will be displayed separately for subgroups.

eGFR at baseline subgroups:

- < 45 mL/min/1.73m2
- >= 45 mL/min/1.73m2

Insulin intake at screening:

- All participants
- Participants on insulin at screening
- Participants not on insulin at screening

4.3.1 Subgroups for primary endpoint

Initial ANCOVA model and Sensitivity analysis 1 will be presented by insulin intake subgroup.

Subgroup analysis for primary endpoint (UACR) will consist of repeating the descriptive analysis and the ANCOVA model for the following subgroups:

- for participants with SGLT-2 inhibitor therapy at screening
- for participants without SGLT-2 inhibitor therapy at screening
- on participants at sites not in Japan

4.3.2 Subgroups for AEs

The list of AE tables that will be summarized by-eGFR subgroup:

- An overview table (including eGFR subgroups summary).
- The number and percentage of participants with most common AEs (frequency of > 5% in any treatment group) presented by PT.
- The number and percentage of participants with any AEs presented by SOC and PT.
- The number and percentage of participants with SAEs presented by SOC and PT.

Additionally, some tables will be presented separately by insulin use at screening:

- An overview table.
- The number and percentage of participants with most common AEs (frequency of > 5% in any treatment group) presented by PT.
- The number and percentage of participants with any AEs presented by SOC and PT.
- All corresponding tables presented by eGFR subgroup.

4.3.3 Subgroups by insulin intake

All CGM endpoints will be displayed by insulin intake at screening.

5.1 Description of the population

5.1.1 Disposition of participants

The number and percentage of participants enrolled, participants randomised, participants who received at least one dose of study IP, participants who completed the treatment and participants who completed the study will be presented in a summary table for each treatment group and overall based on all enrolled participants population.

5.1.2 Demographic and participant-specific characteristics

All demographic characteristics reported in Section 3.2.1 will be presented in summary table for each treatment group and overall; age at screening will be summarised descriptively as continuous variable with n, mean, median, SD, minimum, and maximum; all the other demographic (age group, sex, race, ethnic group, country) will be summarised as categorical variables with the number and percentages of participants by categories.

The table will be based on the ITT population. Baseline and post-baseline definitions are detailed in Section 3.1.2.

5.1.3 Medical history

All medical history (allowed and disallowed) as described in Section 3.2.2 will be presented in summary table as number and percentages of participants by System Organ Class (SOC) and Preferred Term (PT) for each treatment group and overall. Participants with multiple events in the same SOC/PT will be counted only once in that SOC/PT. Participants with events in more than one SOC/PT will be counted once in each of those SOC/PT. Table will be sorted alphabetically by SOC and PT. Table will be based on the ITT population.

5.2 Overview of the effect on safety variables

5.2.1 Adverse events

After having assigned the AEs to the corresponding study phase as described in Section 3.1.3, the TEAEs will be summarised for each treatment group. The AEs tables will be based on the as-treated population.

Summary tables listed below will be displayed according to Section 4.2.7.1:

- An overview table.
- Summary tables by PT.
- Lists of key participant information.
- Tables by eGFR subgroup at baseline.
- Specific outputs for nausea and vomiting.
- Number of participants with injection site reactions by high level term (HLT) and PT

Additionally, the following summary tables will be presented by SOC and PT (using guidance for multiple events in the same SOC/PT as per Section 4.2.7.1):

- The number and percentage of participants with any AEs
- The number and percentage of participants with AEs with outcome of death,
- The number and percentage of participants with SAEs
- The number and percentage of participants with AEs leading to discontinuation
- Number of participants with AEs by maximum reported intensity occurring in greater than 5% of participants in any treatment group.

All the AEs regardless of the study phases will also be listed for all participants included in the as-treated population.

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
B-Leukocyte differential count (absolute count): includes neutrophils, lymphocytes, monocytes, eosinophils, basophils	S/P-Aspartate transaminase		eGFR calculation (using CKD-EPI formula) – efficacy parameter added
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]		
	[redacted]		
	[redacted]		
	[redacted]		
	[redacted]		
	[redacted]		
	[redacted]		

5.2.3 Vital signs

Vital signs (BP, pulse rate, RPP, temperature and RR) are described in Section 3.3.2.3. Baseline and post-baseline definitions are detailed in Section 3.1.2. Vital signs tables will be based on the as-treated population and presented for each treatment group.

Vital signs will be summarized descriptively as continuous variables with n, mean, median, SD, minimum, and maximum, at each visit and time point within visit and for change from baseline.

The number of participants in SBP change categories with maximum pulse rate absolute change from baseline > 20 bpm at concurrent visit will also be summarised. Only measurements done predose will be considered.

Mean and standard error of the observed values and change from baseline will also be visualised by means of graphical presentations.

5.2.4 dECG

dECG parameters are described in Section 3.3.2.4. Baseline and post-baseline definitions are detailed in Section 3.1.2 dECG tables and listings will be based on the as-treated population and presented for each treatment group.

dECG parameters (except for the overall evaluation) will be summarised in SI units with n, mean, median, SD, minimum, and maximum, at each visit and for change from baseline.

dECG parameters will also be listed for all participants. Overall evaluation will be listed for participants with abnormalities together with findings if any.

[redacted]

Both variables will be summarised descriptively as normally distributed continuous variables as described in Section 4.1 based on the ITT population and presented for each treatment group.

5.4 COVID-19 analysis

Additional analyses will be performed to explore the impact of COVID-19 and implemented contingency measures. All outputs will be based on the ITT population if not stated otherwise. The number and percentage will be provided for the following categories:

- participants discontinued from study or study treatment due to COVID-19 (for all enrolled participants)
- listing of participants affected by the COVID-19 related study disruption
- listing of participants with reported issues in the Risk and Issues Management due to COVID-19 pandemic.

6 SUBPOPULATION ANALYSIS FOR PARTICIPANTS AT SITES IN JAPAN

A subpopulation analysis for only participants at sites in Japan after the completion of 26 weeks of dosing and safety follow-up will also be conducted. This subpopulation analysis will be reported separately from the CSR.

6.1 Disposition of participants and IPDs

Participant disposition and IPDs will be presented only in tables as described in Sections 4.2.1 and 4.2.2 respectively. No listings will be displayed.

6.2 Baseline assessment and other participant-specific characteristics

6.2.1 Demographic and participant-specific characteristics

All demographic and participant-specific characteristics except stratification factors will be presented in tables as described in Section 4.2.3.1. No listings will be displayed.

6.2.2 Medical history

Medical history will be presented as described in Section 4.2.3.2.

6.3 Primary/Secondary efficacy endpoints

6.3.1 UACR

UACR will be presented in tables and figures as described in Section 4.2.4.1. Sensitivity analysis 6 and subgroup analyses on participants at site not in Japan will be disregarded for this subpopulation analysis. No listings will be displayed.

6.4 Secondary efficacy endpoints

Secondary efficacy endpoints will be presented in tables as described in Section 4.2.5. PK plasma concentrations over time by Anti-Drug Antibody category will be disregarded for this subpopulation analysis. No listings will be displayed.

[redacted]

Other vital signs (temperature, RR) will be analysed in safety section.

6.5.2 Renal function and exploratory renal and cardiac biomarkers

eGFR slope for change from baseline will be analysed using the mixed model with random effects as described in Section 4.1.4.

Mean and standard error of the eGFR change from baseline value will also be visualised by means of graphical presentations.

[redacted]

6.6 Safety endpoints

6.6.1 Adverse events

After having assigned the AEs to the corresponding study phase as described in Section 3.1.3, the AEs will be summarised for each treatment group. The AEs tables will be based on the as-treated population.

All summary tables will be displayed for the following phases:

- on-treatment phase
- follow-up phase.

Summary tables listed below will be displayed according to Section 4.2.7.1:

- An overview table.
- Summary tables by PT.
- Specific outputs for nausea and vomiting.
- Number of participants with injection site reactions by high level term (HLT) and PT
- Event rates for AEs and SAEs of hypoglycaemia, overall and separately for participants taking/not taking insulin at baseline.
- The number of participants with adjudicated events by category and outcome of adjudication.

Additionally, the following summary tables will be presented by SOC and PT (using guidance for multiple events in the same SOC/PT as per Section 4.2.7.1):

- The number and percentage of participants with any AEs
- The number of AEs and SAEs
- The number and percentage of participants with AEs with outcome of death,
- The number and percentage of participants with SAEs
- The number and percentage of participants with AEs leading to discontinuation
- Number of participants with AEs by maximum reported intensity.
- The number and percentage of participants with any AEs and investigator's causality assessment. If a participant has multiple events in the same PT, the event with the strongest relationship will be counted.

6.6.2 Laboratory evaluation

Laboratory evaluation will be presented only in tables and figures as described in Section 4.2.7.2. List of key participants with potential Hy's law and listing will not be provided for this subpopulation analysis.

6.6.3 Vital signs and ECG

Vital signs and ECG will be presented only in tables as described in Section 4.2.7.3 and 4.2.7.4 respectively. No listings will be displayed.

[redacted]

6.7 Treatment compliance

Exposure and compliance will be presented only in tables as described in Sections 4.2.8.1 and 4.2.8.2 respectively. No listings will be displayed.

6.8 Concomitant medications and concomitant procedures

Concomitant medications will be presented as described in Section 4.2.9.

6.9 COVID-19 analysis

Additional analyses will be performed to explore the impact of COVID-19 and implemented contingency measures. All outputs will be based on the ITT population if not stated otherwise. The number and percentage will be provided for the following categories:

- participants discontinued from study or study treatment due to COVID-19 (for all enrolled participants)
- protocol deviations related to COVID-19
- summary of COVID-19 study disruptions.

7 CHANGES OF ANALYSIS FROM PROTOCOL

This SAP is based on study protocol D5676C00001 Amendment 1.0 dated 29JUN2020. Any further amendment of the study protocol that could have an impact on the SAP will lead to an amendment of this document. Changes of analysis from D5676C00001 Amendment 1.0 dated 29JUN2020 are listed here below:

Section 1.2.5 Schedule of activities

No changes were made to the methodology of the ADA assay however, due to change in reporting of minimum ADA titer from 5 to 15, ADA-negative samples are reported with titer <

15 and ADA-positive samples have a titer ≥ 15. Consequently, participants with a 3-month post-study ADA titre ≥ 30 (previously ≥ 10) will be asked to return for a sample at 3-month intervals until the titre is < 30 (previously < 10). This change affects only reporting of ADA and has no effect on the measurement or interpretation of ADA results.

Section 3 Objectives and Endpoints

- Primary endpoint is change and percentage change in UACR versus placebo from baseline to the end of 14 weeks of dosing. First secondary endpoint is change and percentage change in UACR versus placebo from baseline to the end of 26 weeks of dosing. In SAP these two endpoints are reported within the same Section "4.2.4.1 UACR". In addition, we will analyse only the percent change as UACR is log-normally distributed parameter.
- Exploratory endpoints for renal function and exploratory renal and cardiac biomarkers are percentage and absolute change from baseline to the end of 14 and 26 weeks of dosing for corresponding parameters. In this SAP we will analyse change or percent change depending on the distribution of the parameter.
- Exploratory endpoints for markers of liver health are change and percentage change from baseline to the end of 14 and 26 weeks of dosing for corresponding parameters. In this SAP we will analyse change or percent change depending on the distribution of the parameter.
- Exploratory endpoints for PRO assessments are change from baseline to the end of 14 and 26 weeks for corresponding parameters. In this SAP we will not apply ANCOVA model for PRO as the questionnaires are not mandatory to be entered and this can lead to a lack of data for modelling.
- Several endpoints are not mentioned in the protocol as those to be compared with semaglutide. However, according to this SAP (as per sponsor's request) we will display semaglutide summary statistics for all available measurements (not available only for ADA and ABPM). Additional groups of assessments not mentioned in CSP:
  - Markers of liver health
  - PRO questionnaires
  - Safety assessments.
- If the same parameter is mentioned in different endpoints, in this SAP it will be mentioned only once when firstly mentioned in the list of endpoints:
  - UACR – only in "Primary endpoint"
  - HbA1c and fasting glucose – only in "Secondary endpoints"
  - 10-day average glucose and 10-day percent time spent in different glucose ranges as measured by CGM – only in "Secondary endpoints".
  - Effect on body weight – only in "Secondary endpoints".
- Safety endpoints for AEs are TEAEs and TESAEs. TEAEs are defined as on-treatment evens, while we analyse both on-treatment and off-treatment as per TEAEs guidelines.
- Change from baseline or percentage change from baseline can be used in objectives disregarding distributions of the variables. In this SAP we are using "change from baseline" for normally parameters values and "percent change from baseline" for log-normally distributed parameters. The only exceptions: weight and total daily insulin dose are analysed for both absolute change and regular percent change.

Section 9.4.2.1 Primary Endpoint

8 REFERENCES

1. Service, FJ et al. Mean amplitude of glycemic excursions, a measure of diabetic instability. Diabetes. 1970;19(9):644-55.

2. Service FJ, Molnar GD, Rosevear JW, Ackerman E, Gatewood LC, and Taylor WF, "Mean amplitude of glycemic excursions, a measure of diabetic instability," Diabetes, vol. 19, no. 9, pp. 644–655, 1970.

9 APPENDIX

9.1 Appendix 1 Changes made to the SAP after initial sign-off

9.1.1 Version 1.0

NA

9.1.2 Version 2.0

Overall:

Updating units.

"Subjects" replaced by "participants" to follow CSP wording.

"Time point" wording used throughout.

Section 1.2.4

[redacted]

Participants may be rescreened.

Section 2.1

All-enrolled population changed to All enrolled to follow standards.

[redacted]

[redacted]

Section fully added.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

SIGNATURE PAGE

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Document Name: d5676c00001-sap-ed-5		
Document Title:	Statistical Analysis Plan Edition 5	
Document ID:	Doc ID-004379538	
Version Label:	7.0 CURRENT LATEST APPROVED	
[redacted]	**Signed by**	**Meaning of Signature**
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.