Clinical Study Protocol	
Study Intervention	Cotadutide
Study Code	D5676C00001
Version	Amendment 2
Date	04Jan2021

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

Global Sponsor: AstraZeneca AB**,** 151 85 Södertälje, Sweden

Local Sponsor: AstraZeneca KK**,** 3-1, Ofuka-cho, Kita-ku, Osaka 530-0011

Manufacturers:
AstraZeneca and a third party (cotadutide)
Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark (semaglutide [OZEMPIC®])

Regulatory Agency Identifier Number(s):
EudraCT Number: 2020-000255-12

This clinical study protocol has been subject to a peer review according to AstraZeneca Standard procedures. The clinical study protocol is publicly registered, and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Amendment Number: Amendment 2

Study Intervention: Cotadutide

Study Phase: 2b

Short Title: Phase 2b Study of Cotadutide in Participants Who Have Chronic Kidney Disease with Type 2 Diabetes Mellitus

Study physician name and contact information will be provided separately.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	04Jan2021
Amendment 1	29Jun2020
Original Protocol	01Apr2020

Amendment 2 (04Jan2021)

Overall Rationale for the Amendment:

This global amendment contains revisions to Amendment 1 of the global protocol dated (29Jun2020) to add time windows for specific visits to make the study more accessible to participants during the current coronavirus disease (COVID-19) pandemic. Other minor revisions such as clarifications and correction of typos were made. This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study. Changes in global Amendment 2 are presented in the table below.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Figure 1	Updated to reflect measures to increase protocol flexibility detailed in SoA	For enhanced site flexibility, in particular due to circumstances presented by the COVID-19 pandemic	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.3 (Schedule of Activities)	• Time window added to Follow-up visit +/- 3 days • Increased time window for screening period by 8 days • Remote contact to advise on insulin dose adjustment prior to first dose (if required) and optional visit permitted on Day -2 or -1  • Flexibility added to time of vital sign collection (footnote f) • Increased time window added to time of 4 hour PK sample (footnote l) • Flexibility added to time of randomisation (footnote s)	For enhanced site flexibility, in particular due to circumstances presented by the COVID-19 pandemic	Non-substantial
1.3 (Schedule of Activities)	Optional status of visit on Day -2 made clearer in table	For clarification	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.3 (Schedule of Activities)	Day -2 eligibility verification updated for consistency with other aspects of protocol; screening labs (UACR, HbA1c, eGFR and calcitonin) form part of eligibility check at Day -2	For clarification	Non-substantial
1.3 (Schedule of Activities)	[redacted]	For clarification	Non-substantial
1.3 (Schedule of Activities)	Notes: removal of wording “every 4 weeks”	Correction of typo	Non-substantial
4.1.3 Dose reduction	More detailed clarification of circumstances under which dose reduction may occur	For clarification	Non-substantial
5.4 (Screen Failures)	Clarification around repeat screening	For clarification	Non-substantial
6.5 (Concomitant Therapy; Tables 8 and 13)	Clarified all alpha-glucosidase inhibitors are permitted concomitant and rescue therapies	For clarification	Non-substantial
6.5.1.2 (Insulin Dose Adjustments)	Adjustment of text to provide consistency with updates in SoA	For consistency	Non-substantial
8.2.4 (Retinal Assessments)	Changes made to image storage conditions and removal of historical assessments as baseline	For clarification	Non-substantial
9.4.4 (Other Analyses; Immunogenicity Analysis)	Clarification on handling of ADA cross-reactivity results post study completion	For clarification	Non-substantial
Appendix A 6 (Data Quality Assurance)	Correction to confirm that records and documents will be retained for 25 years at sites	Correction of typo	Non-substantial
Appendix G (Summary of Changes)	Created to cover SOC to Amendment 1 (29Jun2020)	Administrative change	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial

[redacted] ADA = anti-drug antibody; eGFR = estimated glomerular filtration rate; COVID-19 = coronavirus disease; HbA1C = Glycated haemoglobin; PK = pharmacokinetic; SoA = schedule of assessments; SOC = System organ class; UACR = urine albumin to creatinine ratio

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: 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

Short Title: Phase 2b Study of Cotadutide in Participants Who Have Chronic Kidney Disease with Type 2 Diabetes Mellitus

Rationale:
Chronic kidney disease (CKD) leads to progressive decline of renal function and arises due to a combination of age-related decline in renal function exacerbated by conditions such as diabetes mellitus, hypertension, obesity, and primary renal disorders (Hill et al, 2016). The global prevalence of CKD is approximately 11-13% and is increasing in parallel with aging populations and escalating prevalence of type 2 diabetes mellitus (T2DM) and obesity. Per 2016 estimates, kidney disease is the ninth most common cause of death in high income countries globally (World Health Organization, 2018). The main causes of CKD are diabetes and high blood pressure (National Institute of Diabetes and Digestive and Kidney Diseases, 2016), and diabetes accounts for 44% of new cases of kidney failure (National Kidney Foundation, 2016). Because dedicated treatments for CKD with T2DM are limited, a large unmet need exists for this patient group. This Phase 2b study is designed to evaluate the efficacy, safety, tolerability, and pharmacokinetic (PK) profile of cotadutide at different dose levels in participants who have CKD with T2DM.

Objectives and Endpoints

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
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

For tertiary/exploratory objectives and endpoints, see Section 3 of the protocol.

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 subcutaneously (SC) once daily over 26 weeks in participants who have CKD with T2DM (estimated glomerular filtration rate [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.

Disclosure Statement: This is a parallel treatment, double-blind study with 5 arms.

Number of Participants:

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

Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but are not randomly assigned to study intervention, are considered “screen failures,” unless otherwise specified by the protocol.

Intervention Groups and Duration:

Participants will be randomised to cotadutide 100, 300, or 600 µg, placebo, or semaglutide 1.0 mg following differing periods of titration. Each cotadutide treatment arm will be placebo-matched with respect to titration schedule and dose levels. Cotadutide and placebo will be administered SC once daily and semaglutide SC once weekly for a total of 26 weeks. Cotadutide, placebo, and semaglutide will be administered via injection pen devices. [redacted]
physician before implementing.

Data Monitoring Committee: No

Statistical Methods

The total study sample size is 225 participants.

Participants will be randomised in a 1:1:1:1:1 ratio to 1 of 3 cotadutide arms, a placebo arm, or open-label semaglutide arm.

The sample size was determined to provide [redacted]

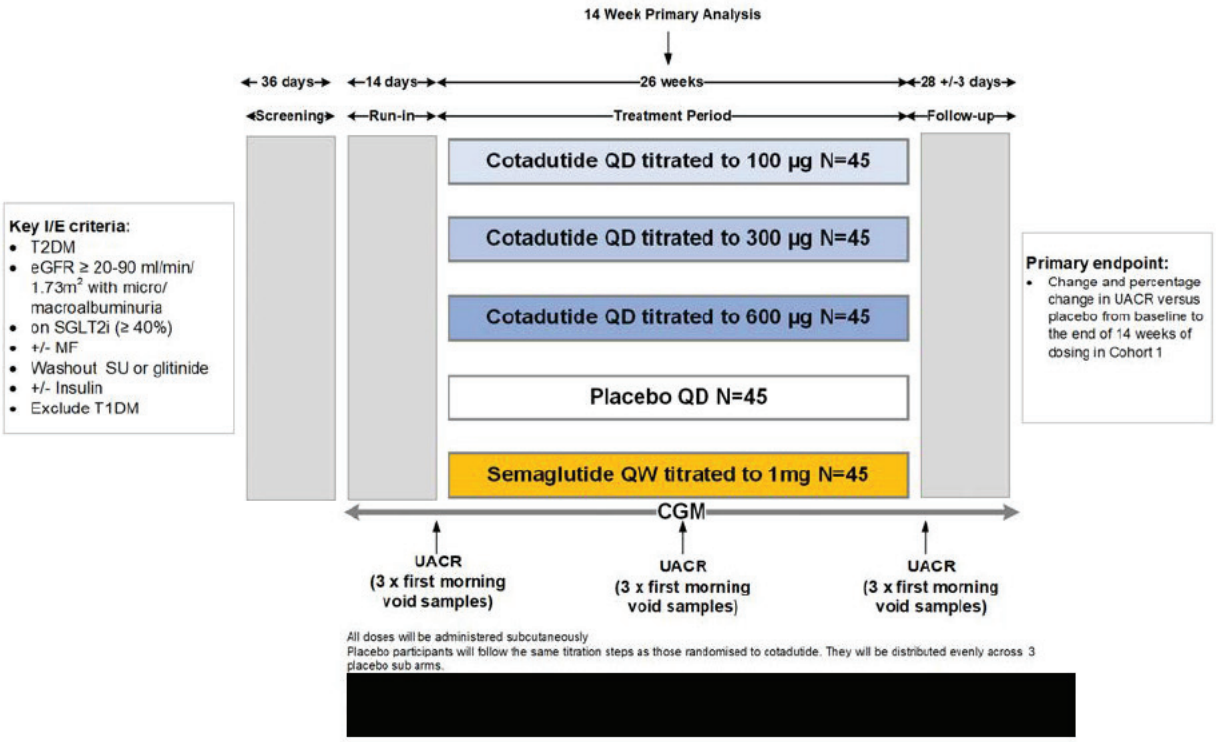
Two analyses are planned for this study:

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

Formal statistical modelling analysis for certain prespecified efficacy endpoints will be conducted but will not be performed for all endpoints. 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, and the scope of the analysis will be defined in the statistical analysis plan (SAP).

1.2 Schema

Figure 1 Study Design



CGM = continuous glucose monitoring; d = day; eGFR = estimated glomerular filtration rate; I/E = inclusion/exclusion; MF = metformin; N = number of participants; QD = once daily; QW = once weekly; SGLT2i = sodium-glucose cotransporter 2 inhibitor; SU = sulfonylurea; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; UACR = urine albumin to creatinine ratio

1.3 Schedule of Activities

Table 2 Schedule of Activities

Study Period	Screening	Run-in (Days -14 to -1)[a]			Treatment											E/D ± 7[b]	Follow-up (28 days after last dose) ± 3	Notes	Details in CSP section or Appendix
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																			Section 5.1
Optional informed [redacted]	[redacted]																			[redacted]
[redacted]	[redacted]																			[redacted]

Table 2 Schedule of Activities

Study Period	Screening	Run-in (Days -14 to -1)[a]			Treatment												E/D ± 7[b]	Follow-up (28 days after last dose) ± 3	Notes	Details in CSP section or Appendix
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**				
Verify inclusion and exclusion criteria[c]	X			X															Assess and verify prior to random-isation	Section 5.1 and 5.2
Fasting by participant 8 hours prior to outpatient visit					X							X				X				Section 5.3.1
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																			Section 6.5

Table 2 Schedule of Activities

Study Period	Screening	Run-in (Days -14 to -1)[a]			Treatment											E/D ± 7[b]	Follow-up (28 days after last dose) ± 3	Notes	Details in CSP section or Appendix
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				
Consider [redacted]						[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]
[redacted]				[redacted]															[redacted]	
Remote contact 3 days prior to visit for participant reminders[e]												X				X				

Table 2 Schedule of Activities

Study Period	Screening	Run-in (Days -14 to -1)[a]			Treatment											E/D ± 7[b]	Follow-up (28 days after last dose) ± 3	Notes	Details in CSP section or Appendix
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**				
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																			Section 8.3.1
SAEs	Monitored continuously throughout the study																			Section 8.3.1
Pregnancy test (serum or urine) if applicable	X (serum only)				X			X			X			X		X	X	X	Testing for women of child-bearing potential	Section 5.1
Full physical examination	X																X			Section 8.2.1

Table 2 Schedule of Activities

Study Period	Screening	Run-in (Days -14 to -1)[a]			Treatment												E/D ± 7[b]	Follow-up (28 days after last dose) ± 3	Notes	Details in CSP section or Appendix
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**				
Abbreviated physical examination			X		X	X	X	X	X	X	X	X	X	X	X	X		X		Section 8.2.1
Vital signs[f]	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 8.2.2
ECG[g]	X				X	X	X	X	X	X		X		X		X	X	X		Section 8.2.3
Urinalysis					X			X				X		X		X	X	X		Section 8.2.5
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		Section 8.2.5
Calcitonin	X				X							X				X	X	X[h]		Section 8.2.6
Lactate, lipase, and amylase					X							X				X	X			Section 8.2.6
C peptide[i]	X				X							X				X				Section 8.2.6
Efficacy Assessments																				

Table 2 Schedule of Activities

Study Period	Screening	Run-in (Days -14 to -1)[a]			Treatment												E/D ± 7[b]	Follow-up (28 days after last dose) ± 3	Notes	Details in CSP section or Appendix
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				
Body weight[j]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 8.1.3
Efficacy Blood Tests																				
HbA1c	X				X			X				X		X		X	X	X		Section 8.1.2
[redacted]					[redacted]							[redacted]				[redacted]				[redacted]
Efficacy Urine Tests																				
UACR[k]	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 8.1.1
[redacted]		[redacted]	[redacted]							[redacted]				[redacted]						[redacted]
Biomarker Assessments																				
[redacted]					[redacted]							[redacted]				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2 Schedule of Activities

Study Period	Screening	Run-in (Days -14 to -1)[a]			Treatment											E/D ± 7[b]	Follow-up (28 days after last dose) ± 3	Notes	Details in CSP section or Appendix
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]					■							■				■				■
Biomarker Urine Tests																				
[redacted]					■							■				■				■
[redacted]					■			■				■				■				■
Pharmacokinetics and Immunogenicity																				
Cotadutide [redacted]					■	■	■		■	■	■			■		■	■		[redacted]	■

Table 2 Schedule of Activities

Study Period	Screening	Run-in (Days -14 to -1)[a]			Treatment												E/D ± 7[b]	Follow-up (28 days after last dose) ± 3	Notes	Details in CSP section or Appendix
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**				
ADA (predose)					X	X	X		X	X	X			X		X	X	X[m]	Not collected from partici-pants random-ised to sema-glutide	Section 8.5.2
Devices and Images																				
[redacted]		[redacted]														[redacted]				[redacted]
[redacted]		[redacted]										[redacted]				[redacted]				
[redacted]		[redacted]										[redacted]				[redacted]			[redacted]	[redacted]

Table 2 Schedule of Activities

Study Period	Screening	Run-in (Days -14 to -1)[a]			Treatment											E/D ± 7[b]	Follow-up (28 days after last dose) ± 3	Notes	Details in CSP section or Appendix
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				
																			for 300 and 600 µg arms only	
CGM device training and explanation		X										X							Pro™ or Flash™ device as appropri-ate	Section 8.1.4
[redacted]		[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]				[redacted]	[redacted]				[redacted]
[redacted]												[redacted]	[redacted]	[redacted]						[redacted]
Training for and provision of glucose/ketone meter and diary		X																		Section 8.2.6

Table 2 Schedule of Activities

Study Period	Screening	Run-in (Days -14 to -1)[a]			Treatment											E/D ± 7[b]	Follow-up (28 days after last dose) ± 3	Notes	Details in CSP section or Appendix
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**				
Injection pen device demonstration and training (as required)				X	X														At investigator's discretion and per site resources, a saline injection technique for training may be used	
Study Intervention Administration and Randomisation																				
Randomisation[s]				X																Section 6.3
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]				

Table 2 Schedule of Activities

Study Period	Screening	Run-in (Days -14 to -1)[a]			Treatment												E/D ± 7[b]	Follow-up (28 days after last dose) ± 3	Notes	Details in CSP section or Appendix
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				
Daily																				

Table 2 Schedule of Activities

Study Period	Screening	Run-in (Days -14 to -1)[a]			Treatment												E/D ± 7[b]	Follow-up (28 days after last dose) ± 3	Notes	Details in CSP section or Appendix
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				
Semaglutide titration step in clinic							X		X											Section 4.1.1
[redacted]																				
[redacted]		[redacted]										[redacted]				[redacted]		[redacted]		[redacted]

[redacted] ADA = anti-drug antibodies; AE = adverse event; BMI = body mass index; CGM = continuous glucose monitoring; CKD-EPI = chronic kidney disease epidemiology collaboration; CSP = clinical study protocol; [redacted] ECG = electrocardiogram; eCRF = electronic case report form; E/D = early discontinuation; eGFR = estimated glomerular filtration rate; [redacted] PK = pharmacokinetics; [redacted] SAE = serious adverse event; SC = subcutaneous; type 1 diabetes mellitus; UACR = urine albumin to creatinine ratio; ULN = upper limit of normal

All activities apply to all arms unless otherwise stated.

[a] Participants may enter the run-in while awaiting results on calcitonin levels from screening.

[b] Performed in event of early discontinuation of study intervention or withdrawal from study

[c] Day -2 eligibility verification is based on screening lab results (HbA1c, eGFR, UACR, and calcitonin) and Day -5 lab results (creatinine, urea plus electrolytes/liver function tests), BMI from the screening visit, and vital signs and the abbreviated physical examination from Day -5.

[d] Where relevant (ie, if the participant is taking insulin), participants should be advised on dose reduction as detailed in Section 6.5.1.2 and Section 6.5.1.3. This ideally should occur as a telephone call on the morning/early afternoon of Day -2 or -1 and should be documented in the source notes, but can occur at any time after randomisation when the investigator will be aware if the participant has been randomised to a blinded (cotadutide or placebo) or open-label semaglutide arm.

[e] Remote contact will be made with participants to remind them about urine collection and to collect any relevant information regarding AEs or concomitant medications. Prior to the visit on Day 113, participants will be contacted and reminded to change their CGM sensor and return their Freestyle Libre Pro™ sensor to the clinic in the envelope provided.

[f] Vital signs including temperature, pulse rate, blood pressure (seated or semi-supine), and respiratory rate measurements will be collected at any point during the visit where indicated unless specified otherwise, and will be measured predose on Day 1 (± 15 minutes) and 4 hours postdose (± 15 minutes) on Days 1, 57 and 71.

[g] Single digital ECG recording will be collected at any point during the visit where indicated unless specified otherwise; on Days 1, 57, and 71, ECGs will be obtained predose and at 4 hours postdose (± 15 minutes).

Table 2 Schedule of Activities

Study Period	Screening	Run-in (Days -14 to -1)[a]			Treatment											E/D ± 7[b]	Follow-up (28 days after last dose) ± 3	Notes	Details in CSP section or Appendix
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				

h Only to be repeated if the calcitonin level was > ULN in the sample taken at the end of dosing

i If C peptide levels are below the lower range of normal, the investigator should perform autoantibody tests to rule out T1DM.

j Body weight should be measured where possible in the morning prior to breakfast, after the participant has toileted and removed bulky clothing including shoes. Calibrated scales appropriate for the participants weight should be used.

k [redacted]

l A PK blood sample will be taken from participants randomised to cotadutide or placebo. PK blood samples will be drawn predose (where applicable) at each visit where indicated. Additionally, on Day 29 and Day 85, a 4-hour sample +/- 15 minutes will be taken.

m [redacted]

n A site that possesses the technical capability to collect [redacted] should be changed every 14 days, and once the old sensor is removed, it should be stored in the envelope provided and returned to the clinic at the next visit.

q On Day 182, participants must be dosed while in the clinical unit, and the precise time of administration [redacted]

s Randomisation may occur any time between Days -3 and Day 1 as long as all baseline UACR samples, ie, Day -5, -4, and -3 have been collected prior to randomisation. In the scenario that the Day -5 UACR collection has not been performed (as described in footnote k) and instead a Day -4, -3, and -2 collection is being conducted, randomisation must occur after UACR collection on Day -2. For participants on insulin where insulin dose reduction is deemed necessary, randomisation should be scheduled to give sufficient opportunity to advise on insulin dose reduction prior to commencing investigational productor semaglutide.

t Outpatient visit on Day -2 is optional and may also occur on Day -1.

2 INTRODUCTION

Cotadutide (MEDI0382) is a glucagon-like peptide 1 (GLP-1) and glucagon receptor co-agonist that is being developed for the treatment of type 2 diabetes mellitus (T2DM), obesity, and nonalcoholic steatohepatitis (NASH).

2.1 Study Rationale

Chronic kidney disease (CKD) leads to progressive decline of renal function and arises due to a combination of age-related decline in renal function exacerbated by conditions such as diabetes mellitus, hypertension, obesity, and primary renal disorders (Hill et al, 2016). The global prevalence of CKD is approximately 11-13% and is increasing in parallel with aging populations and escalating prevalence of T2DM and obesity.

Per 2016 estimates, kidney disease is the ninth most common cause of death in high income countries globally (World Health Organization, 2018). The Global Burden of Disease Study 2015 estimated that 1.2 million people died from kidney failure, which was an increase of 32% since 2005 (GBD 2015 Mortality Causes of Death Collaborators, 2016). The main causes of CKD are diabetes and high blood pressure (National Institute of Diabetes and Digestive and Kidney Diseases, 2016), and diabetes accounts for 44% of new cases of kidney failure (National Kidney Foundation, 2016). Because dedicated treatments for CKD with T2DM are limited, a large unmet need exists for this patient group.

In a Phase 2a study of cotadutide in participants with T2DM and renal impairment (Study D5670C00013), once daily administration of cotadutide titrated from 50 to 300 µg over 32 days demonstrated an acceptable safety and tolerability profile; the overall tolerability of cotadutide in this population with renal impairment was comparable to what had been observed in prior studies of cotadutide in populations without renal impairment. Clinically significant glycaemic control and significant body weight loss were also observed in participants who received cotadutide compared to those who received placebo. An exploratory analysis revealed a numerical reduction in urine albumin to creatinine ratio (UACR; -3.05 mg/mmol versus 2.02 mg/mmol, p = 0.077) along with an unchanged estimated glomerular filtration rate (eGFR) and body water volume.

This Phase 2b study is designed to evaluate the efficacy, safety, tolerability, and pharmacokinetic (PK) profile of cotadutide [redacted] participants who have CKD with T2DM. Participants will have an eGFR $\geq$ 20 mL/min/m^2 and < 90 mL/min/1.73 m^2 and micro- or macroalbuminuria.

2.2 Background

Glucagon-like peptide 1 receptors are expressed in a wide variety of tissues including the pancreas, kidney, heart, gastrointestinal tract, and brain. While GLP-1 receptor agonists are

primarily considered in context of their glucose-dependent stimulation of insulin secretion, they also have important effects on the kidney (Skov, 2014). Glucagon-like peptide 1 has been reported to increase glomerular filtration rate (GFR), renal blood flow, and the fractional excretion both of sodium and potassium, with renal GLP-1 receptors present in afferent arteriolar vascular smooth muscle cells, and some research studies have also reported GLP-1 receptor expression in glomerular endothelial cells and macrophages, juxtaglomerular cells, and the proximal tubule (Bloomgarden, 2018). Glucagon-like peptide 1 receptor agonists have been clinically shown to reduce decline in eGFR in patients with T2DM and moderate to severe CKD (Tuttle et al, 2018). Treatment with liraglutide has been associated with a significant reduction in albuminuria, with nearly a 25% lower likelihood of development of macroalbuminuria, and a 20% reduction in the albumin to creatinine ratio, regardless of grade of chronic kidney disease (CKD) (Marso et al, 2016b). Similarly, semaglutide has shown fewer participants progress to macroalbuminuria over long term follow up (Marso et al, 2016a).

Glucagon receptors are also expressed in the kidney especially in the distal tubule and collecting duct (Bailly et al, 1985). Glucagon has been shown to promote transient increases in GFR and promote natriuresis, and to enhance secretion of urea and uric acid. Additional effects on potassium, calcium, and magnesium homeostasis are also thought to be regulated by glucagon.

Cotadutide is a synthetic peptide with both GLP-1 and glucagon dual receptor agonist activity that promotes glucose lowering and weight loss and is targeted at patients with NASH, obesity, and T2DM. In a prior phase 2b study (Study D5670C00013), 32 days of cotadutide treatment in participants with T2DM and renal impairment (eGFR $\geq$ 30 and $<$ 60 mL/min/1.73 m^2) led to numerical reductions in UACRs and were of a magnitude (51% reduction versus placebo) in the subgroup with baseline micro or macroalbuminuria, which is associated with longer term renoprotection (Heerspink et al, 2019). In addition, safety and tolerability was confirmed to be acceptable in this population, and a single dose PK/PD study (Study D5670C00008) conducted in participants with eGFR from $\geq$ 20-60 ml/min/1.73m^2 demonstrated that cotadutide has an equivalent PK profile in participants with renal impairment to that of participants with no renal impairment, and single doses were confirmed to have acceptable tolerability in participants in this eGFR range.

In a phase 2a study of cotadutide in participants with T2DM who were overweight/obese (Study D5670C00030), cotadutide administered once daily demonstrated an acceptable tolerability and safety profile at higher doses (titrated from 20 µg to higher doses of 600 µg) and over a longer treatment duration (77 days). In this study, PK was linear with a terminal half-life of approximately 15 hours and minimal accumulation after multiple subcutaneous (SC) daily doses.

In a Phase 2b study of cotadutide with an open-label active comparator (liraglutide) arm (Study D5670C00004), treatment with cotadutide for 54 weeks was associated with significant and clinically meaningful reductions in HbA1c and body weight at Week 14, Week 26, and Week 54 at all dose levels compared to placebo. A dose-dependent reduction in liver enzymes was observed in cotadutide-treated participants. The safety profile of cotadutide was generally similar to that observed with GLP-1 receptor agonists.

A detailed description of the chemistry, pharmacology, efficacy, and safety of cotadutide is provided in the Investigator's Brochure.

2.3 Benefit/Risk Assessment

This is the first clinical study in which cotadutide at doses greater than 300 µg will be administered to participants who have CKD with T2DM. Cotadutide has the potential to deliver improvements in proteinuria, glycaemic control, body weight, and lipid homeostasis, and is predicted to be a useful therapy for participants who have CKD with T2DM.

Identified and potential risks for cotadutide are based on available published data for GLP-1 receptor mono-agonists and glucagon receptor mono-agonists, as well as clinical and non-clinical data for cotadutide. Identified risks/adverse drug reactions for cotadutide are nausea, vomiting, injection site reactions and increased heart rate. Potential risks for cotadutide include alterations in blood pressure, QT interval prolongation, anaphylactic-type reactions, skin rash, pancreatitis, pancreatic carcinoma, thyroid cancer, hypoglycaemia (with sulfonylurea/insulin), and diabetic ketoacidosis (following insulin reduction). The potential risk of hypoglycaemia will be updated to include "with glitinides" in an Investigator's Brochure update (Edition 9.0). Due to the CKD with T2DM indication, acute renal failure secondary to dehydration will be included as an additional potential risk in an Investigator's Brochure update (Edition 9.0).

The study design aims to minimise the impact of identified and potential risks to participants in this study based on the proposed inclusion/exclusion criteria, safety monitoring, and up-titration dosing schedule. All participants will be monitored throughout the study to ensure adequate glycaemic control. Participants will be given appropriate training in use of the injection pen device for SC self-administration. Dose uptitrations will only be performed in the clinic. Training will also be provided to all study participants for use of other devices, including continuous glucose monitoring (CGM) devices, heart rate monitors, and glucose/ketone meters.

Taking into account the measures taken to minimise risk to participants in this study, the potential risks identified in association with cotadutide are justified by the anticipated benefits that may be afforded to participants who have CKD with T2DM.

More detailed information about the known and expected benefits and potential risks of cotadutide may be found in the Investigator's Brochure.

3 OBJECTIVES AND ENDPOINTS

Table 3 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
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
[redacted]	
[redacted]	[redacted]

Table 3 Objectives and Endpoints

Objectives	Endpoints
To assess	
	• Percentage and absolute change in NT pro-BNP

Table 3 Objectives and Endpoints

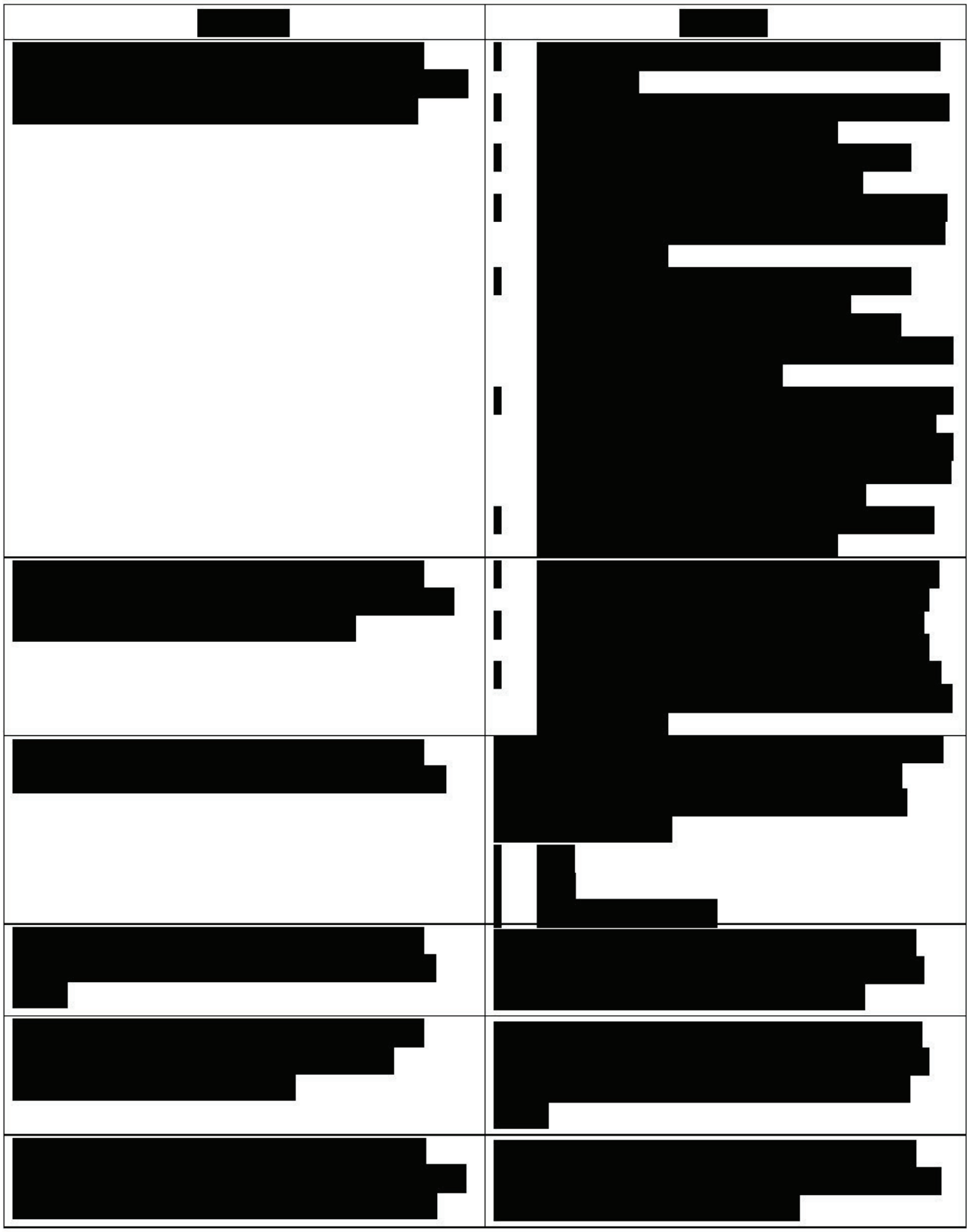


Table 3 Objectives and Endpoints

Objectives	Endpoints
To assess the [redacted]	[redacted]
[redacted]	[redacted]

AST = aspartate transaminase; BMI = body mass index; CGM = continuous glucose monitoring; CKD-EPI = chronic kidney disease epidemiology collaboration; DBP = diastolic blood pressure; [redacted] ECG = electrocardiogram; eGFR= estimated glomerular filtration rate; [redacted]

4 STUDY DESIGN

4.1 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 [redacted] by SC injection over 26 weeks in participants with T2DM and CKD (eGFR ≥ 20 and < 90 mL/min/1.73 m^2 and micro- or macroalbuminuria).

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.

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. 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.

The study will have a 14-day run-in period during which participants will be given advice on diet and exercise and asked to wear a CGM sensor, followed by a 26-week treatment period and 28-day follow-up period. Diet and exercise guidance will be according to local practices.

This study plans to randomise a total of approximately 225 participants across multiple study sites in approximately 8 countries. Participants will be consented, screened for eligibility, and if eligible, randomised within 48-50 days of screening. Participants may enter the run-in period but must not be randomised until confirmation of the calcitonin laboratory test result.

A 4-week washout prior to dosing on Day 1 is required for participants taking a sulfonylurea or glitinide at screening. Treatment with a dipeptidyl peptidase-4 inhibitor may continue at the investigator's discretion as it is not specifically contraindicated; however, it is not a permitted rescue medication.

Once daily dosing with cotadutide or placebo will begin on Day 1 at 50 µg, and participants will follow the titration regimen to which they have been randomised. Participants randomised to the semaglutide arm will receive once weekly doses also beginning on Day 1 at a start dose of 0.25 mg once weekly and follow the titration regimen detailed in the label, reaching 1.0 mg once weekly after 8 weeks.

Urine albumin to creatinine ratio will be measured following three first morning void collections at home prior to the clinic visit during the run in and on Days 99 and 182. All other UACR calculations will be determined from single urine samples taken in the clinic. Participants will attend the visits detailed in the schedule of events and undergo the assessments therein.

The primary analysis will be conducted after all participants have completed 14 weeks of dosing, and a final analyses will be conducted once all participants have completed dosing and follow-up visits. A subpopulation analysis including only participants at sites in Japan will also be conducted once all participants have completed dosing and follow-up visits.

At the primary analysis, an analysis on UACR will be conducted on the subpopulation of participants on an SGLT-2 inhibitor therapy at screening [redacted]

After 68 or 30% of participants [redacted] have completed Week 11, an interim safety review will be conducted. Data will be reviewed by the sponsor's unblinded review committee (URC). Details can be found in the Interim Analysis Charter.

4.1.1 Treatment Groups and Titration Regimens

Participants will be randomised to cotadutide 100, 300, or 600 µg, placebo, or semaglutide for a total of 26 weeks following differing periods of titration. Each cotadutide treatment arm will be placebo-matched with respect to titration schedule and dose levels. Cotadutide and placebo will be administered once daily and semaglutide once weekly, all via SC injection. Study treatments will be titrated in discrete steps as shown in Table 4.

Table 4 [redacted]

Table 4 Titration Regimen

Treatment Arm (N)	Weeks – Dose	Weeks – Dose	Weeks – Dose	Weeks – Dose	Weeks – Dose	Weeks – Dose
Semaglutide 1.0 mg (45)[a]	1 to 4 – 0.25 mg	5 to 8 – 0.5 mg	9 to 26 – 1.0 mg			

N = number of participants
[a] Participants at sites in Japan will not be randomised to the semaglutide arm.
[b] Participants randomised to placebo will follow 1 of 3 titration regimens matched to the cotadutide arms and will be distributed evenly across the placebo arms.

4.1.2 Dose Escalation

Cotadutide/Placebo Arms

For participants assigned to cotadutide or [redacted]

Semaglutide Arm

For participants assigned to semaglutide, doses will commence at 0.25 mg and will be uptitrated every 4 weeks to a final dose of 1.0 mg (see Section 4.1.1).

4.1.3 Dose Reduction

[redacted]

The semaglutide Summary of Product Characteristics (SmPC) does not provide advice on dose adjustment in the event of nausea, vomiting, or other gastrointestinal symptoms. In exceptional circumstances and if intolerable gastrointestinal AEs occur in a participant treated with semaglutide, it may be possible to switch the participant to a lower dose level, but this decision must be discussed with the study physician beforehand.

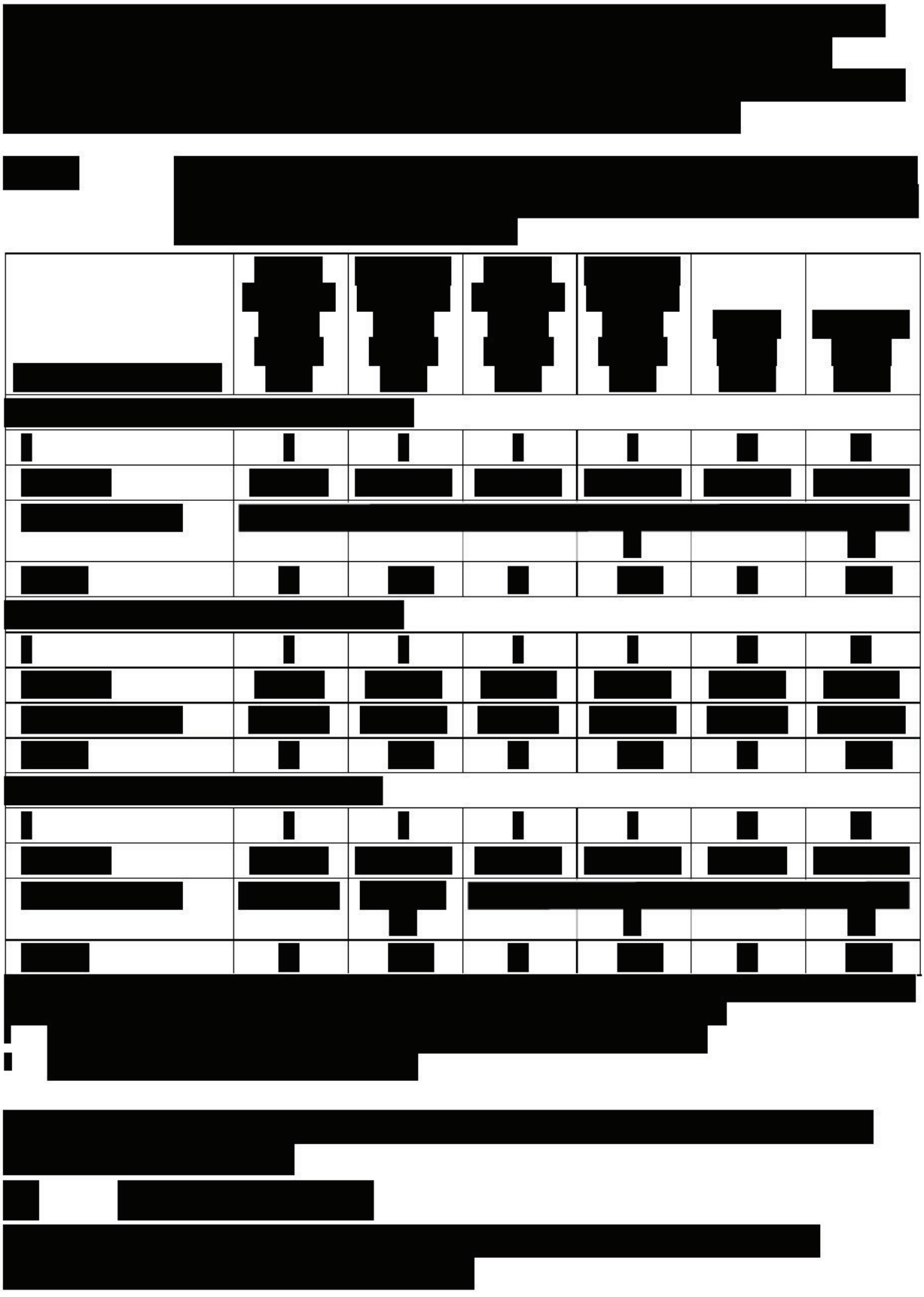
4.2 Scientific Rationale for Study Design

Urine albumin to creatinine ratio is an established biomarker of renal disease and prior studies have demonstrated that improvements in UACR predict improvement in longer term renal outcomes (Heerspink et al, 2019). The primary endpoint of UACR will be measured by taking the average of three first morning void urine samples at baseline and at the end of treatment to evaluate the efficacy of each dose of cotadutide in this population of CKD with T2DM.

Safety and tolerability in this population of CKD with T2DM will be studied at three different dose levels and treatment-emergent adverse events (AEs) and serious adverse events (SAEs) will be recorded. Additional measures of safety as secondary endpoints will include vital signs (pulse rate, blood pressure, temperature, and respiratory rate), laboratory tests (including creatinine, eGFR, lipase, amylase and electrolyte levels) and CGM to detect occult hypoglycaemia and hyperglycaemia, and electrocardiograms (ECGs).

To better characterise the glucose-lowering efficacy of cotadutide in renally impaired T2DM participants, additional markers of glucose control including HbA1c and fasting glucose level will be measured, alongside measures of the percentage of time spent within a target glucose range measured by CGM. Further exploratory analyses based on CGM readings will be generated to enable comparison across different dose levels and with semaglutide. Weight will also be measured to enable comparison across different dose levels.

4.2.1 [redacted]



[redacted]

[redacted]

AUC = area under the concentration-time curve; AUC_{tau} = area under the concentration-time curve during a dosing interval; BMI = body mass index; C_{max} = maximum observed concentration; NOAEL = no-observed-adverse-effect level
Note: The information in this table is based on BMI of 35 kg/m^2.
[a] NOAEL = 90 µg/kg/day

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities (SoA).

The end of the study is defined as the date of the last scheduled procedure shown in the SoA

for the last participant in the study globally.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1 Participants must be ≥ 18 and ≤ 79 years of age at the time of signing the informed consent.

Type of Participants and Disease Characteristics

2 Estimated glomerular filtration rate ≥ 20 to < 90 mL/min/1.73 m^2 determined at the screening visit or a documented occurrence in their medical history at least 3 months prior to randomisation. Estimated glomerular filtration rate will be determined using the CKD epidemiology collaboration equation. Retesting for eGFR may be repeated twice.

3 Receiving background standard of care treatment for renal disease and/or T2DM and being treated according to locally recognised guidelines, as appropriate. Guideline-recommended medications should be used at recommended doses.

4 Receiving optimised and stable treatment with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor antagonist for ≥ 3 months at screening at the maximum tolerated dose (MTD) unless contraindicated, not tolerated, or in the opinion of the investigator, not practically available or suitable. Participants who cannot tolerate an ACE inhibitor or an angiotensin II receptor antagonist may still be eligible to enter the study at the investigator's discretion.

5 Micro- or macroalbuminuria as defined by UACR > 50 mg/g or 5.7 mg/mmol. Retesting on UACR may be repeated twice.

6 Diagnosed with T2DM with glucose control managed with any insulin and/or any oral therapy combination including metformin, SGLT2 inhibitor, thiazolidinedione, or acarbose where no major dose changes (eg, > 50% increase in dose) have occurred within the 4 weeks prior to the start of the run-in period. Participants taking sulfonylureas or glitinides may be randomised following a 4-week washout period of the sulfonylurea/glitinide.

7 Haemoglobin A1c range of 6.5 % to 12.5% (inclusive) at screening

Weight

8 Body mass index > 25 kg/m^2 at screening or > 23 kg/m^2 for participants enrolled in Japan

Sex

9 Males and females

Reproduction

10 Negative pregnancy test at screening (serum only) and randomisation (serum or urine) for female participants of childbearing potential and must not be breastfeeding. Women of childbearing potential are defined as those who are not surgically sterile (ie, surgical sterilisation includes bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or those who are 1 year postmenopausal (defined as 12 months with no menses without an alternative medical cause).

11 Female participants of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. They should have been stable on their chosen method of birth control for a minimum of 3 months before entering the study to 5 weeks after the last dose.

(a) Highly effective birth control methods include: total sexual abstinence (true abstinence in line with the preferred and usual lifestyle choice of the participant), vasectomised partner, tubal occlusion, intrauterine device (provided coils are copper-banded), levonorgestrel intrauterine system, medroxyprogesterone injections, etonogestrel implants, normal and low dose combined oral pills, norelgestromin/ethinylestradiol transdermal system (eg, Evra Patch), intravaginal device (eg, ethinylestradiol and etonogestrel-NuvaRing), and Cerazette (desogestrel). Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

Informed Consent

12 Capable of giving signed informed consent as described in Appendix A, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

13 Provision of signed and dated informed consent prior to any mandatory study-specific procedures, sampling, and analyses

14 Provision of signed and dated optional informed consent prior to collection of samples for genetic research that supports the Genomic Initiative

15 Provision of signed and dated optional informed consent prior to collection of samples for future nongenetic biomarker research

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1 History or presence of significant medical or psychological conditions, including significant abnormalities in laboratory parameters or vital signs including ECG, which in the opinion of the investigator, would compromise the participant's safety or successful participation in the study. As an example, severe anaemia (haemoglobin < 7.0 g/dL) could be exclusionary due to blood sampling required by the protocol, at the discretion of investigator

2 Receiving renal replacement therapy or expected to require it within 6 months of being randomised

3 Renal transplant or on the waiting list for renal transplantation

Prior/Concomitant Therapy

4 Received a GLP-1 analogue-containing preparation within the last 30 days or 5 half-lives of the drug, if known (whichever is longer), at the time of Visit 2

5 Received any of the following medications within the specified time frame prior to the start of the study (Visit 2):

   (a) Aspirin (acetylsalicylic acid) at a dose greater than 150 mg once daily and within the last 3 days prior to the start of the run-in period (Visit 2)

   (b) Paracetamol (acetaminophen) or paracetamol-containing preparations at a total daily dose of greater than 3000 mg and within the last 3 days prior to the start of the run-in period (Visit 2)

   (c) Ascorbic acid (vitamin C) supplements at a total daily dose of greater than 1000 mg and within the last 3 days prior to the start of the run-in period (Visit 2)

Prior/Concurrent Clinical Study Experience

6 Participation in another clinical study with an investigational product administered in the last 30 days or 5 half-lives of the drug, if known (whichever is longer)

7 Participants with a known severe allergy/hypersensitivity to any of the proposed study interventions or excipients of the product

Diagnostic Assessments

8 Symptoms of acutely decompensated blood glucose control (eg, thirst, polyuria, weight loss) or recent episodes of severe hypoglycaemia

9 Type 1 diabetes mellitus (T1DM), history of diabetic ketoacidosis, or clinical suspicion of T1DM (eg, undetectable levels of C peptide and positive tests for antibodies indicative of T1DM)

10 Participants with recent acute or subacute renal function deterioration (eg, participants with large fluctuations of creatinine values documented within the 3 months prior to screening)

11 Significant inflammatory bowel disease, gastroparesis, or other severe disease or surgery affecting the upper gastrointestinal tract (including weight-reducing surgery and procedures) that may affect gastric emptying or could affect the interpretation of safety and tolerability data

12 History of acute or chronic pancreatitis

13 Significant hepatic disease (except for non-alcoholic steatohepatitis or nonalcoholic fatty liver disease without portal hypertension or cirrhosis) and/or participants with any of the following results:

(a) Aspartate transaminase (AST) $\geq 3 \times$ upper limit of normal (ULN)

(b) Alanine transaminase (ALT) $\geq 3 \times$ ULN

(c) Total bilirubin $\geq 2 \times$ ULN

14 Poorly controlled hypertension defined as:

(a) Systolic blood pressure (SBP) > 180 mm Hg

(b) Diastolic blood pressure (DBP) ≥ 90 mm Hg

– After 10 minutes of seated or semi-supine rest and confirmed by repeated measurement at screening

– Participants who fail blood pressure screening criteria may be considered for 24-hour ambulatory blood pressure monitoring at the discretion of the investigator. Participants who maintain a mean 24-hour SBP ≤ 180 or DBP < 90 mm Hg with a preserved nocturnal dip of > 15% will be considered eligible.

15 Unstable angina pectoris, myocardial infarction, transient ischemic attack or stroke within 3 months prior to screening, or participants who have undergone percutaneous coronary intervention or a coronary artery bypass graft within the past 6 months or who are due to undergo these procedures at the time of screening

16 Decompensated heart failure or hospitalisation for heart failure in the 3 months prior to screening or symptoms consistent with New York Heart Association heart failure Class III/IV

17 Basal calcitonin level > 50 ng/L at screening or history/family history of medullary thyroid carcinoma or multiple endocrine neoplasia

18 History of neoplastic disease within 5 years prior to screening, except for adequately treated basal cell skin cancer, squamous cell skin cancer, or in situ cervical cancer

Other Exclusions

19 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)

20 Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions and requirements

5.3 Lifestyle Considerations

Participants will be given general advice on diet and exercise during the run-in period and periodically reminded of such throughout the study. The guidance will be in accordance with the sites' local processes.

Participants should be made aware that the site may contact them regularly by telephone or other means to provide reminders and provide or gather information on topics such as but not limited to dosing, AEs, and concomitant medication

Participants should be made aware they will be required to store investigational product in their home refrigerator.

5.3.1 Meals and Dietary Restrictions

Participants are required to fast for a minimum of 8 hours prior to attending the clinical unit on Days 1, 99, and 182; however, water is allowed ad libitum. It is recommended these visits are conducted in the morning to minimise participant discomfort, and participants may receive breakfast after fasted blood samples are collected.

5.3.2 Tobacco

Participants who use tobacco products will be instructed that use of such products may be restricted while they are in the clinical unit.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure

details, eligibility criteria, and any SAE.

Participants who fail screening should have the reason for study withdrawal recorded in the electronic case report form (eCRF).

Individuals who do not meet the eGFR and UACR inclusion criteria for participation in this study may have their eGFR and UACR retested twice as part of the screening procedure (see Section 5.1). Retesting is only allowed in the study for the eGFR and UACR inclusion criteria.

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.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Intervention(s) Administered

6.1.1 [redacted]

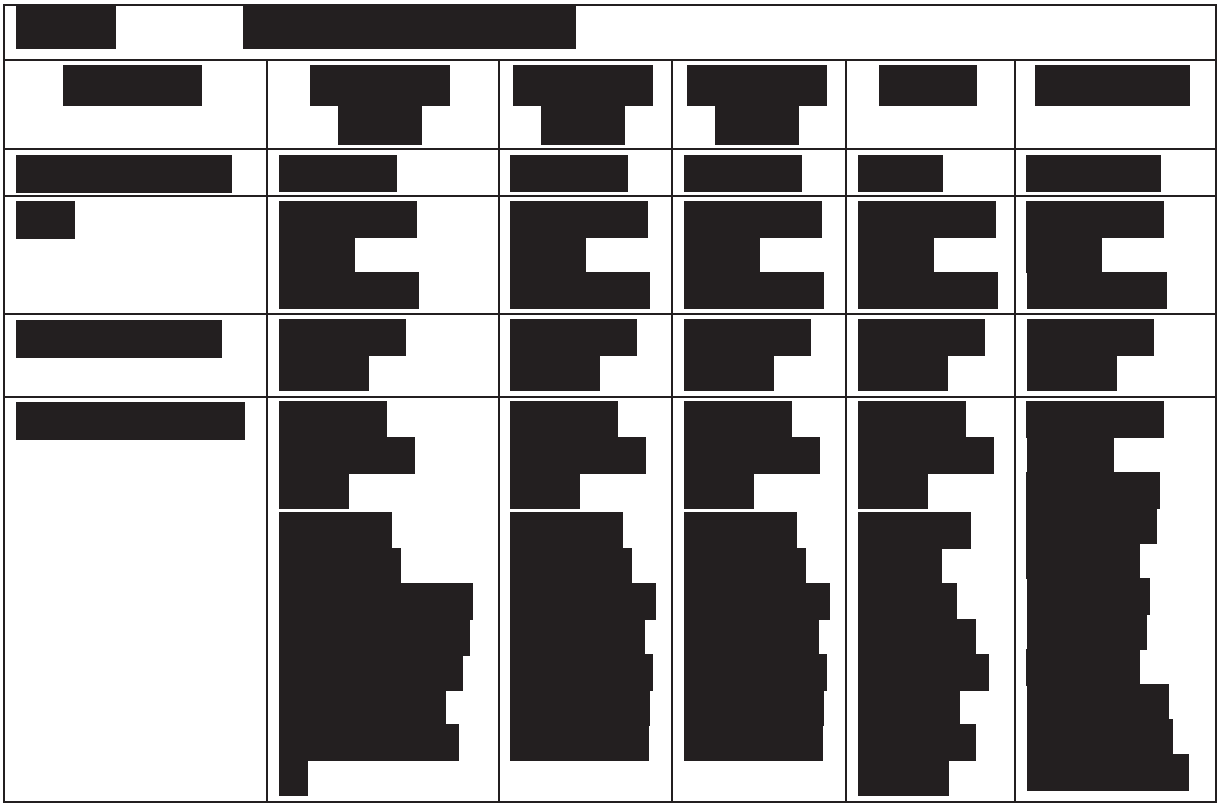
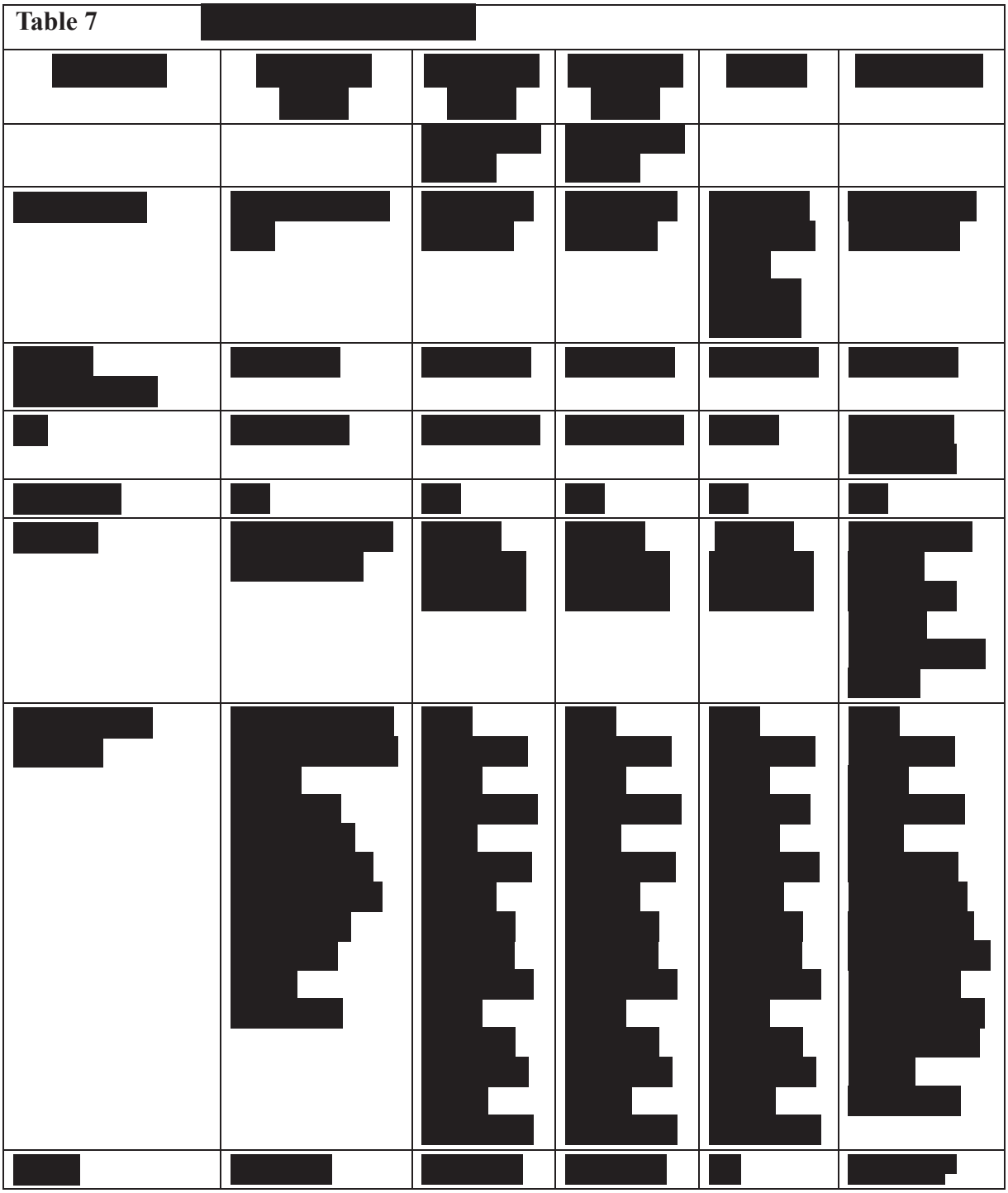


Table 7 [redacted]



IMP = investigational medicinal product; NA = not applicable; NIMP = noninvestigational medicinal product; SC = subcutaneous

[a] Both the liquid drug product and prefilled pen constitute the investigational product. Adverse events and SAEs that occur with the investigational product should be reported per the processes outlined in Section 8.3.

6.1.2 Medical Devices

1 Medical devices not manufactured by AstraZeneca but provided for use in this study are:

(i) Needles to be used with the cotadutide prefilled pens

(ii) NovoFine® Plus needles to be used with the semaglutide (OZEMPIC®) prefilled pens

(iii) FreeStyle Libre Pro™ and Flash™ CGM devices

[redacted]

(v) A glucose/ketone meter device

2 Medical devices will be used per manufacturer's instructions.

3 All device deficiencies (including malfunction, use error, and inadequate labelling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.3.11) and appropriately managed by the sponsor.

6.2 Preparation/Handling/Storage/Accountability of Interventions

1 The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

2 Only participants enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

3 The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

4 Further guidance and information for the final disposition of unused study interventions are provided in the Investigational Medicinal Product Manual.

6.3 Measures to Minimise Bias: Randomisation and Blinding

Study randomisation using IVRS/IWRS	All participants will be centrally assigned to randomised study intervention using an Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information and directions for the IWRS will be provided to each site. Study intervention will be dispensed at the study visits summarised in the SoA. Returned study intervention should not be redispensed to the participants.

IVRS = interactive voice response system; IWRS = interactive web response system; SOA = schedule of activities

Cotadutide and Placebo Arms

Blinded studies using IVRS/IWRS	The IVRS/IWRS will provide to the investigator(s) or pharmacists the kit identification number to be allocated to the participant at the dispensing visit. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre. The randomisation code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomisation. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff. AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Randomisation codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented. The exception to the above is for those personnel analysing the PK samples. The randomisation code will be provided to ensure that only samples from participants who were on active study treatment are analysed. Samples from participants not dosed with the relevant active study treatment will only be analysed on a 'for cause' basis (eg, if there is suspicion that a participant has been dosed incorrectly). The treatment allocation information will be kept in a secure location until the end of the study.
Blind Break (IVRS/IWRS)	The IVRS/IWRS will be programmed with blind-breaking instructions. In case of an emergency, in which the knowledge of the specific blinded study treatment will affect the immediate management of the participant's condition (eg, antidote available), the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

IVRS = interactive voice response system; IWRS = interactive web response system; PK = pharmacokinetic; SAE = serious adverse event

The sponsor, site, and participants will be blinded through the 14-week primary analysis. Thereafter, the sponsor will be unblinded, but the site and participants will remain blinded to minimise bias.

Semaglutide Arm

Open-label using central randomisation via (IVRS/IWRS)	This is an open-label arm; however, the specific intervention to be taken by a participant will be assigned using an IVRS/IWRS. The site will contact the IVRS/IWRS prior to the start of study intervention administration for each participant. The site will record the intervention assignment on the applicable case report form, if required. Potential bias will be reduced by central randomisation.

IVRS = interactive voice response system; IWRS = interactive web response system

6.4 Study Intervention Compliance

Dosing at Site

When participants are dosed at the site, they will self-administer the study intervention 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.

Dosing at Home

When participants self-administer study interventions at home, the percent compliance is defined as the total dose consumed divided by the total dose that should have been taken between the site visits and multiplied by 100%.

6.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The medications listed in Table 8 are permitted. See Section 5.1 for additional details.

Table 8 Permitted Medications

• Standard of care treatment for renal disease and/or T2DM
• ACE inhibitor or an angiotensin II receptor antagonist
• Insulin and/or any oral therapy combination including metformin, SGLT2 inhibitor, thiazolidinedione, or acarbose/alpha-glucosidase inhibitors
• Pharmacological treatments administered for hypoglycaemia (eg, dextrose/glucose tablets, glucagon)

ACE = angiotensin-converting enzyme; SGLT2 = sodium-glucose cotransporter 2 inhibitor; T2DM = type 2 diabetes mellitus

The medications listed in Table 9 are prohibited. See Section 5.2 for additional details.

Table 9 Prohibited Medications

• GLP-1 analogue-containing preparation
• Aspirin (acetylsalicylic acid) > 150 mg once daily
• Paracetamol (acetaminophen) or paracetamol-containing preparations, total daily dose > 3000 mg
• Ascorbic acid (vitamin C) supplements, total daily dose > 1000 mg

GLP-1 = glucagon-like peptide 1

The study physician should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Management of Toxicities

Advice and guidance apply to participants treated in the cotadutide, placebo, or semaglutide arms unless otherwise stated.

6.5.1.1 Management of Nausea and/or Vomiting

If a participant experiences nausea and/or vomiting in relation to cotadutide or semaglutide, in the first instance, conservative measures should be advised, including reducing meal size and maintaining adequate hydration. If there is persistent vomiting, a participant may be given an antiemetic to control his/her symptoms; a 5-hydroxytryptamine-3 receptor antagonist (eg, ondansetron) or cyclizine is preferable rather than antiemetics, which may affect gastric emptying, and dopamine receptor antagonists (eg, metoclopramide or domperidone). In addition, for participants taking diuretics (eg, thiazides, loop diuretics), the investigator should consider temporarily stopping these agents to avoid further dehydration and acute kidney injury (AKI) risk. Investigators should monitor participants with vomiting for signs of hypovolemia. Participants with impaired renal function could be extra sensitive to hypovolemia; such participants should be informed about the importance of adequate hydration in case of nausea and vomiting. These participants should also undergo additional laboratory testing for potential creatinine increases as appropriate.

Dose reductions of cotadutide or semaglutide may be considered following discussion with the study physician. Please see Section 4.1.3 for further details.

6.5.1.2 Insulin Dose Adjustments Prior to Initiation of Investigational Product

For participants in the cotadutide or placebo arms:

Investigators should consider insulin dose reduction for any participant whom they consider may be at risk of hypoglycaemia upon initiation of investigational product. Investigators should be mindful to advise on both quick-acting and long-acting and premixed insulin preparations. Dose reductions of long-acting insulin preparations may occur the night before dosing (Day -1) if an evening dose is to be taken; dose reductions of quick-acting and premixed insulin preparations may occur the morning before dosing (Day 1). Regular contact should be maintained with participants, particularly during the first 2 weeks of treatment with investigational product, to ensure any insulin dose reductions have been appropriate and

participant safety is maintained.

A 30% reduction in insulin dose is recommended to be made from Day -1 for any participant taking insulin who has a screening HbA1c of < 8.0% and eGFR of < 50 mL/min/1.73 m^2 (see Table 10); this reduced dose of insulin should be continued for the remainder of the study or until insulin dose titration is deemed necessary by the investigator. If a participant's screening HbA1c is ≥ 8 and eGFR ≥ 50 mL/min/1.73 m^2, a 20% reduction in insulin dose should be considered (see Table 11).

Investigators/the study team should inform participants of this initial dose reduction as detailed in the SoA. At the end of the study during the follow-up visits, investigators/the study team should aim to establish the participant back on their original regimen (or close to it) as guided by CGM and/or capillary plasma glucose readings and HbA1c measurements.

Table 10 Initial Insulin Dose Adjustment, Participants with Screening HbA1c

[redacted]

haemoglobin A1c; NPH = neutral protamine Hagedorn

For participants in the semaglutide arm:
The semaglutide SmPc states that patients treated with semaglutide in combination with a sulfonylurea or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with semaglutide.

Investigators should use their discretion as to whether an insulin dose reduction is required and what magnitude of reduction is required for participants who are initiated on semaglutide.

6.5.1.3 Insulin Dose Adjustments During the Dosing and Follow-up Period

Once a dose reduction of insulin has occurred, it should be continued for the remainder of the study or until insulin dose titration is deemed necessary by the investigator. At the end of the study during the follow-up visit, investigators/the study team should aim to establish the participant back on their original regimen (or close to this) as guided by CGM and/or capillary plasma glucose readings and HbA1c measurements.

Insulin dose adjustment may also be considered at visits where fasting is required; investigators/the study team should use their discretion as to whether a change is required, and what dose change is appropriate (see Table 12) in accordance with ongoing glucose readings (CGM, venous plasma, or capillary plasma readings) and the timetable of procedures at these visits.

Further dose adjustments of insulin (up or down) should be made at the discretion of the investigator and study team who may use results of capillary plasma glucose readings, HbA1c measurements, venous plasma glucose levels, or CGM readings obtained at each study visit. Table 12 may be used as a guide for adjustment of insulin doses during the study if required. All changes in insulin (including recording of the change in units) should be documented in the eCRF at each visit.

[redacted]

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

Table 12 A Guide for Insulin Dose Adjustments According to CGM Readings

CGM = continuous glucose monitoring

[a] Applies to all insulin doses administered over a 24-hour period, ie, a 10% reduction in a regime of 10 units of quick-acting insulin 3 times daily and 20 units of long-acting insulin once daily would reduce to 9 units of quick-acting insulin 3 times daily and 18 units of long-acting once daily, unless an alternative dose adjustment is deemed preferable by the investigator.

6.5.1.4 Management of Hyperglycaemia

For participants where hyperglycaemia is suspected, additional venous fasting plasma glucose measurements may be performed, if necessary, to investigate further. In addition, and where applicable, study teams may provide ketone meters to participants if hyperglycaemia is suspected for additional monitoring.

See Section 6.5.2 for details on rescue therapy for participants who have sustained hyperglycaemia.

6.5.1.5 Management of Hypoglycaemia

A hypoglycaemic event is considered severe if associated with severe cognitive impairment requiring external assistance for recovery, as defined by the American Diabetes Association; clinically significant hypoglycaemia is defined as a capillary or venous plasma glucose reading of < 3.0 mmol/L (54 mg/dL). Few events of clinically significant hypoglycaemia (< 3 mmol/L) have been reported in participants treated with cotadutide up to 300 µg. In Study D5670C000013 conducted in participants with T2DM and an eGFR of 30-60 ml/min/1.73m^2 3/21 (14.3%), participants who were treated with ≥ 20 units of insulin reported an AE of hypoglycaemia in comparison to 1/20 (5%) participants treated with placebo. No episodes of severe hypoglycaemia warranting third party assistance were observed. In addition, participants treated with cotadutide spent up to 2.9% of time in a clinically significant hypoglycaemic range (glucose < 3.0 mmol/l) on CGM.

Per the semaglutide SmPC, clinically significant hypoglycaemia is reported to be very common with semaglutide in conjunction with insulin or sulfonylureas and common in association with other oral antidiabetic agents.

All participants will be provided with a diary and a glucose meter and will be advised to check their capillary plasma glucose level if they have symptoms of hypoglycaemia (hunger, dizziness, shaking, sweating, or irritability) or feel unwell and will be expected to record the level in their diary. Local protocols for treatment and follow-up of any hypoglycaemic episode should be followed. Any clinically significant hypoglycaemia (glucose < 3.0 mmol/l) should be reported by investigators as an AE regardless of whether the participant is experiencing symptoms or not. Pharmacological treatments administered for hypoglycaemia (eg, dextrose/glucose tablets, glucagon, etc) should be recorded in the eCRF as concomitant medications.

For participants who experience a severe hypoglycaemic episode or a clinically significant episode of hypoglycaemia (defined as a capillary or venous plasma glucose reading of 3.0 mmol/L (< 54 mg/dL) or an interstitial glucose reading 3.0 mmol/L (< 54 mg/dL) recorded on CGM on 2 occasions across 15 minutes, a reduction in total daily dose of insulin of 20% should be considered from the time of awareness of the event. If the participant is not using insulin during the study, a 50% dose reduction in oral medication should be considered in the following order of preference: sulfonylureas, glitinide, pioglitazone, metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors. Dose reduction should also be considered at the discretion of the investigator and/or following discussion with the study physician if > 2% of interstitial glucose readings on CGM are 3.9 mmol/L (< 70 mg/dL).

6.5.1.6 Management of Decline in Renal Function

For participants who have a eGFR of 30-60 mL/min/1.73 m^2 (inclusive) at screening and are taking an existing dose of metformin that is higher than the recommended dose for that degree of renal impairment, the dose of metformin should be reduced or discontinued at Visit 2 in accordance with local guidelines on metformin prescription in renal impairment, or to 500 mg once daily if no guidance is in place. Similarly, any participant experiencing a decline in eGFR during the study to 30-60 mL/min/1.73 m^2 (inclusive) should have their dose of metformin reduced or discontinued as described above.

Participants who have an eGFR < 30 mL/min/1.73 m^2 at baseline or who experience a decline in renal function to eGFR < 30 mL/min/1.73 m^2 during the study should be advised to stop metformin therapy. Any other medications that are contraindicated for this degree of renal impairment should be reviewed and discontinued where deemed appropriate by the investigator.

For participants who are eligible to take part in the study and are taking other medications for diabetes that are prescribed at a higher dose than recommended for their degree of renal insufficiency, dose reduction should be performed at Visit 2 in accordance with local treatment guidelines or the drug labelling.

For participants who are found to have a decline in renal function to eGFR < 15 mL/min/1.73 m^2 during the study, the participant should undergo a repeat eGFR level one week later, and if the eGFR remains < 15 mL/min/1.73 m^2 on a second consecutive test, the investigational product or semaglutide should be discontinued, and the participant should also be advised to stop metformin therapy (if they have not already done so) and any other medications that are contraindicated for this degree of renal impairment. However, the participant should remain in the study for all other study procedures until their scheduled end of study.

6.5.2 Rescue Medicine

In participants who have sustained hyperglycaemia despite adjustment of insulin as described

in Section 6.5.1 (Insulin Dose Adjustments During the Dosing and Follow-up Period), additional open-label rescue therapy should be considered by the investigator and should be documented in the relevant section of the eCRF.

Rescue therapy should be considered by the investigator following discussion with the study physician if any of the following apply:

- Fasting plasma glucose 11.1 mmol/L (> 200 mg/dL) on 2 occasions less than 8 days apart
- 3 capillary plasma glucose levels 13.9 mmol/L (> 250 mg/dL) in 1 week
- > 30% of readings in hyperglycaemic range on CGM defined as 13.9 mmol/L (> 250 mg/dL) in 1 week
- 2 capillary plasma ketone levels > 1.6 mmol/L in 1 day

Rescue therapy with an increase in insulin and/or re-initiation of sulfonylurea/glitinide dose (if these agents were washed out at the beginning of the study) is the preferred option, but additional drug classes may also be used at the discretion of the investigator (see Table 13). Rescue therapy with a sodium glucose cotransporter-2 (SGLT2) inhibitor, any GLP-1 analogue, or DPP-4 inhibitor-based intervention is prohibited (Table 14); the latter is not contraindicated, but would not be expected to provide additional glucose-lowering in conjunction with a GLP-1 and glucagon receptor co-agonist.

If rescue medication is required, participants should continue to participate in the study and receive their study medication. An interim prescription of the rescue medication will be provided by the study site if necessary, but continued prescription of rescue therapy will remain the responsibility of the primary care physician or usual diabetes physician. Rescue medication will not be provided by the sponsor for this study.

Investigators should consider discontinuing the study intervention in participants with persistent fasting venous plasma glucose level of 14.4 mmol/L (> 260 mg/dL), despite an MTD of rescue therapy, to enable optimisation of the participant's glycaemic control. However, the participant should remain in the study for all other study procedures and continued follow-up until their scheduled end of study date.

Table 13 Allowed Rescue Therapies

• Any type of insulin
• Sulfonylurea
• Glitinide
• Pioglitazone
• Acarbose/alpha-glucosidase inhibitors

Table 14 Prohibited Rescue Therapies

- GLP-1 analogue
- DPP-4 inhibitor
- GLP-1 analogue/insulin combination (eg, IDegLira)
- Pramlintide
- SGLT2 inhibitor

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide 1; SGLT2 = sodium-glucose cotransporter 2

6.6 Dose Modification

For management of nausea and/or vomiting, dose reductions of cotadutide or semaglutide may be considered following discussion with the study physician. See Section 4.1.3 for additional details.

6.7 Intervention after the End of the Study

There is no intervention following the end of the study.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention (ie, definitive discontinuation). If study intervention is permanently discontinued, the participant will be encouraged to remain in the study for all remaining study procedures as outlined in the SoA. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Note that discontinuation from study intervention is NOT the same thing as withdrawal from the study (see Section 7.2).

An individual participant will not receive any further investigational product if any of the following occur:

1 Withdrawal of consent/assent from further treatment with investigational product
2 Lost to follow-up
3 An AE that, in the opinion of the investigator or the sponsor, contraindicates further dosing; specific examples include:
   – Dose-limiting symptoms with respect to gastrointestinal tolerability, and in particular, if a participant requires intravenous fluids to treat volume depletion secondary to nausea and vomiting, even after measures are taken to reduce the risk of vomiting (eg, 2 dose reductions) and after discussion with the study physician

- Any signs or symptoms of severe hepatic impairment including abnormal laboratory values as follows:
  - ALT and/or AST > 3 × ULN and total bilirubin > 2 × ULN
  - ALT and/or AST > 5 × ULN for ≥ 14 consecutive days at any time after initial confirmatory results
  - ALT and/or AST > 8 × ULN
- eGFR < 15 mL/min/1.73 m^2 on 2 consecutive blood tests across 1 week
- AKI as defined by:
  - An increase in serum creatinine by ≥ 0.3 mg/dL (26.5 µmol/L) in at least 2 readings within 48 hours
  - An increase in serum creatinine to ≥ 1.5 times baseline in at least 2 readings within 48 hours

  Participants with serum creatinine above these levels will have their study medication held and a repeated serum creatinine test should be performed within 7 days. If serum creatinine is still elevated as specified above (increase ≥ 0.3 mg/dL (26.5 µmol/L) or ≥ 1.5 times baseline), the participant should permanently discontinue the clinical study medication. If after interruption of study medication serum creatinine values are below these values, study medication can be re-started if appropriate in the judgement of the investigator and following consultation with the study physician.
- A clinically significant tachyarrhythmia, including but not limited to a life-threatening arrhythmia (eg, sustained ventricular tachycardia or ventricular fibrillation)
- Persistent fasting glucose level of 14.4 mmol/L (> 260 mg/dL) despite an MTD of rescue therapy to enable optimisation of the participant's glycaemic control

4 Noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal (eg, refusal to adhere to scheduled visits)

5 Pregnancy in a female participant

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

- At the time of withdrawal from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
  - The participant will discontinue the study intervention and be withdrawn from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomised, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
  - The COVID-19 pandemic and associated guidelines, recommendations, national laws, and local restrictions are constantly evolving. Thus, where possible, other measures for carrying out protocol-related activities, such as but not limited to home nursing, may be required to ensure participant safety.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA.

Laboratory efficacy assessments are shown in Table 15.

Table 15 Laboratory Efficacy Variables

Urine	Clinical Chemistry (Serum or Plasma)
U-Albumin (mg/dL)[a] U-Creatinine (g/dL)[a] [redacted]	[redacted] [redacted] [redacted] S/P-HbA1c[b] P-Fasting glucose [redacted]
[redacted] UACR = urine albumin to creatinine ratio	

[a] For primary outcome variable (UACR)
[b] For secondary outcome variable

Urine samples for determination of primary endpoint will be gathered as 3 consecutive daily morning void samples of urine for each visit.

8.1.1 Primary Outcome (UACR)

Urine albumin to creatinine ratio (milligrams of albumin per grams of creatinine) will be assessed by a central laboratory. First morning void urine samples will be used for assessment of UACR. The mean UACR will be reported for each time point based on all samples collected (first morning void urine samples 1, 2, and 3). Participants will receive a urine sample collection kit allowing them to collect the first morning void urine on 3 consecutive days. Collected samples will be refrigerated until they can be brought to the study site for further processing in accordance with the laboratory manual. Ideally, the urine samples should be collected 2 days before a study visit, the day before and on the day of, to minimise storage and transportation of collected samples. 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). In the absence of results from 3 analysed samples, the UACR for a time point will be calculated based on the available results.

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.

8.1.2 Secondary Outcomes

Secondary outcome measures of renal function include:

- eGFR calculated using the CKD-epidemiology collaboration (CKD-EPI equation)
- [redacted]

Secondary outcome measures of T2DM-related metabolic effects include:

- HbA1c
- Fasting glucose
- [redacted]

Secondary outcome [redacted]

8.1.3 Body Weight

Body weight will be measured at the time points specified in the SoA. Body weight should be measured in the morning while the participant is fasted and prior to breakfast. Body weight will be measured after the participant has toileted and removed bulky clothing including shoes. Whenever possible, after screening, the same properly calibrated scale should be used for each measurement for any given participant. The participant's body weight will be recorded in kg to 1 decimal place at a minimum.

8.1.4 Glucose Measurements

A device for CGM should be worn continuously throughout the study. The device will be either a Freestyle Libre Pro™ or Freestyle Libre Flash™ CGM device in accordance with the SoA. The sensor should be applied to the arm with consideration of participant preference. The sensor applied to the skin is single-use and may not be reattached once removed. Participant training for CGM use should be conducted prior to use and prior to changing the type of sensor worn. The CGM sensor must be changed according to the schedule listed in the SOA. CGM sensor application should occur at approximately the same time each scheduled sensor change day. If the sensor fails or needs to be replaced, it should be reapplied as soon as possible. Participants should report to the clinical site to have the sensor replaced at the earliest convenient opportunity. Approximately 1 hour after a new CGM sensor is applied, the site staff or participant should place the monitor in close proximity with the sensor to transfer data and ensure that the sensor and monitor are functioning adequately.

[redacted]

[redacted]

[redacted]

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Physical Examinations

- A full physical examination will be performed and include assessments of the following: general appearance, respiratory, cardiovascular, abdomen, and neurological systems.
- An abbreviated physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

A physical examination will be performed at the time points specified in the SoA.

8.2.2 Vital Signs

Vital signs, including temperature, pulse rate, blood pressure (seated or semi-supine), and respiratory rate, will be performed at the time points specified in the SoA.

8.2.3 Electrocardiograms

Electrocardiograms will be performed at the time points specified in the SoA.

8.2.4 [redacted]

[redacted]

8.2.5 Clinical Safety Laboratory Assessments

A laboratory manual that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information specific to this clinical research study, will be provided to sites.

Clinical laboratory safety assessments will be performed in a licensed central clinical laboratory. Urine pregnancy tests may be performed at the site using a licensed test (eg, a urine dipstick human chorionic gonadotropin test). Abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be collected at the time points specified in the SoA.

The following laboratory safety variables will be measured:

Table 16 Laboratory Safety Variables

Haematology (Whole Blood)	**Clinical Chemistry (Serum or Plasma)**	**Urinalysis** (dipstick)
B-Haemoglobin	S/P-Bilirubin, total	U-Hb/Erythrocytes/Blood
B-Leukocyte count	S/P-Alkaline phosphatase	U-Glucose
B-Leukocyte differential count (absolute count)	S/P-Aspartate transaminase	U-pH
B-Platelet count	S/P-Alanine transaminase	U-Bilirubin
B-Haematocrit	S/P-Albumin	U-Ketones
B-RBC	S/P-Potassium	U-Urobilinogen
B-Mean corpuscular volume	S/P-Calcium, total	U-Nitrite
B-Mean corpuscular haemoglobin concentration	S/P-Sodium	U-Leukocyte esterase
	S/P Glucose	U-Protein
	S/P-Bicarbonate	U-Specific gravity
	S/P-BUN	U-Color
	S/P-Phosphate	U-Appearance
	S/P-Creatinine	U- Microscopy
	S/P-Magnesium	
	S/P-Beta-hydroxybutyrate	
ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; BUN = blood urea nitrogen; Hb = haemoglobin; RBC = red blood cell; U = urinalysis; WBC = white blood cell		

In case a participant shows an AST **or** ALT ≥ 3x ULN together with total bilirubin ≥ 2x ULN,

please refer to Appendix E for further instructions.

8.2.6 Other Safety Assessments

Calcitonin, lactate, lipase, amylase, and C peptide levels will also be assessed as indicated in the SoA. All participants will be provided with a glucose/ketone meter and a diary during the run-in period, and site staff will explain how the glucose/ketone meter works and allow participants to demonstrate proper use under supervision before being discharged from the clinic. Participants will be advised to use the glucose meter to check their capillary blood glucose level as per their usual schedule, and if they have symptoms of hypoglycaemia (hunger, dizziness, shaking, sweating, or irritability) or feel unwell, participants will be expected to record their glucose levels and symptoms in their diaries. Participants must also use their ketometer to check their blood ketones if they have the following symptoms:

- Polyuria, polydipsia
- Malaise, generalised weakness, or fatigability
- Nausea and vomiting that may be associated with diffuse abdominal pain, decreased appetite, and anorexia
- Altered consciousness (eg, mild disorientation, confusion)

If a measured blood ketone value is > 3.0 mmol/L upon repeat testing, participants must contact the study site immediately. At the unit, the investigator should assess and determine whether the participant is at risk to develop ketoacidosis or is progressing towards ketoacidosis based on the participant's medical history, physical examination, and supportive laboratory results.

Participants treated with either cotadutide or placebo (300 and 600 µg arms only) will also be provided with an ABPM device to wear for approximately 24 hours at the time points specified in the SoA.

8.3 Adverse Events and Serious Adverse Events

The principal investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events and SAEs will be collected from time of signature of the informed consent form throughout the treatment period and including the follow-up period (28 days post last dose).

If the investigator becomes aware of an SAE with a suspected causal relationship to the investigational medicinal product that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the SAE to the sponsor.

8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse event variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Intensity
- Whether the AE is serious or not
- Investigator causality rating against the investigational product(s) (yes or no)
- Action taken with regard to investigational product(s)
- AE caused participant's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death

- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.3.3 Causality Collection

The investigator should assess causal relationship between investigational product and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.5 Adverse Events Based on Examinations and Tests

Results from the mandated laboratory tests and vital signs will be summarised in the clinical study report (CSR).

Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the investigational product or are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study treatment, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3.6 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3x ULN together with total bilirubin ≥ 2x ULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.3.7 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform the appropriate AstraZeneca representatives within 1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the electronic data capture (EDC) system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone and via paper back-up SAE form.

The AstraZeneca representative will advise the investigator/study site staff how to proceed.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca

drug (cotadutide) and the SmPC for the comparator product (semaglutide).

8.3.8 Clinical Event Adjudication

A Clinical Event Adjudication (CEA) committee, blinded to the treatment of the participant, will independently adjudicate certain clinical AEs. The CEA committee will operate in accordance with the CEA Charter and Event Handling Manual for sites and site monitors.

The CEA committee will adjudicate events possibly related to the following:

1 All deaths
2 Cardiac ischaemic events: myocardial infarction or unstable angina
3 Cerebrovascular events: stroke or transient ischaemic attack
4 Renal events: AKI and end-stage renal disease
5 Hospitalisation for heart failure
6 Pancreatitis
7 Pancreatic carcinoma
8 Thyroid neoplasm
9 Diabetic ketoacidosis

For all clinical events identified for adjudication, the investigator will complete the appropriate modules of the eCRF, and provide source documentation. In order to provide the independent CEA with appropriate and adequate information for adjudication of the listed events, please consult the CEA Charter and Event Handling Manual for Sites and site monitors.

8.3.9 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study drug
- Pregnancies in the partner of male participants

8.3.9.1 Maternal Exposure

If a participant becomes pregnant during the course of the study despite contraceptive measures outlined in Section 5.1, the investigational product should be discontinued immediately, and the pregnancy reported to AstraZeneca.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day (ie, immediately but **no later than 24 hours** of when he or she becomes aware of it).

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

When the eCRF module is used include the following: The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

8.3.10 Medication Error

If a medication error occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day (ie, immediately but no later than 24 hours of when he or she becomes aware of it).

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow up

Fatal/Life-Threatening) or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the medication error and within 30 days for all other medication errors.

The definition of a medication error can be found in Appendix B.

8.3.11 Medical Device Deficiencies

Medical devices are being provided for use in this study (see Section 6.1.2). In order to fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency is as follows:

Device Deficiency Definition

A device deficiency is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labelling or the instructions for use.

NOTE: Incidents that fulfil the definition of an AE/SAE will follow the processes outlined in Section 8.3.3.

8.3.11.1 Time Period for Detecting Medical Device Deficiencies

- Medical device incidents or malfunctions of the device will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and the incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

8.3.11.2 Follow-up of Medical Device Deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.3.11.3 Prompt Reporting of Device Deficiencies to Sponsor

- Device deficiencies will be reported to the sponsor within 1 calendar day after the investigator determines that the event meets the protocol definition of a medical device deficiency.
- Device deficiencies can be reported through site monitors to the sponsor.

8.3.11.4 Regulatory Reporting Requirements for Device Deficiencies

- The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

8.4 Overdose

For this study, any dose of cotadutide [redacted] a 24-hour time period and any dose of semaglutide greater than 1.0 mg within a 7-day time period will be considered an overdose.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module

If an overdose on an AstraZeneca study drug occurs in the course of the study, the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for overdoses associated with an SAE (see Section 8.3.7) and within 30 days for all other overdoses.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Sample, see Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- Pharmacokinetic samples will be disposed of after CSR finalisation, unless consented for future analyses.
  - Pharmacokinetic samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining anti-drug antibody (ADA) sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterisation of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

8.5.1 Pharmacokinetics

- Plasma samples will be collected for measurement of cotadutide concentrations as specified in the SoA.
- Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor (eg, for safety reasons). The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.
- Plasma samples will be used to analyse the PK of cotadutide. Samples collected for analyses of cotadutide concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Samples will be collected, labelled, stored, and shipped as detailed in the laboratory manual.
- Pharmacokinetic samples will not be collected from participants randomised to the semaglutide arm.

8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentration in plasma will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

8.5.2 Immunogenicity Assessments

Blood samples for determination of ADA in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca using an appropriately validated bioanalytical method. Full details of the methods used will be described in a separate report.

Anti-drug antibody samples may also be further tested for characterisation of the ADA response.

Samples will be collected, labelled, stored, and shipped as detailed in the laboratory manual.

Anti-drug antibody samples will not be collected from participants randomised to the semaglutide arm.

8.5.3 Pharmacodynamics

There will be no pharmacodynamic assessments for this study.

8.5.3.1 Collection of Samples

Blood samples will be collected for measurement as specified in the SoA.

Urine samples will be collected for measurement as specified in the SoA.

For storage, reuse, and destruction of pharmacodynamic samples see Section 8.5 and Appendix C.

8.6 [redacted]

collection and shipment and destruction of these samples can be found either in the appendices or in the laboratory manual.

For storage and destruction of genetic samples see Appendix D.

8.8 Health Economics or Medical Resource Utilisation and Health Economics

Neither health economics nor medical resource utilisation and health economics parameters will be evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 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.

Secondary Hypotheses

Administration of cotadutide once daily titrated up to a dose level of 600 µg will result in a 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.

9.2 Sample Size Determination

[redacted]

At the primary analysis, an analysis on UACR will be conducted on the subpopulation of participants on an SGLT-2 inhibitor therapy at screening. Based on the analysis results of this subpopulation for placebo and 2 optimal cotadutide arms, more participants may be enrolled to achieve 80% power for comparison of cotadutide versus placebo. In the event this is required, up to 22 more participants will be recruited into the placebo arm and to each of the 2 selected cotadutide arms for a total of 66 additional participants. If the calculated sample size of each arm for this subpopulation exceeds 40 (including the participants for primary analysis), further enrolment may not be done. Additional details will be described in the statistical analysis plan (SAP).

9.3 Populations for Analyses

Table 17 Populations for Analyses

Population/Analysis Set	Description
All-enrolled	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.
As-treated	Randomised participants who receive any study intervention will be included in the as-treated population and will be analysed according to the intervention they actually received.
ITT Population	Randomised participants included in the ITT population will be analysed according to the intervention they were randomised to.
Per Protocol Population	The Per Protocol population will include all enrolled participants who are randomised and who have received at least one dose of study intervention except for those who have discontinued study intervention and those with relevant IPDs. Relevant IPDs are those that have the potential to affect the result of the primary efficacy results. The PP population will be analysed according to the randomised treatment group.
PK Population	Randomised participants who have at least one measurable concentration time point of cotadutide will be included in the PK population.
Immunogenicity Population	Randomised participants who have at least one serum sample for immunogenicity testing will be included in the Immunogenicity population.

IPD = important protocol deviation; ITT = intent-to-treat; PK = pharmacokinetic

9.4 Statistical Analyses

The SAP will be finalised prior to first participant dosed and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.4.1 General Considerations

Participants will be randomised in a 1:1:1:1:1 ratio to 1 of 3 blinded cotadutide arms, a blinded placebo arm, or an open-label semaglutide arm. 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.

The randomisation will be stratified according to whether a participant is from Japan or not and on the use of SGLT2 inhibitor therapy at screening. Up to approximately 20% of participants will be recruited in Japan.

Two analyses are planned for this study:

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

Formal statistical modelling analysis for certain prespecified efficacy endpoints will be conducted but will not be performed for all endpoints. 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, and the scope of the analysis will be defined in the SAP.

9.4.2 Efficacy

9.4.2.1 Primary Endpoint

The primary efficacy analysis will be performed using the intent-to-treat population. The primary efficacy endpoint, percentage change in UACR from baseline to the end of 14 weeks of treatment, will be analysed using an analysis of covariance (ANCOVA) model with a two-sided significance level of 0.05. Fold change of UACR in original scale will firstly be log-transformed, and then the ANCOVA analysis results will be transformed back to original scale for interpretation purposes. The model will include fixed effect of treatment 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. Absolute change in UACR will only be summarised.

A sensitivity analysis including only data when participants are on treatment will be performed using a similar method. Another sensitivity analysis including data from all available visits using a mixed model with repeated measurements will be performed with similar covariates.

9.4.2.2 Secondary Endpoints

An ANCOVA model with fixed effect of treatment 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 will be used for continuous endpoints. Urine albumin to creatinine ratio-related analyses will follow a similar method as that for the primary endpoint. For proportion-related endpoints, a logistic regression model will be used with fixed effect of treatment and baseline measurement as a covariate.

9.4.2.3 Tertiary/Exploratory Endpoints

For analyses of the exploratory endpoints, an ANCOVA model similar to the secondary pharmacodynamic analysis will be used for continuous endpoints. For proportion-related endpoints, a logistic regression model will be used with fixed effects of treatment and baseline measurement. For eGFR slope analysis, a mixed model will be used.

For the following endpoints, if both percentage and absolute changes are needed, visualisation normality test will be performed first, then if log-transformation is needed, the similar analysis approach as that for the primary endpoint will be conducted. The relevant endpoints are: urine albumin, urinary creatinine, renal function, and exploratory renal and cardiac biomarkers (eGFR not to be tested – assumed to be normally distributed), markers of liver health, lipid profile and echocardiography-determined parameters.

9.4.3 Safety

Safety is a secondary endpoint. AEs and SAEs will be coded by the most updated version of Medical Dictionary for Regulatory Activities (MedDRA), and the type, incidence, severity, and relationship to study investigational product will be summarised by MedDRA System Organ Class and Preferred Term and by treatment. Adverse events leading to discontinuation, AEs leading to death, and deaths will also be summarised and will be marked in the listings or will be in a separate listing. Specific AEs will be counted once for each participant for calculating percentages. In addition, if the same AE occurs multiple times within a particular participant, the highest severity and level of relationship observed will be reported. Participant-level data listings of all AEs will be presented.

9.4.4 Other Analyses

Immunogenicity Analysis

As a secondary endpoint, samples confirmed positive for ADA will be tested and analyzed for antibody titre and reported. The incidence and impact of ADA to cotadutide will be tabulated for each treatment. The number and percentage of participants with confirmed positive serum antibodies to cotadutide will be reported by dose level. Data on titres and cross-reactivity to GLP-1 and glucagon (where applicable) will be provided in the CSR as an appendix or part of the main results if available prior to publishing of the final CSR. If warranted by the data, the association of ADA positives with observed PK data may be explored.

Pharmacokinetics Analysis

As an exploratory endpoint, cotadutide plasma concentrations prior to injection and 4 hours post injection at steady state at different dose levels and different visits will be summarised descriptively by arms. Population PK analysis will be performed but will not be reported in the CSR.

The PK of semaglutide will not be measured.

Patient Reported Outcomes

Descriptive analyses will be performed.

9.5 Interim Safety Review

An interim safety review is planned after 68 or 30% of participants have completed Week 11. Data will be reviewed by the sponsor's URC. No study team members involved in the conduct of the study should be unblinded for the purpose of the interim analysis; however, in case any study team members need to serve in the unblinded analysis group, they will stop day-to-day work on the study and other pre-selected personnel will take over these roles for the remainder of the study. The details and scope of the analysis can be found in the Interim Analysis Charter.

9.6 Data Monitoring Committee

No Data Monitoring Committee will be appointed for this study.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a contract research organisation, but the accountability remains with AstraZeneca.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.

A 4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 6 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring and other study plans.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organisations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 7 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the source data verification plan.

A 8 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment will be when the first participant is screened, which will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

A 9 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of adverse events

An adverse event 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 (for example 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.

B 2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse Events (AEs) for **malignant tumours** reported during a study should generally be assessed as **Serious** AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **Non-Serious** AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as Serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as Non-Serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

Intensity rating scale:

mild (awareness of sign or symptom, but easily tolerated)

moderate (discomfort sufficient to cause interference with normal activities)

severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of

intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough

information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- occurred
- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error (eg, medication prepared incorrectly, even if it was not actually given to the participant)
- Drug not administered as indicated (eg, wrong route or wrong site of administration)
- Drug not taken as indicated (eg, tablet dissolved in water when it should be taken as a solid tablet)
- Drug not stored as instructed (eg, kept in the fridge when it should be at room temperature)
- Wrong participant received the medication (excluding interactive voice response system [IVRS]/ interactive web response system [IWRS] errors)
- Wrong drug administered to participant (excluding IVRS/IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) (eg, forgot to take medication)

- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AstraZeneca product

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

Appendix C Handling of Human Biological Samples

C 1 Chain of custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each centre keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples while at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

C 2 Withdrawal of Informed Consent for donated biological samples

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action documented and study site notified.

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A pathogens are (eg, Ebola, Lassa fever virus). Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900:

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are (eg, hepatitis A, C, D, and E viruses). They are assigned the following UN number and proper shipping name

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations.
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.

Appendix D [redacted]

[redacted]

collection

[redacted]

- [redacted]

[redacted]

- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]g this genetics research component, are outlined in Appendix A.

[redacted]

Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

E 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study, the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated total bilirubin (TBL) from a local laboratory.

The investigator will also review Adverse Event data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug induced liver injury (DILI) caused by the investigational medicinal product.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting serious adverse events (SAEs) and adverse events (AEs) according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law (PHL)
Aspartate transaminase (AST) or alanine transaminase (ALT) ≥ 3x upper Limit of Normal (ULN) **together with** TBL ≥ 2x ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)
AST or ALT ≥ 3x ULN **together with** TBL ≥ 2x ULN, where no other reason, other than the investigational medicinal product, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified time frame within which the elevations in transaminases and TBL must occur.

E 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL, it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3x ULN
- AST ≥ 3x ULN
- TBL ≥ 2x ULN

Central laboratories being used:

When a participant meets any of the PHL identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the investigator (also sent to AstraZeneca representative).

The investigator will also remain vigilant for any local laboratory reports where the PHL identification criteria are met, where this is the case the investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory without delay
- Complete the appropriate unscheduled laboratory eCRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the investigator will without delay:

- Determine whether the participant meets PHL criteria (see Section E 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

Local laboratories being used:

The investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative

- Determine whether the participant meets PHL criteria (see Section E 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria not met

If the participant does not meet PHL criteria the investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria
- Perform follow-up on subsequent laboratory results according to the guidance provided in the clinical study protocol.

E 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the investigator will:

- Notify the AstraZeneca representative who will then inform the central study team
- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to the clinical study protocol process for SAE reporting.

- For participants that met PHL criteria prior to starting investigational medicinal product, the investigator is not required to submit a PHL SAE unless there is a significant change# in the participant's condition

- The study physician contacts the investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data

- Subsequent to this contact the investigator will:

  – Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  – Investigate the aetiology of the event and perform diagnostic investigations as discussed with the study physician. This includes deciding which tests available in the Hy's law lab kit should be used.
  – Complete the three Liver eCRF Modules as information becomes available

#A 'significant' change in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the study physician if there is any uncertainty.

E 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the study physician contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than drug-induced liver injury (DILI) caused by the investigational medicinal product, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF
- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the investigational medicinal product:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of PHL, (report term now 'Hy's Law case') ensuring causality assessment is related to investigational medicinal product and seriousness criteria is medically important, according to the clinical study protocol process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following the clinical study protocol process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Laboratory tests

Hy's Law lab kit for central laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HBsAg HBV DNA[a] IgG anti-HCV HCV RNA[a] IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin[b]
Autoimmune hepatitis	Antinuclear antibody Anti-Liver/Kidney Microsomal Ab Anti-Smooth Muscle Ab
Metabolic diseases	Alpha-1-antitrypsin Ceruloplasmin Iron
	Ferritin Transferrin[b]

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
	Transferrin saturation

Ab = antibody; ANA = antinuclear antibody; anti-LKM = anti-liver/kidney microsomal; ASMA = anti-smooth muscle antibody; CD = carbohydrate deficient; CMV = cytomegalovirus; EBV = Epstein-Barr virus; GGT = gamma-glutamyl transferase; HAV = hepatitis A virus; HBc = hepatitis B core; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HEV = hepatitis E virus; HSV = herpes simplex virus; Ig = immunoglobulin; INR = international normalised ratio; LDH = lactate dehydrogenase

[a] HCV RNA; HCV DNA are only tested when IgG anti-HCV is positive or inconclusive.

[b] CD-transferrin and Transferrin are not available in China. Study teams should amend this list accordingly.

E 7 References

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Appendix F Abbreviations

Abbreviation or special term	Explanation
[redacted]	[redacted]
ACE	angiotensin-converting enzyme
ADA	anti-drug antibody
AE	adverse event
AKI	acute kidney injury
ALP	alkaline phosphatase
ALT	alanine transaminase
ANCOVA	analysis of covariance
AST	aspartate transaminase
AUC	area under the concentration-time curve
CEA	clinical event adjudication
CGM	continuous glucose monitoring
CKD	chronic kidney disease
CKD-EPI	chronic kidney disease-epidemiology collaboration
C_{max}	maximum observed concentration
COVID-19	coronavirus disease
CrCl	creatinine clearance
CSR	clinical study report
CV	cardiovascular
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DPP-4	dipeptidyl peptidase-4
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide 1
GFR	glomerular filtration rate
HbA1c	haemoglobin A1c
HL	Hy's law
IATA	International Airline Transportation Association
ICH	International Council for Harmonisation

Abbreviation or special term	Explanation
ICF	informed consent form
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IVRS	interactive voice response system
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NASH	nonalcoholic steatohepatitis
NOAEL	no observed adverse effect level
PHL	potential Hy's law
PK	pharmacokinetic(s)
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	subcutaneous(ly)
SD	standard deviation
SGLT2	sodium-glucose cotransporter 2
SmPC	Summary of Product Characteristics
SoA	schedule of activities
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TBL	total bilirubin
UACR	urine albumin to creatinine ratio
ULN	upper limit of normal
URC	Unblinded Review Committee

Appendix G Summary of Changes

G 1 Amendment 01 (29Jun2020)

Overall Rationale for the Amendment:

This global amendment contains revisions to the original global protocol dated (01Apr2020) to remove Cohort 2, which is no longer needed due to completion of Study D5671C00003 earlier than originally planned. Other minor revisions such as clarifications and correction of typos were made. This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study. Changes in global amendment 1 are presented in the table below.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Title page, 1.1 (Synopsis: Intervention			

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.1 (Synopsis: Overall Design), 3	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.1 (Synopsis: Statistical Methods), 4.1			
	questionnaires		

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
3 (Objectives and [redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
9.1 (Statistical Hypotheses)	Clarified primary and		

[redacted] = anti-drug antibody; AUC = area under the concentration-time curve; BP = blood pressure; CGM = continuous glucose monitoring; COVID-19 = coronavirus disease; electrocardiogram; DBP = diastolic blood pressure; E/D = early discontinuation; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; [redacted] SBP = systolic blood pressure; SGLT2i = sodium-glucose cotransporter 2 inhibitor; UACR = urine albumin to creatinine ratio; UK = United Kingdom; US = United States

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