Clinical Study Protocol	
Study Intervention	AZD9977 and dapagliflozin
Study Code	D6402C00001
Version	7.0
Date	02 Feb 2022

A Phase 2b, Randomised, Double-Blind, Active-Controlled, Multi-Centre Study to Evaluate the Efficacy, Safety and Tolerability of Oral AZD9977 and Dapagliflozin Treatment in Patients with Heart Failure and Chronic Kidney Disease

Sponsor Name: AstraZeneca AB

Legal Registered Address: AstraZeneca AB, 151 85 Södertälje, Sweden

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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 Number: D6402C00001

Amendment Number: 6
Study Intervention: AZD9977 and dapagliflozin
Study Phase: Phase 2b

Short Title: Efficacy, safety, and tolerability of AZD9977 and dapagliflozin in patients with heart failure and chronic kidney disease

Acronym: MIRACLE (MIneRAlocorticoid reCeptor moduLator and sodium-glucosE cotransporter-2-inhibitor in HF and CKD trial)

Study Physician Name and Contact Information will be provided separately

International co-ordinating investigators: PPD (University of Glasgow, United Kingdom); PPD (Harvard Medical School, United States); PPD (National Heart Centre, Singapore)

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Version 1.0	25 August 2020
Amendment 1, Version 2.0	06 October 2020
Amendment 2, Version 3.0	26 January 2021
Amendment 3, Version 4.0	19 March 2021
Amendment 4, Version 5.0	15 July 2021
Amendment 5, Version 6.0	20 December 2021
Amendment 6, Version 7.0	02 February 2022

A summary of changes for the previous amendments is provided in Appendix K.

Amendment 6 (02 February 2022)

This amendment is considered to be substantial due to being a correction and clarification of CSP Amendment 5/CSP 6.0 which is a substantial amendment 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.

Overall Rationale for the Amendment

The previous Clinical Study Protocol (CSP) version, version 6.0, dated 20 December 2021 has been updated. The updates are summarised below.

Section Number and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities, Table 1	Blood samples for cardiovascular biomarkers to be collected at Follow-Up Visit 11.	Correction of typo to align with Section 8.6.1.
Section 1.3 Schedule of Activities, Table 1 (footnote) Section 7.1 Discontinuation of Study Intervention	Text added on open label dapagliflozin use during Safety Follow-Up period.	Clarification of study procedures.
Section 2.3.1 Risk Assessment, Table 2; Section 11 References	Inclusion of an additional literature reference.	To provide the correct literature reference.
Section 5.4 Screen Failures	New definition of Screen Failures.	Correction of definition to align with revised study design.

In addition, the following administrative changes were made:

- Tables of Contents updated.

- Minor editorial changes.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2b, Randomised, Double-Blind, Active-Controlled, Multi-Centre Study to Evaluate the Efficacy, Safety and Tolerability of Oral AZD9977 and Dapagliflozin Treatment in Patients with Heart Failure and Chronic Kidney Disease

Short Title: Efficacy, safety, and tolerability of AZD9977 and dapagliflozin in patients with heart failure and chronic kidney disease

Rationale: Although mineralocorticoid receptor antagonists (MRAs) are an important standard therapy for heart failure (HF), they are currently contraindicated in patients with estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 and are highly underused in patients with eGFR < 60 mL/min/1.73 m^2 due to risk of hyperkalaemia.

AZD9977 is a selective mineralocorticoid receptor (MR) modulator, with a differentiated mode of action compared with the currently prescribed MRAs (eg, spironolactone/eplerenone).

The mechanisms of action of AZD9977 and dapagliflozin are different and outcome of the combination treatment is expected to be synergistic since the main biological effects of AZD9977 would be to block MR driven oxidative stress, inflammation and fibrosis and of dapagliflozin to inhibit sodium-glucose co-transporter-2 (SGLT2)-driven metabolic dysfunction, volume overload, and endothelial cell dysfunction.

The overall clinical evidence suggests that the combination of AZD9977 and dapagliflozin would have clinical benefit and an acceptable safety profile in patients with HF and that further development is warranted. Hence, a global, randomised, Phase 2b study is planned to evaluate the efficacy and safety of AZD9977 and dapagliflozin in patients with HF.

The purpose of the study is to establish a dose-response for effect on urinary albumin to creatinine ratio (UACR) and assess the safety of AZD9977 given in combination with dapagliflozin 10 mg once daily, considering serum/plasma potassium$^+$ (K^+) and safety topics of interest (hyperkalaemia, hypotension and deteriorating renal function) in addition to general safety.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of AZD9977 in combination with dapagliflozin compared with dapagliflozin alone on UACR	• Percent change from baseline in UACR at the end of 12 weeks of study treatment
Secondary	
• To assess the dose-response relationship of dapagliflozin (10 mg) alone and 3 doses of AZD9977 (15, 50, or 150 mg) combined with dapagliflozin (10 mg) on UACR	• Percent change from baseline in UACR at the end of 12 weeks of study treatment
Safety	
• To assess the general safety and tolerability of AZD9977 in combination with dapagliflozin compared with dapagliflozin alone	• AE/SAE reporting • Vital signs (BP, pulse rate) • Clinical laboratory tests (clinical chemistry, haematology, and urinalysis) • Digital 12-lead safety ECG assessments • Safety topics of interest (hyperkalaemia, hypotension and deteriorating renal function)
• To assess the effect of AZD9977 in combination with dapagliflozin compared with dapagliflozin alone on serum K^+ and eGFR	• Absolute value and change from baseline in serum K^+ and eGFR over time

AE=adverse event; BP=blood pressure; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; K^+=potassium; SAE=serious adverse event; UACR=urinary albumin to creatinine ratio.

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

Overall Design: This is a Phase 2b, multi-centre, randomised, double-blind, active-controlled parallel group, study to assess the efficacy, safety and tolerability of AZD9977 and dapagliflozin administered for 12 weeks in patients with HF (LVEF below 60%) and chronic kidney disease (CKD) (eGFR ≥ 20 and ≤ 60 mL/min/1.73 m^2), with at least 20% of patients with eGFR ≥ 20 to < 30 mL/min/1.73 m^2 and a maximum of 35% of patients with eGFR ≥ 45 mL/min/1.73 m^2.

The study will be conducted at approximately 150 to 250 sites in approximately 20 countries including North America, Asia-Pacific, and European countries.

Patients who meet the eligibility criteria will be randomised to one of the following 4 treatment groups:

- AZD9977 15 mg + dapagliflozin 10 mg
- AZD9977 50 mg + dapagliflozin 10 mg
- AZD9977 150 mg + dapagliflozin 10 mg
- Dapagliflozin 10 mg

Participants will be stratified according to T2DM (yes/no) and eGFR (≥ 20 to < 30 mL/min/1.73 m^2; or ≥ 30 to < 45 mL/min/1.73 m^2; or ≥ 45 mL/min/1.73 m^2) based on the latest eGFR assessment prior to the start of study treatment (eGFR assessment at Visit 2).

A Safety Unblinded Data Review Committee will be set up for this study for ongoing safety monitoring. In addition to general safety/tolerability, the committee will focus on potential risks related to hypotension, deteriorating renal function and hyperkalaemia.

An Interim Unblinded Data Review Committee will be set up to review data from the pre-planned interim analysis and make recommendations regarding future clinical development.

Disclosure Statement: This is a parallel group treatment study with 4 arms that is participant- and investigator-blinded.

Number of Participants:

Approximately 500 participants will be randomly assigned to study intervention (125 participants per group) such that approximately 476 evaluable participants (119 per group) complete the study.

Intervention Groups and Duration:

For each participant, the total duration of participation will be approximately 22 to 24 weeks, including a 1-week screening period, followed by up to 7-week run-in period followed by a

12-week treatment period (including 6 visits), the end of treatment (EOT) visit, and a 4-week safety follow-up after last dose (including 1 visit). An optional pre-screening visit may be scheduled. Week and day for pre-screening visit will be at the discretion of the investigator.

After screening, eligible participants currently on treatment with a SGLT2i other than dapagliflozin should stop taking the SGLT2i and start on dapagliflozin 10 mg. Participants on dapagliflozin treatment will continue on treatment but the medication will be provided. Participants will then undergo a 4 to 5-week run-in period to ensure washout of forbidden medications and stable doses of allowed background medications.

For participants eligible after screening, and not on treatment with a SGLT2i, treatment with dapagliflozin 10 mg will be initiated. Participants will then undergo a 6 to 7-week run-in period to ensure washout of forbidden medications and stable doses of allowed background medications.

During the treatment period, participants will be randomly assigned in a 1:1:1:1 ratio to receive once daily administration of one of the 4 study treatments as described below. To ensure blinding, the study treatment will be administered in the form of 3 oral capsules and 1 oral tablet in the following combinations:

Study Treatment	Capsule 1	Capsule 2	Capsule 3	Tablet
AZD9977 15 mg + Dapagliflozin 10 mg	AZD9977 15 mg	Placebo	Placebo	Dapagliflozin 10 mg
AZD9977 50 mg + Dapagliflozin 10 mg	Placebo	AZD9977 50 mg	Placebo	Dapagliflozin 10 mg
AZD9977 150 mg + Dapagliflozin 10 mg	Placebo	AZD9977 50 mg	AZD9977 100 mg	Dapagliflozin 10 mg
Dapagliflozin 10 mg alone	Placebo	Placebo	Placebo	Dapagliflozin 10 mg

No dose modifications are allowed during the study.

Data Monitoring Committee: Yes

Statistical Methods

The primary hypothesis for this study is that AZD9977 in combination with dapagliflozin will induce a reduction of albuminuria greater than with dapagliflozin alone, as assessed by the percent change from baseline in UACR at 12 weeks.

A total of 119 evaluable participants per arm will provide 80% power to detect a 30% difference in a AZD9977 dose group combined with dapagliflozin 10 mg compared to dapagliflozin 10 mg alone in percent change from baseline in UACR at 12 weeks, assuming a standard deviation (SD) of 1.0 on the natural log-scale and alpha = 0.05. To account for

approximately 5% drop-out from the study, approximately 500 participants will be randomly assigned to study intervention (125 participants per group) such that approximately 476 evaluable participants (119 per group) complete the study.

Patients randomised according to CSP versions 1.0 to 5.0 (before dropping placebo and AZD9977 150 mg monotherapy arms) will be considered as part of Cohort 1, while patients randomised subsequently will be included in the Cohort 2. The primary analysis for remaining 4 treatment groups will combine data from both cohorts, while the accrued data from discontinued treatment groups will be analysed descriptively.

The primary efficacy endpoint for this study is the percent change from baseline in UACR at 12 weeks. The mean log percent changes in UACR at 12 weeks for each of the 3 doses of AZD9977 combined with dapagliflozin 10 mg, and dapagliflozin alone will be estimated in a mixed model for repeated measures (Visits 7, 8, 9, and 10). The values will be back-transformed onto the original scale to give the geometric mean relative change from baseline at 12 weeks. The analysis model will include UACR baseline value, treatment, and visit as fixed effect, and the stratifying factors (T2DM [yes/no] and eGFR [$\geq$ 20 to < 30 mL/min/1.73 m^2; or $\geq$ 30 to < 45 mL/min/1.73 m^2; or $\geq$ 45 mL/min/1.73 m^2]) as well as the Cohort variable (1 or 2) as covariates. Moreover, treatment-by-visit interaction will also be included in the model. The final analytical approach will be described in detail in the Statistical Analysis Plan (SAP).

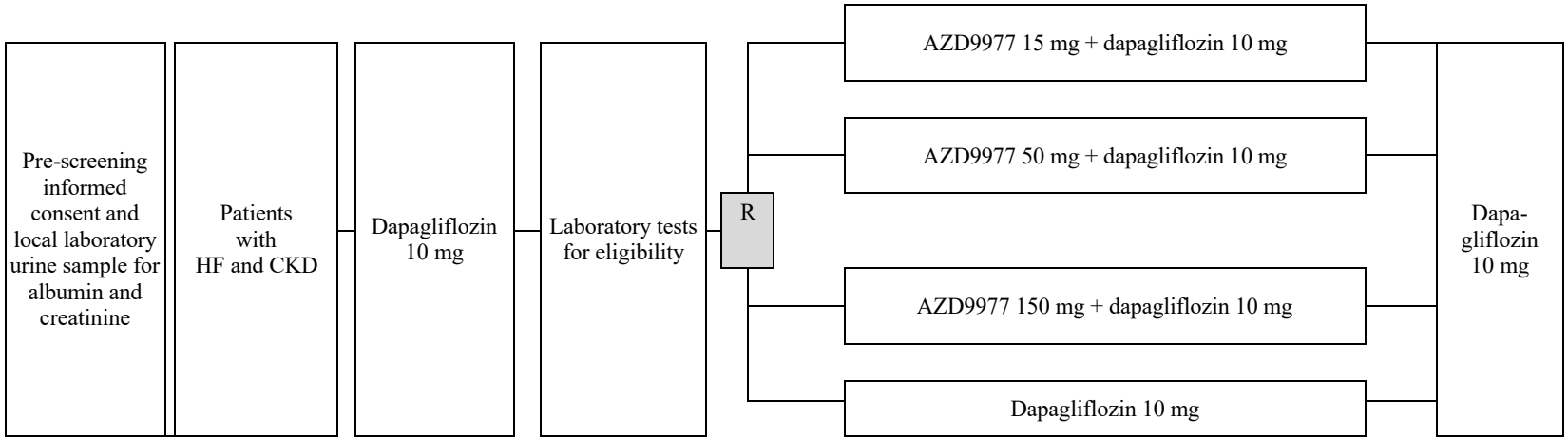
For the primary analysis, the main treatment comparisons to be evaluated are (in a fixed sequence of testing):

1 Overall comparison of the percentage changes from baseline in UACR at week 12 across all 4 treatment groups
2 Each of the 3 doses of AZD9977 in combination with dapagliflozin 10 mg versus dapagliflozin 10 mg in the following order:
    1. AZD9977 150 mg + dapagliflozin 10 mg versus dapagliflozin 10 mg
    2. AZD9977 50 mg + dapagliflozin 10 mg versus dapagliflozin 10 mg
    3. AZD9977 15 mg + dapagliflozin 10 mg versus dapagliflozin 10 mg

For the analysis addressing the secondary objective, the dose-response relationship of percent change from baseline in UACR at 12 weeks will be assessed using data from dapagliflozin (10 mg) alone and 3 doses of AZD9977 (15, 50, or 150 mg) combined with dapagliflozin (10 mg).

1.2 Schema

Figure 1 Study Design



	Pre-screening	Screening	Start Run-in [b]	Pre-Randomisation	Baseline	Treatment period (12 weeks)						EOT/ ET	Safety follow-up (4 weeks)
Visit	**Optional**	1a	1b	2	3	4	5	6	7	8	9	10	11
Weeks	[a]	(-8 to -7) [c] -6 to -5	(-7 to -6) [c] -5 to -4	-1	1		2	3	4	7	10	13	17
Day	[a]	-56 to -49) [c] -42 to -35	(-49 to -42) [c] -35 to -28	-10 to -3	1	3	8	15	22	43	64	85	113

CKD=chronic kidney disease; EOT=end of treatment; ET=early termination; HF=heart failure; R=randomisation
Note: Visits at Week 7 and Week 13 (Visits 8 and 10) correspond to visits after completion of 6 weeks and 12 weeks of study treatment, respectively.
[a] Week and day for pre-screening will be at the discretion of the investigator.
[b] Duration of run-in period for patients on treatment with a SGLT2i: 4 to 5 weeks
Duration of run-in period for patients not on treatment with a SGLT2i: 6 to 7 weeks
[c] Applies to SGLT2i naïve patients

1.3 Schedule of Activities

Table 1 Schedule of Activities

Procedure	Pre-screening	Screening	Start Run-in	Pre-randomisation	Baseline/ Randomisation	Treatment Period						EOT/ET [a]	Safety Follow-up	Notes	Details in CSP Section or Appendix
Visit [b]	**Optional**	**1a**	**1b**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**		
Week	[c]	**(-8 to -7)* -6 to -5**	**(-7 to -6)* -5 to -4**	**-1**	**1**	**1**	**2**	**3**	**4**	**7**	**10**	**13**	**17**	* Applies to SGLT2i naïve patients	**For details on run-in period see Section 4.1**
Day	[c]	**(-56 to -49)* -42 to -35**	**(-49 to -42)* -35 to -28**	**-10 to -3**	**1**	**3 ± 1**	**8 ±2**	**15 ±3**	**22 ±3**	**43 ±3**	**64 ±3**	**85 ±3**	**113 ±4**		
Informed consent	X	X													Appendix A 3
Local laboratory urine samples for albumin and creatinine	X													Sample according to local clinical practice.	Section 8.2.4
Inclusion and exclusion criteria		X	X		X										Sections 5.1, 5.2
Enrolment in RTSM		X													Section 6.3
Demography, height, smoking history, alcohol consumption		X													Sections 5.1, 5.2
Physical examination, weight		X			X (pre-dose)							X	X	For site visits only.	Section 8.2.1

Procedure	**Pre-screening**	**Screening**	**Start Run-in**	**Pre-randomisation**	**Baseline/ Randomisation**	**Treatment Period**						**EOT/ET** [a]	**Safety Follow-up**	**Notes**	**Details in CSP Section or Appendix**
Visit [b]	**Optional**	**1a**	**1b**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**		
Week	[c]	**(-8 to -7)* -6 to -5**	**(-7 to -6)* -5 to -4**	**-1**	**1**	**1**	**2**	**3**	**4**	**7**	**10**	**13**	**17**	* Applies to SGLT2i naïve patients	**For details on run-in period see Section 4.1**
Day	[c]	**(-56 to -49)* -42 to -35**	**(-49 to -42)* -35 to -28**	**-10 to -3**	**1**	**3 ± 1**	**8 ±2**	**15 ±3**	**22 ±3**	**43 ±3**	**64 ±3**	**85 ±3**	**113 ±4**		
Medical/ surgical history		X			X										Sections 5.1, 5.2
Concomitant medication		X		X	X	X	X	X	X	X	X	X	X		Section 6.5
Adverse events		SAEs only		SAEs only	X	X	X	X	X	X	X	X	X		Section 8.3
Vital signs (blood pressure, pulse rate)		X			X (pre-dose)	X	X	X	X	X	X	X	X	Background treatment for hypertension should be individually optimised and stable for 3 weeks before randomisation (Visit 3); BP assessed for eligibility at Visit 3.	Sections 5.1, 6.5.2, 8.2.2
Digital 12-lead safety ECG		X [d]			X (pre-dose)	X		X		X		X		ECGs to be added as clinically indicated.	Section 8.2.3

Procedure	**Pre-screening**	**Screening**	**Start Run-in**	**Pre-randomisation**	**Baseline/ Randomisation**	**Treatment Period**						**EOT/ET** [a]	**Safety Follow-up**	**Notes**	**Details in CSP Section or Appendix**
Visit [b]	**Optional**	**1a**	**1b**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**		
Week	[c]	**(-8 to -7)* -6 to -5**	**(-7 to -6)* -5 to -4**	**-1**	**1**	**1**	**2**	**3**	**4**	**7**	**10**	**13**	**17**	* Applies to SGLT2i naïve patients	**For details on run-in period see Section 4.1**
Day	[c]	**(-56 to -49)* -42 to -35**	**(-49 to -42)* -35 to -28**	**-10 to -3**	**1**	**3 ± 1**	**8 ±2**	**15 ±3**	**22 ±3**	**43 ±3**	**64 ±3**	**85 ±3**	**113 ±4**		
Local echocardiography		X [d]												Needed to confirm eligibility if not assessed in past 12 months	Section 8.2.3
Local laboratory blood samples for clinical chemistry and haematology		X [d]													Section 8.2.4
Local laboratory urine sample for albumin, creatinine, and urinalysis		X [d]												Spot urine sample	Sections 8.1.1, 8.2.4
Local laboratory blood sample for NT-proBNP		X [d]													Section 8.5.2

Procedure	**Pre-screening**	**Screening**	**Start Run-in**	**Pre-randomisation**	**Baseline/ Randomisation**	**Treatment Period**						**EOT/ET** [a]	**Safety Follow-up**	**Notes**	**Details in CSP Section or Appendix**
Visit [b]	**Optional**	**1a**	**1b**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**		
Week	[c]	**(-8 to -7)* -6 to -5**	**(-7 to -6)* -5 to -4**	**-1**	**1**	**1**	**2**	**3**	**4**	**7**	**10**	**13**	**17**	* Applies to SGLT2i naïve patients	**For details on run-in period see Section 4.1**
Day	[c]	**(-56 to -49)* -42 to -35**	**(-49 to -42)* -35 to -28**	**-10 to -3**	**1**	**3 ± 1**	**8 ±2**	**15 ±3**	**22 ±3**	**43 ±3**	**64 ±3**	**85 ±3**	**113 ±4**		
Local laboratory blood sample for FSH measurement		X [d]												To confirm postmenopausal status of women (only women of non-child-bearing potential will be included in the study).	Sections 5.1 and 8.2.4
Local laboratory RT-PCR test for SARS-CoV-2				X [e]										Optional. If available at site.	Section 8.2.4

Procedure	**Pre-screening**	**Screening**	**Start Run-in**	**Pre-randomisation**	**Baseline/ Randomisation**	**Treatment Period**						**EOT/ET** [a]	**Safety Follow-up**	**Notes**	**Details in CSP Section or Appendix**
Visit [b]	**Optional**	**1a**	**1b**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**		
Week	[c]	**(-8 to -7)* -6 to -5**	**(-7 to -6)* -5 to -4**	**-1**	**1**	**1**	**2**	**3**	**4**	**7**	**10**	**13**	**17**	* Applies to SGLT2i naïve patients	**For details on run-in period see Section 4.1**
Day	[c]	**(-56 to -49)* -42 to -35**	**(-49 to -42)* -35 to -28**	**-10 to -3**	**1**	**3 ± 1**	**8 ±2**	**15 ±3**	**22 ±3**	**43 ±3**	**64 ±3**	**85 ±3**	**113 ±4**		
Local laboratory serum/plasma samples for K^+ and Na^+				X [e]	X	X	X	X	X	X	X	X		Results needed for eligibility and to assess discontinuation criteria at each visit	Section 8.2.4
Local laboratory serum/plasma samples for creatinine including eGFR calculation					X	X	X	X	X	X	X	X			Section 8.2.4
Central laboratory blood samples for clinical chemistry and haematology; and plasma sample for K^+ measurement					X (pre-dose)	X	X	X	X	X	X	X	X		Section 8.2.4

Procedure	**Pre-screening**	**Screening**	**Start Run-in**	**Pre-randomisation**	**Baseline/ Randomisation**	**Treatment Period**						**EOT/ET** [a]	**Safety Follow-up**	**Notes**	**Details in CSP Section or Appendix**
Visit [b]	**Optional**	**1a**	**1b**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**		
Week	[c]	**(-8 to -7)* -6 to -5**	**(-7 to -6)* -5 to -4**	**-1**	**1**	**1**	**2**	**3**	**4**	**7**	**10**	**13**	**17**	* Applies to SGLT2i naïve patients	**For details on run-in period see Section 4.1**
Day	[c]	**(-56 to -49)* -42 to -35**	**(-49 to -42)* -35 to -28**	**-10 to -3**	**1**	**3 ± 1**	**8 ±2**	**15 ±3**	**22 ±3**	**43 ±3**	**64 ±3**	**85 ±3**	**113 ±4**		
Central laboratory serum sample for creatinine for eGFR calculation				X [e]											Section 8.2.4
Central laboratory serum sample for cystatin C for eGFR calculation				X [e]	X (pre-dose)	X	X	X	X	X	X	X	X		Section 8.2.4
Central laboratory blood samples for HbA1c, cholesterol, and lipids					X (pre-dose)							X	X	After at least 8-hour fasting for lipids.	Section 8.2.4
Central laboratory urinalysis					X (pre-dose)					X		X	X		Section 8.2.4

Procedure	Pre-screening	Screening	Start Run-in	Pre-randomisation	Baseline/ Randomisation	Treatment Period						EOT/ET [a]	Safety Follow-up	Notes	Details in CSP Section or Appendix
Visit [b]	**Optional**	**1a**	**1b**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**		
Week	[c]	**(-8 to -7)* -6 to -5**	**(-7 to -6)* -5 to -4**	**-1**	**1**	**1**	**2**	**3**	**4**	**7**	**10**	**13**	**17**	* Applies to SGLT2i naïve patients	**For details on run-in period see Section 4.1**
Day	[c]	**(-56 to -49)* -42 to -35**	**(-49 to -42)* -35 to -28**	**-10 to -3**	**1**	**3 ±1**	**8 ±2**	**15 ±3**	**22 ±3**	**43 ±3**	**64 ±3**	**85 ±3**	**113 ±4**		
Central laboratory urine samples for albumin, creatinine (for UACR calculation), Na^+, K^+, uric acid, urea, osmolality, glucose, and cortisol [f]				X [e, f]			X		X	X	X	X	X	First morning void urine sample collected at home in provided vials over 3 consecutive days until the visit day.	Sections 8.1.1, 8.5.2, 8.6.1
Pharmaco-kinetics															
Predose sample for AZD9977 and dapagliflozin plasma concentrations							X		X			X		Collected before dose intake at site, or 1 day after last dose for the EOT/ET visit.	Section 8.5.1

Procedure	**Pre-screening**	**Screening**	**Start Run-in**	**Pre-randomisation**	**Baseline/ Randomisation**	**Treatment Period**						**EOT/ET** [a]	**Safety Follow-up**	**Notes**	**Details in CSP Section or Appendix**
Visit [b]	**Optional**	**1a**	**1b**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**		
Week	[c]	**(-8 to -7)* -6 to -5**	**(-7 to -6)* -5 to -4**	**-1**	**1**	**1**	**2**	**3**	**4**	**7**	**10**	**13**	**17**	* Applies to SGLT2i naïve patients	**For details on run-in period see Section 4.1**
Day	[c]	**(-56 to -49)* -42 to -35**	**(-49 to -42)* -35 to -28**	**-10 to -3**	**1**	**3 ±1**	**8 ±2**	**15 ±3**	**22 ±3**	**43 ±3**	**64 ±3**	**85 ±3**	**113 ±4**		
Optional postdose plasma samples for AZD9977 and dapagliflozin concentrations									X					Collected at 1 (±0.25), 2 (±0.25), 4 (±0.5), and 6 (±1) hours postdose.	Section 8.5.1

Procedure	**Pre-screening**	**Screening**	**Start Run-in**	**Pre-randomisation**	**Baseline/ Randomisation**	**Treatment Period**						**EOT/ET** [a]	**Safety Follow-up**	**Notes**	**Details in CSP Section or Appendix**
Visit [b]	**Optional**	**1a**	**1b**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**		
Week	[c]	**(-8 to -7)* -6 to -5**	**(-7 to -6)* -5 to -4**	**-1**	**1**	**1**	**2**	**3**	**4**	**7**	**10**	**13**	**17**	* Applies to SGLT2i naïve patients	**For details on run-in period see Section 4.1**
Day	[c]	**(-56 to -49)* -42 to -35**	**(-49 to -42)* -35 to -28**	**-10 to -3**	**1**	**3 ±1**	**8 ±2**	**15 ±3**	**22 ±3**	**43 ±3**	**64 ±3**	**85 ±3**	**113 ±4**		
Pharmaco-dynamics (Central laboratory)															
Blood samples for NT-proBNP, aldosterone, renin, ACTH, cortisol, copeptin, and FPG					X (pre-dose)		X		X			X	X	Collected at the same time of the day. After at least 8-hour fasting for FPG.	Section 8.5.2
Exploratory measurements and biomarkers															
Serum/plasma samples for cardiovascular biomarkers					X (pre-dose)				X			X	X	Central laboratory.	Section 8.6.1

Procedure	**Pre-screening**	**Screening**	**Start Run-in**	**Pre-randomisation**	**Baseline/ Randomisation**	**Treatment Period**						**EOT/ET** [a]	**Safety Follow-up**	**Notes**	**Details in CSP Section or Appendix**
Visit [b]	**Optional**	**1a**	**1b**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**		
Week	[c]	**(-8 to -7)* -6 to -5**	**(-7 to -6)* -5 to -4**	**-1**	**1**	**1**	**2**	**3**	**4**	**7**	**10**	**13**	**17**	* Applies to SGLT2i naïve patients	**For details on run-in period see Section 4.1**
Day	[c]	**(-56 to -49)* -42 to -35**	**(-49 to -42)* -35 to -28**	**-10 to -3**	**1**	**3 ± 1**	**8 ±2**	**15 ±3**	**22 ±3**	**43 ±3**	**64 ±3**	**85 ±3**	**113 ±4**		
Optional serum, plasma, and urine samples for exploratory assessment of biomarkers					X (pre-dose)				X			X			Section 8.6.2
Optional genetic sample for Genomics Initiative exploratory analysis					X (pre-dose)										Section 8.7, Appendix D
Study treatments															
Randomisation in RTSM					X										Section 6.3
Dapagliflozin 10 mg			Daily-(morning) self-administration									Daily-(morning) self-administration [a]			Sections 4.1, 6.1.1, and 6.7

Procedure	**Pre-screening**	**Screening**	**Start Run-in**	**Pre-randomisation**	**Baseline/ Randomisation**	**Treatment Period**						**EOT/ET [a]**	**Safety Follow-up**	**Notes**	**Details in CSP Section or Appendix**
Visit [b]	**Optional**	**1a**	**1b**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**		
Week	[c]	**(-8 to -7)* -6 to -5**	**(-7 to -6)* -5 to -4**	**-1**	**1**	**1**	**2**	**3**	**4**	**7**	**10**	**13**	**17**	* Applies to SGLT2i naïve patients	**For details on run-in period see Section 4.1**
Day	[c]	**(-56 to -49)* -42 to -35**	**(-49 to -42)* -35 to -28**	**-10 to -3**	**1**	**3 ±1**	**8 ±2**	**15 ±3**	**22 ±3**	**43 ±3**	**64 ±3**	**85 ±3**	**113 ±4**		
Study treatment					Daily (morning) self-administration of the assigned study treatment									Taken at the site on visit days, after completing all predose procedures.	Sections 4.1, 6.2, 6.4
Drug dispensation			X		X				X	X	X	X			Sections 6.2, 6.3, and 6.4
Drug accountability					X	X	X	X	X	X	X	X	X		Sections 6.2, 6.4

ACTH=adrenocorticotropic hormone; BP=blood pressure; BUN=blood urea nitrogen; CKD=chronic kidney disease; CSP=Clinical Study Protocol; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; EOT=end of treatment; ET=early termination; FPG=fasting plasma glucose; FSH=follicle stimulating hormone; HbA1c=glycated haemoglobin; HF=heart failure; K^+=potassium; Na^+=sodium; NT-proBNP=N-terminal natriuretic peptide; RT-PCR=reverse transcriptase polymerase chain reaction; RTSM=Randomisation and Trial Supply Management, SAE=serious adverse event; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; UACR=urinary albumin to creatinine ratio.

Note: Visits at Week 7 and Week 13 (Visits 8 and 10) correspond to visits after completion of 6 weeks and 12 weeks of study treatment, respectively.

[a] Patients will continue on open label dapagliflozin 10 mg after the EOT visit during the safety follow up period up to Visit 11. Patients who discontinue study treatment early may continue on open label dapagliflozin 10 mg after the ET visit during the safety follow up period up to Visit 11, as judged by the investigator. Patients who withdraw consent may perform an ET visit but the safety follow-up will not be performed.

[b] If site visits are not possible due to local SARS-CoV-2 restrictions, home nursing visits may be considered after discussion with and approval by the Sponsor.

[c] Week and day for pre-screening will be at the discretion of the investigator.

[d] Results from the screening tests are needed to confirm eligibility before the run-in period can start.

[e] Results are needed to confirm eligibility before randomisation. Serum/plasma Na^+ will be assessed at Visit 2 only. The eGFR-based participant stratification will rely on central eGFR assessment at Visit 2.

[f] Phone call will occur prior to the visit to remind the participants to collect the first morning void samples.

2 INTRODUCTION

2.1 Study Rationale

Although MRAs are an important standard therapy for HF, they are currently contraindicated in patients with eGFR < 30 mL/min/1.73 m^2 and are highly underused in patients with eGFR < 60 mL/min/1.73 m^2 due to risk of hyperkalaemia.

AZD9977 is a selective MR modulator, with a differentiated mode of action compared with the currently prescribed MRAs (eg, spironolactone/eplerenone).

The mechanism of action for AZD9977 and dapagliflozin are different and outcome of treatment is expected to be synergistic since the main biological effects of AZD9977 would be to block MR driven oxidative stress, inflammation and fibrosis and dapagliflozin to inhibit SGLT2-driven metabolic dysfunction, volume overload, and endothelial cell dysfunction.

The overall clinical evidence suggests that the combination of AZD9977 and dapagliflozin would have clinical benefit and an acceptable safety profile in patients with HF and that further development is warranted. Hence, a global, randomised, Phase 2b study is planned to evaluate the efficacy and safety of AZD9977 and dapagliflozin in patients with HF.

The purpose of the study is to establish a dose-response for effect on UACR and assess the safety of AZD9977 given in combination with dapagliflozin 10 mg once daily, considering serum/plasma K^+ and safety topics of interest (hyperkalaemia, hypotension and deteriorating renal function) in addition to general safety.

2.2 Background

The presence of significant concomitant renal dysfunction in patients with HF severely limits the use and the benefits of proven HF medications, such as ACEIs, ARBs, MRAs, and ARNIs. In the absence of evidence-based therapies capable of both renal and cardiovascular protection, new treatments are warranted.

Mineralocorticoid receptor antagonists have proven benefits on HF, but use has been limited due to risks associated with hyperkalaemia, in particular in patients with reduced renal function, although existing evidence suggests that MRAs also provide benefit in HF patients with CKD. Sodium-glucose co-transporter-2 inhibitors have proven benefits on HF, as well as potential beneficial effects on kidney function. In the recent DAPA-HF trial (D1699C00001) the treatment benefit of dapagliflozin was observed in HFrEF patients both with T2DM and without diabetes. In that study, approximately 70% of the patients were treated with MRAs and effect of dapagliflozin was independent of baseline MRA therapy, suggesting additive effects on top of MRA treatment (McMurray et al 2019). In the recent DAPA-CKD trial (D169AC00001), among patients with CKD, regardless of the presence or absence of T2DM,

the risk of a composite of a sustained decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo (Heerspink et al 2020). Combination of AZD9977 with dapagliflozin, could have synergistic effects and importantly improve outcomes in HF patients, especially those with lower GFR who do not receive MRA treatment. By providing differential effects on disease mechanisms related to MR driven inflammation and fibrosis as well as SGLT2-driven mechanisms the action of both drugs is anticipated to provide significant patient benefit.

2.2.1 Heart Failure with Chronic Kidney Disease

2.2.1.1 Prevalence of Heart Failure

Chronic HF continues to be a major cause of mortality, hospitalisations, and suboptimal quality of life. Even with the best possible treatment, the 5-year survival rate for HF patients is worse than for most cancers (Braunwald 2015). Moreover, the prevalence of chronic HF continues to increase globally. An estimated 38 million people are affected worldwide (Braunwald 2015), with over 1 million hospitalisations annually in both the United States and Europe (Ambrosy et al 2014). The annual global economic burden in 2012 was estimated to be $108 billion (Cook et al 2014) and will increase dramatically as the population ages.

2.2.1.2 Heart Failure Management

Foundations of HF management rely on volume status with appropriate diuretic dosing, control of BP, treatment of contributing risk factors such as sleep apnoea, coronary artery disease and valvular disease, alongside with dietary education. The ACCF/AHA guidelines (Yancy et al 2017) support the use of beta-blockers, ACEI, ARBs and MRAs. Angiotensin receptor-neprilysin inhibitors can replace ACEI or ARB in patients with HF who remain symptomatic despite optimal treatment with an ACEI or ARB, a beta-blocker and an MRA. Isosorbide dinitrate/hydralazine and the If-channel inhibitor (ivabradine) and digoxin can be prescribed in some patients, as appropriate. The European Society of Cardiology guidelines now include a Class-1 recommendation for treatment with dapagliflozin or empagliflozin for patients with HFrEF to reduce the risk of HF hospitalization and death (ESC Guidelines 2021).

Heart failure patients with CKD have even higher risk and fewer treatment options resulting in a patient group with high unmet medical need. Studies have indicated that between 20% and 67% of patients with HF also have CKD (Sarraf et al 2009). Patients with both HF and renal insufficiency have approximately 25% to 30% higher risk of mortality compared with patients with HF without CKD (Ather et al 2012). However, in patients with poor kidney function (eGFR< 30 mL/min/1.73 m^2) there are no specific therapies approved for renal impairment and recommended treatments for HF are underused because of intolerance and safety concerns and may even be contraindicated in some individuals.

This type of concern primarily involves inhibitors of the RAAS, including MRAs, and RAAS blockers. An additional and related concern is the risk of hyperkalaemia, which is greatest for MRAs, with potential risk of or actual hyperkalaemia events being a major cause of underuse of this type of therapy. While concerns about worsening renal function and hyperkalaemia result in underutilisation of MRAs, there is evidence from randomised clinical trials that patients with HF and renal impairment have important clinical benefit from MRA therapy (Pitt et al 1999, Zannad et al 2011). Recent data from the FIDELIO-DKD and FIGARO-DKD trials assessing the non-steroidal MRA finerenone in patients with CKD and T2DM established that MRAs also are reno-protective in the long term and reduce the CV risks in this patient population (Bakris et al 2020, Pitt et al 2021).

2.2.1.3 Mineralocorticoid Receptor Antagonist for Treatment of Heart Failure and Chronic Kidney Disease

The steroidal MRAs spironolactone and eplerenone reduce mortality and hospitalisations for HF in patients with HFrEF (Pitt et al 1999, Zannad et al 2011) and have a class 1A recommendation for the treatment of this patient population in international guidelines. In patients with CKD, MRA treatment has been shown to reduce albuminuria and may improve long-term kidney function (Kato et al 2015, Bakris et al 2015). The mineralocorticoid receptor antagonist finerenone was recently shown to prevent the development of cardiovascular disease and progression to end-stage kidney disease in patients with CKD and T2DM (Bakris et al 2020, Pitt et al 2021).

One of the primary safety concerns related to MRA treatment is the development of hyperkalaemia, especially in patients taking concomitant medications associated with K^+ retention (such as ACEIs or ARBs), and in patients with diabetes mellitus and/or kidney dysfunction (Cooper et al 2017). In placebo-controlled clinical trials with MRAs in HF patients, the incidence of hyperkalaemia is approximately 9%, with 54% of these being truly attributable to MRA therapy (Vukadinović et al 2017). However, real world data suggest that the incidence of hyperkalaemia in patients with HF could be greater than this (Abbas et al 2015). Concern about hyperkalaemia, especially in patients with reduced kidney function results in underuse and suboptimal dosing of MRAs in these HF patients (Savarese et al 2018).

While dose escalation with existing MRA therapies is limited by the risk of hyperkalaemia, this may not be the case with novel MR modulators (such as AZD9977), as the dose-response relationship for acute effects on urinary electrolyte excretion may differ from that for organ protection (Bamberg et al 2018). Novel MR antagonists or modulators should increase the therapeutic window by increasing selectivity against other steroid nuclear receptors thereby avoiding gynaecomastia (eg, with spironolactone) as well as improving the separation of cardiac and kidney protective effects from electrolyte regulation thereby avoiding hyperkalaemia (seen with spironolactone and eplerenone) (Capelli et al 2020). Pre-clinical

data have demonstrated that AZD9977 at clinically relevant exposures is effective in reducing MR-mediated cardiac and renal pathology, as well as reducing the risk of treatment-related hyperkalaemia, when compared to currently available MR antagonists. AZD9977 has been evaluated in 7 Phase 1 studies involving healthy volunteers at doses up to 1200 mg as a single dose and multiple dosing of 300 mg twice daily, with no clinically relevant effect on serum K^+ levels (see the Investigator's Brochure of AZD9977). In addition, a Phase 1b study comparing AZD9977 to spironolactone in patients with HF with preserved LVEF > 40%) and CKD with eGFR between 40 and 70 mL/min/1.73 m^2 was recently completed (NCT 03682497). Recently, the novel non-steroidal MRA finerenone was found to be safe and to reduce adverse kidney and cardiovascular outcomes in patients with CKD and diabetes (Bakris et al 2020).

2.2.1.4 Sodium-glucose Co-transporter 2 Inhibitors in Heart Failure and Chronic Kidney Disease

Recent data from cardiovascular outcome studies of the SGLT2i dapagliflozin and real world studies (including patients treated with dapagliflozin) show that treatment with dapagliflozin can reduce the risk of cardiovascular death and hospitalisation due to HF in patients with and without T2DM (Zinman et al 2015, Ferrannini et al 2016, Fitchett et al 2016, Neal et al 2017, Rådholm et al 2018, McMurray et al 2019, Petrie et al 2020).

It has been postulated that kidney protection along with diuretic and natriuretic effects induced by SGLT2i may contribute to the reductions in HF hospitalisation in the EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58 trials (Zelniker et al 2019). Moreover, the reduction in HF hospitalisation in these trials was greater in patients with worse baseline kidney function; a 40% reduction in HF hospitalisation was observed in patients with eGFR < 60 mL/min/1.73 m^2 compared with 31% in patients with eGFR > 60 to < 90 mL/min/1.73 m^2 and 12% reduction in patients with eGFR > 90 mL/min/1.73 m^2 (Zelniker et al 2019). Dapagliflozin also reduced UACR by 21% in T2DM patients in the DELIGHT study (Pollock et al 2019). In the recent DAPA-HF trial (D1699C00001), dapagliflozin demonstrated a reassuring safety profile in a population with a broad range of kidney function (including patients with eGFR < 45 and a few with eGFR < 30 mL/min/1.73 m^2). In this study, approximately 70% of the patients were treated with MRAs and effect of dapagliflozin was independent of baseline MRA, suggesting additive effects on top of MRA treatment. In the DAPA-CKD trial (D169AC00001), an event-driven study in patients with CKD (eGFR ≥ 25 and ≤ 75 mL/min/1.73 m^2) with albuminuria (UACR ≥ 200 and ≤ 5000 mg/g) with T2DM or without diabetes, dapagliflozin was superior to placebo in reducing the incidence of the primary composite endpoint of ≥ 50% sustained decline in eGFR, reaching ESRD, cardiovascular or renal death when added to current background therapy. Treatment effects on ESRD were driven by reductions in sustained eGFR ≤ 15 mL/min/1.73 m^2 and chronic dialysis. There were 11 events (3 in dapagliflozin, 8 in placebo group) of renal transplants in the study. Treatment effects on the exploratory composite endpoint of renal death, renal transplant, and chronic dialysis were consistent with

effects on ESRD. In addition, dapagliflozin was superior to placebo for time to first event of the composite of ≥ 50% sustained decline in eGFR, reaching ESRD, and renal death; time to first event of the composite of cardiovascular death and hospitalisation for HF; and time to death from any cause. Treatment benefit was observed in CKD patients both with T2DM and without diabetes (Jongs et al 2021).

A detailed description of the chemistry, pharmacology, efficacy, and safety of AZD9977 and dapagliflozin is provided in the Investigator's Brochure of each product.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of AZD9977 and dapagliflozin may be found in their respective Investigator's Brochures.

2.3.1 Risk Assessment

Table 2 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Dapagliflozin		
Diabetic ketoacidosis in patients with diabetes mellitus	Diabetic ketoacidosis was only observed in patients with diabetes mellitus: • Type 2 diabetes mellitus: In the DECLARE study with a median exposure time of 48 months, events of DKA were reported in 27 out of 8574 patients in the dapagliflozin 10 mg group and 12 out of 8569 patients in the placebo group. The events were evenly distributed over the study period. Of the 27 patients with DKA events in the dapagliflozin group, 22 had concomitant insulin treatment at the time of the event. Precipitating factors for DKA were as expected in a T2DM population. In the DAPA-HF study, events of DKA were reported in 3 patients with T2DM in the dapagliflozin group and none in the placebo group. In the DAPA-CKD study, DKA was not reported in any patient in the dapagliflozin group and in 2 patients with T2DM in the placebo group. • Type 1 diabetes mellitus: In the 2 placebo-controlled clinical trials of dapagliflozin in T1DM, patients were advised to monitor blood ketones in case of suspected symptoms of DKA and seek medical advice/attention if their self-measured blood ketone reading was ≥ 0.6 mmol/L. In the pooled 24-week data, events of DKA were reported in 11 (1.9%) patients in the dapagliflozin 10 mg group and 3 (0.6%) patients in the placebo group. DKA events occurred evenly distributed over the	Patients with uncontrolled diabetes mellitus (HbA1c > 10%) and patients with T1DM are excluded from the study (see exclusion criteria #6 and #7). If ketoacidosis is suspected, discontinuation or temporary interruption of dapagliflozin/placebo should be considered and the patient should be promptly evaluated (see Section 7.1).

Table 2 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	study period. Inadequate insulin doses (missed insulin dose or insulin pump failure) were the most common precipitating factors. Three of the 11 patients with DKA in the dapagliflozin 10 mg group had blood glucose in the euglycemic range (< 14 mmol/L or 250 mg/dL). Patients with DKA events responded to conventional treatment for DKA. • In addition, there have been post marketing reports of ketoacidosis, including diabetic ketoacidosis, in patients with T1DM and T2DM taking dapagliflozin or other SGLT2i.	
AZD9977		
Hyperkalaemia	The primary safety concern related to the on-target effects of MR antagonism is the potential for development of hyperkalaemia. The pre-clinical data generated for AZD9977 suggests that the risk of hyperkalaemia will be significantly lower than for approved MR antagonist drugs (namely spironolactone and eplerenone) due to its different mechanism of action. No clinically significant changes were seen in serum K^+ levels in completed healthy volunteer studies. In the phase 1b study in patients with HFmrEF or HFpEF and eGFR ≥ 40 and ≤ 70 mL/min/1.73 m^2, there were generally small increases in serum potassium from baseline in the AZD9977 and spironolactone groups that were generally similar and not considered clinically relevant, and there were no discontinuations due to hyperkalaemia (confirmed serum K^+ ≥ 5.6 mmol/L). **Considerations for combination with dapagliflozin:** In the DAPA-HF trial, patients treated with dapagliflozin in conjunction with an MRA at baseline showed a reduced incidence of mild and moderate/severe hyperkalaemia compared to patients treated with placebo (McMurray et al 2019).	Patients enrolled in the study should have serum/plasma K^+ level ≥ 3.5 and < 5.0 mmol/L (see inclusion criterion #7). During the study, changes in serum/plasma K^+ will be closely monitored (see SoA). Specific discontinuation criteria and instructions for management of hyperkalaemia are provided (see Section 7.1 and Appendix F 1).
Deteriorating Renal Function/Initial eGFR decrease	In HF patients, MRA treatment is associated with an early modest decrease in GFR (Rossignol et al 2014). In healthy volunteer clinical studies with AZD9977, no clinically significant changes in GFR or creatinine were observed. In the phase 1b study in patients with HFmrEF or HFpEF and eGFR ≥ 40 and ≤ 70 mL/min/1.73 m^2, there were small decreases in eGFR from baseline in the AZD9977 and spironolactone groups that were not considered clinically relevant and showed improvement at follow-up/after last dose. **Considerations for combination with dapagliflozin**: SGLT2 inhibitor classes (including dapagliflozin) are	During the study, changes in eGFR will be closely monitored (see SoA). Specific discontinuation criteria and instructions for the management of deteriorating renal function are provided (see Section 7.1 and Appendix F 2).

Table 2 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	known to be associated with an initial modest decrease in eGFR though long-term effects are thought to be nephroprotective.	
Hypotension	Treatment with MRAs is associated with a BP lowering effect and some MRAs, including spironolactone, are used in resistant hypertension. In dog toxicology studies, tachycardia and decreased BP were observed with high AZD9977 doses. In healthy volunteer clinical studies, no clinically significant effect on BP was observed. In the phase 1b study in patients with HFmrEF or HFpEF and eGFR ≥ 40 and ≤ 70 mL/min/1.73 m^2, there were generally decreases from baseline in systolic and diastolic blood pressure in both treatment groups, though the reduction in systolic blood pressure was numerically larger with AZD9977 than with spironolactone. These changes were not considered clinically relevant from a safety perspective. **Considerations for combination with dapagliflozin**: SGLT2 inhibitor classes (including dapagliflozin) are known to be associated with modest decreases in BP.	Monitoring of BP according to the SoA.
Cardiovascular effects	In dog toxicology studies, increases in HR, decreases in BP, and cardiac perivascular proliferation were observed with high AZD9977 doses. A follow-up study in dog and modelling showed that cardiac pathology was related to the HR increase and that no pathology occurred with a mean HR below 135 bpm, and HR monitoring was used as a biomarker for cardiac pathology in the initial healthy volunteer studies. In healthy volunteer clinical studies and in the Phase 1b study in patients with HFmrEF or HFpEF and eGFR ≥ 40 and ≤ 70 mL/min/1.73 m^2, no clinically significant effects on HR or BP were observed. The cardiac injury biomarkers troponin and NT-proBNP were measured in the majority of the healthy volunteer studies, including multiple ascending dose studies, with no clinically significant effects observed.	Monitoring heart rate, BP, and ECGs according to the SoA.
Hepatotoxicity	In both rats and dogs isolated plasma chemistry changes in GLDH, AST, ALT and ALP were noted in some animals in the non-GLP studies. None had correlating histopathological findings and the findings were not reproduced in longer term studies up to 6 and 9 months in rat and dog, respectively. In healthy volunteer clinical studies and in the Phase 1b study in patients with HFmrEF or HFpEF and eGFR ≥ 40 and ≤ 70 mL/min/1.73 m^2, no clinically relevant trends were observed in liver chemistry values.	During the study, changes in AST, ALT, ALP and bilirubin and potential Hy's law cases will be monitored (see SoA and Appendix E).

Table 2 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Metabolic control	Increases in HbA1c by 0.4% and 0.6% were noted in 2 previously published clinical studies with spironolactone (Nielsen et al 2012, Matsumoto et al 2006). In the 1-month and 6-month rat GLP studies with AZD9977, there was a dose-dependent increase in blood glucose, but glucose levels remained in the normal range at all doses tested In GLP studies up to 9 months in dogs, once daily administration of AZD9977 was not associated with increased blood glucose. In healthy volunteer clinical studies, no clinically relevant trends were observed in plasma glucose values. In addition, there were no clinically relevant effects of AZD9977 on glucose control during an OGTT in the MAD study.	During the study, changes in HbA1c will be monitored (see SoA).
Other		
COVID-19 pandemic risks	There is currently an outbreak of respiratory disease (COVID-19) caused by a novel SARS-CoV-2, for which the WHO declared a pandemic situation on 12 March 2020. The mechanism of action of AZD9977 and dapagliflozin are unlikely impact the course of infection with SARS-CoV-2. Therefore, the risk of the participants exposure to SARS-CoV-2 or to suffer from COVID-19 is expected to be similar to the background population with the same co-morbidities as those in the study, in particular CKD and HF. The risk of exposure to infected people cannot be completely excluded as the participants may need to expose themselves to public areas (eg, commute to the site) and have additional human contact (eg, with site staff and other participants of the clinical study).	Patients with signs or confirmation of infection are excluded from the study (see exclusion criterion #25). Further risk mitigation measures are detailed in Appendix G.

ALP=alkaline phosphatase; ALT=alanine transaminase; AST=aspartate transaminase; BP=blood pressure; bpm=beats per minute; CKD=chronic kidney disease; COVID-19=coronavirus disease 2019; DKA=diabetic ketoacidosis; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; GFR=glomerular filtration rate; GLDH=gamma-lactone dehydrogenase; GLP=Good Laboratory Practice; HbA1c=glycated haemoglobin; HF=heart failure; HFmrEF=heart failure mid-range ejection fraction; HFpEF=heart failure preserved ejection fraction; HR=heart rate; MAD=multiple ascending dose; MR=mineralocorticoid receptor; MRA= mineralocorticoid receptor antagonist; NT-proBNP=N-terminal pro-brain natriuretic peptide; OGTT=oral glucose tolerance test; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SGLT2i=sodium-glucose co-transporter-2 inhibitor; SoA=schedule of activities; T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus; WHO=World Health Organization.

The 3-month combination toxicology studies in rats with AZD9977 and dapagliflozin did not reveal aggravated or additional effects not seen with the compounds when studied separately.

2.3.2 Benefit Assessment

Based on available clinical data with MRAs and dapagliflozin, it is expected that patients enrolled in the study will benefit from treatment with dapagliflozin and/or AZD9977:

- Clinical data from patients with HF and CKD suggest clinical benefit of MRAs in preventing the development of cardiovascular disease and progression to end-stage kidney disease in patients with CKD (see Section 2.2.1.3).
- Recent data from cardiovascular outcome studies of dapagliflozin and real world studies (including patients treated with dapagliflozin) show that treatment with dapagliflozin can reduce the risk of cardiovascular death and hospitalisation due to HF in patients with and without T2DM (also when given in addition to an MRA), and it has been postulated that the kidney protection and natriuretic effects induced by SGLT2 inhibitors may account for the reductions in HF hospitalisation (see Section 2.2.1.4).
- Recent data from an event-driven study with dapagliflozin in patients with CKD show that treatment with dapagliflozin is superior to placebo in reducing the incidence of the primary composite endpoint of ≥ 50% sustained decline in eGFR, reaching ESRD, cardiovascular or renal death when added to current background therapy (see Section 2.2.1.4).

2.3.3 Overall Benefit: Risk Conclusion

The overall clinical evidence suggests that the combination of AZD9977 and dapagliflozin would have clinical benefit and an acceptable safety profile in patients with HF and that further development is warranted.

3 OBJECTIVES AND ENDPOINTS

Table 3 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of AZD9977 in combination with dapagliflozin compared with dapagliflozin alone on UACR	• Percent change from baseline in UACR at the end of 12 weeks of study treatment
Secondary	
• To assess the dose-response relationship of dapagliflozin (10 mg) alone and 3 doses of AZD9977 (15, 50, or 150 mg) combined with dapagliflozin (10 mg) on UACR	• Percent change from baseline in UACR at the end of 12 weeks of study treatment
Safety	
• To assess the general safety and tolerability of AZD9977 in combination with dapagliflozin compared with dapagliflozin alone	• AE/SAE reporting • Vital signs (BP, pulse rate) • Clinical laboratory tests (clinical chemistry, haematology, and urinalysis) • Digital 12-lead safety ECG assessments • Safety topics of interest (hyperkalaemia, hypotension and deteriorating renal function)
• To assess the effect of AZD9977 in combination with dapagliflozin compared with dapagliflozin alone on serum K^+ and eGFR	• Absolute value and change from baseline in serum K^+ and eGFR over time
Exploratory	
• To assess the effect of AZD9977 in combination with dapagliflozin compared with dapagliflozin alone on serum NT-proBNP levels	• Change from baseline in serum NT-proBNP over time

• To assess plasma exposure of AZD9977 and dapagliflozin	• Plasma concentrations of AZD9977 and dapagliflozin
• To explore the relationships between AZD9977 and dapagliflozin dose/exposure and safety/pharmacodynamic variables	• Dose/exposure of AZD9977 and dapagliflozin relative to safety and pharmacodynamic variables (eg, serum/plasma K^+, eGFR, aldosterone)
• To assess the effect of AZD9977 in combination with dapagliflozin compared with dapagliflozin alone on blood uric acid, BUN, fasting plasma glucose, haematocrit, renin, ACTH, cortisol and copeptin levels	• Change from baseline in blood uric acid, BUN, FPG, haematocrit, renin, ACTH, cortisol and copeptin levels over time
• To assess the effect of AZD9977 in combination with dapagliflozin compared with dapagliflozin alone on MCV, MCHC, RBC distribution width, erythrocyte count	• Change from baseline in blood MCV, MCHC, RBC distribution width, erythrocyte count over time
• To assess the effect of AZD9977 in combination with dapagliflozin compared with dapagliflozin alone on urine Na^+, K^+, uric acid, urea, osmolality, glucose, creatinine, and cortisol	• Change from baseline in urine Na^+, K^+, uric acid, urea, osmolality, glucose, creatinine, and cortisol levels over time
• To assess the effect of AZD9977 in combination with dapagliflozin compared with dapagliflozin alone on cardiovascular biomarkers in blood	• Evaluation of changes in blood biomarkers (including but not limited to hsTnT, PIIIP3, GDF-15, ST2, ADMA, SDMA, L-Arg, ICAM, NGAL) over time
• **Optional**: To collect and store serum, plasma, and urine samples for future exploratory biomarker research related to PK, pharmacodynamics, safety, and tolerability of AZD9977 or dapagliflozin; or related to cardiorenal diseases	• Biomarker assessment in serum, plasma, and urine samples

• **Optional**: To collect and store blood samples for genetic research (according to each country's local and ethical procedures)	• Exploratory research into genes/genetic variation that may influence response to treatment

ACTH=adrenocorticotropic hormone; ADMA=asymmetric dimethylarginine; AE=adverse event; BP=blood pressure; BUN=blood urea nitrogen; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; FPG=fasting plasma glucose; GDF-15=growth differentiation factor-15; hsTnT=high sensitivity troponin T; ICAM=intercellular adhesion molecule; K^+=potassium; L-Arg=l-arginine; MCHC=mean corpuscular haemoglobin concentration; MCV=mean corpuscular volume; Na^+=sodium; NGAL=neutrophil gelatinase-associated lipocalin; NT-proBNP=N-terminal pro-brain natriuretic peptide; PIIIP3=procollagen type III N-terminal propeptide; PK=pharmacokinetics; RBC=red blood cell; SAE=serious adverse event; SDMA=symmetric dimethylarginine; ST2=suppression of tumourigenicity 2; UACR=urinary albumin to creatinine ratio.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2b, multi-centre, randomised, double-blind, active-controlled parallel group, study to assess the efficacy, safety and tolerability of AZD9977 and dapagliflozin administered for 12 weeks in patients with HF and CKD (eGFR ≥ 20 and ≤ 60 mL/min/1.73 m^2, with at least 20 % of patients with eGFR ≥ 20 to < 30 mL/min/1.73 m^2 and a maximum of 35% of patients with eGFR ≥ 45 mL/min/1.73 m^2).

The study will be conducted at approximately 150 to 250 sites in approximately 20 countries including North America, Asia/Pacific, and European countries.

For each participant, the total duration of participation will be approximately 22 to 24 weeks, including a 1-week screening period, followed by up to 7-week run-in period followed by a 12-week treatment period (including 6 visits), the EOT visit, and a 4-week safety follow-up after last dose (including 1 visit). An optional pre-screening visit may be scheduled. Week and day for pre-screening visit will be at the discretion of the investigator.

After screening, eligible participants currently on treatment with a SGLT2i other than dapagliflozin should stop taking the SGLT2i and start on dapagliflozin 10 mg. Participants on dapagliflozin treatment will continue on treatment but the medication will be provided. Participants will then undergo a 4 to 5-week run-in period to ensure washout of forbidden medications and stable doses of allowed background medications.

For participants eligible after screening not on treatment with a SGLT2i, treatment with dapagliflozin 10 mg will be initiated. Participants will then undergo a 6 to 7-week run-in period to ensure washout of forbidden medications and stable doses of allowed background medications.

During the treatment period, participants will be randomly assigned in a 1:1:1:1 ratio to receive once daily administration of one of the 4 study treatments as described below. To ensure blinding, the study treatment will be administered in the form of 3 oral capsules and 1 oral tablet in the following combinations.

Table 4 Study Treatments

Study Treatment	Capsule 1	Capsule 2	Capsule 3	Tablet
AZD9977 15 mg + Dapagliflozin 10 mg	AZD9977 15 mg	Placebo	Placebo	Dapagliflozin 10 mg
AZD9977 50 mg + Dapagliflozin 10 mg	Placebo	AZD9977 50 mg	Placebo	Dapagliflozin 10 mg
AZD9977 150 mg + Dapagliflozin 10 mg	Placebo	AZD9977 50 mg	AZD9977 100 mg	Dapagliflozin 10 mg
Dapagliflozin 10 mg alone	Placebo	Placebo	Placebo	Dapagliflozin 10 mg

Participants will be stratified according to T2DM (yes/no) and eGFR (≥ 20 to < 30 mL/min/1.73 m^2; or ≥ 30 to < 45 mL/min/1.73 m^2; or ≥ 45 mL/min/1.73 m^2) based on the latest eGFR assessment prior to the start of study treatment (eGFR at Visit 2).

4.1.1 Optional Pre-screening

Patients who perform the optional pre-screening visit to evaluate UACR should sign a separate, abbreviated ICF. Samples should be obtained for analysis in a local laboratory. The results are to be recorded in the medical records only.

4.2 Scientific Rationale for Study Design

The study is designed to evaluate the effect of AZD9977 in combination with dapagliflozin compared with dapagliflozin alone on UACR. The secondary objective is to assess the dose-response relationship of dapagliflozin (10 mg) alone and 3 doses of AZD9977 (15, 50, or 150 mg) combined with dapagliflozin (10 mg) on UACR.

The primary endpoint (percent change from baseline in UACR at 12 weeks) is an established key surrogate marker of the MRA mechanism of action. This marker has also shown to be predictive for adverse cardiovascular outcomes in patients with HF (Selvaraj et al 2018). Reported studies have shown a clear dose-response with UACR for MRAs (eg, finerenone), unlike other biomarkers relevant for HF such as the cardiac biomarker NT-proBNP. Clear effects on UACR have also been established for dapagliflozin (Pollock et al 2019), while dapagliflozin did not significantly reduce NT-proBNP over 12 weeks compared with placebo (Nassif et al 2019).

The study will evaluate general safety and tolerability with special focus on serum/plasma K^+, eGFR, and hypotension of treatment with AZD9977 and dapagliflozin in combination and alone. Exploratory objectives include PK, NT-proBNP, biomarkers reflecting cardiac fibrosis, endothelial function, and other aspects of cardiovascular function as well as markers of the potential mechanisms of action of SGLT2 inhibitors and AZD9977.

4.3 Justification for Dose

The doses of AZD9977 for combination therapy were selected to enable characterisation of the dose-response for UACR and to evaluate safety in this patient population.

The wide (10-fold) range of doses for AZD9977 (15 to 150 mg) given in combination with dapagliflozin 10 mg and dapagliflozin treatment alone will provide a sufficiently large range of AZD9977 exposures to evaluate the dose/exposure response relationship between UACR and AZD9977 + dapagliflozin in relation to dapagliflozin alone. About one third of the dose is excreted as unchanged AZD9977 in urine suggesting that renal clearance is contributing to the overall elimination of AZD9977. The main metabolic enzyme for AZD9977 is CYP3A4 that may have changed capacity in patients with low renal function. CCI [redacted]. The ongoing PK renal impairment study (D6401C00008) will confirm the PK profile of AZD9977 in patients with low renal function including those with an eGFR < 30 mL/min/1.73 m^2. This data will be available ahead of including patients with eGFR< 30 mL/min/1.73 m^2 into this study (D6402C00001). The dose selection for AZD9977 is based on PK, pharmacodynamic and safety data from previous studies in healthy subjects and in patients with HF. Using in vitro and clinical literature data for eplerenone, a translational PK/pharmacodynamic model for UACR reduction was developed. This model could well predict the UACR reduction for both spironolactone and finerenone assuming the same in vitro: in vivo ratio for IC50 and was therefore used to predict the UACR reduction for AZD9977. The 3 selected doses of AZD9977 are anticipated to yield an effect on UACR covering the whole dose-response curve from approximately 20 to 60% UACR reduction.

Dapagliflozin is currently under investigation in HF patients with LVEF >40% (HFmrEF and HFpEF) in the DELIVER◦study (NCT03619213). The dapagliflozin dose of 10 mg once daily is approved for treatment of patients with T2DM, for patients with heart failure and reduced ejection fraction with or without T2DM, and for patients with chronic kidney disease with or without T2DM.

There is a low risk for metabolic drug-drug interactions between AZD9977 and dapagliflozin. AZD9977 is mainly eliminated by CYP3A4-mediated metabolism and dapagliflozin is not an inhibitor of that metabolic enzyme (Kasichayanula et al 2012). Dapagliflozin is mainly eliminated by UGT1A9-mediated metabolism and AZD9977 is not an inhibitor of that metabolic enzyme.

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 safety follow-up visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

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 at screening (Visit 1a):

Age

1 Participant must be 21 years of age or older, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2 Documented diagnosis of stable symptomatic HF (NYHA class II-III) at screening (Visit 1a), and a medical history of typical symptoms and signs of HF in those who are currently receiving loop diuretic treatment.

- Typical symptoms associated with HF: breathlessness, orthopnoea, paroxysmal nocturnal dyspnoea, reduced exercise tolerance, fatigue, tiredness, increased time to recover after exercise.
- Signs associated with HF:
  - More specific: elevated jugular venous pressure, hepatojugular reflex, third heart sound (gallop rhythm), laterally displaced apical impulse.
  - Less specific: weight gain (> 2 kg/week), weight loss (in advanced HF), tissue wasting (cachexia), cardiac murmur, peripheral oedema (ankle, sacral, scrotal), pulmonary crepitations, reduced air entry and dullness to percussion at lung bases (pleural effusion), tachycardia, irregular pulse, tachypnoea, Cheyne Stokes respiration, hepatomegaly, ascites, cold extremities, oliguria, narrow pulse pressure.

3 Left ventricular ejection fraction < 60% documented by the most recent echocardiogram 2D or 3D or cardiac magnetic resonance imaging within the last 12 months prior to screening.

If patient has experienced an acute myocardial event/injury associated with release of cardiac troponin within the previous 12 months, then a more recent echocardiogram to determine eligibility for participation in the study must be at least 12 weeks after the most recent cardiac event.

4 Patients should be treated for HF, hypertension, T2DM, or renal disease according to guidelines.

Note: Background treatment should be in line with locally recognised treatment guidelines in each indication, as described in Section 6.5.2. Both patients with or without SGLT2i treatment can be included in the study (Section 6.1.1).

5 NT-proBNP ≥ 300 pg/mL for patients with sinus rhythm at screening; and NT proBNP ≥ 600 pg/mL for patients with atrial fibrillation/flutter at screening, using local laboratory sample.

6 eGFR ≥ 30 and ≤ 60 mL/min/1.73 m^2 (by CKD-EPI formula based on local laboratory sample).

Note: Recruitment will start with patients who have eGFR ≥ 30 mL/min/1.73 m^2. During the study, the Safety Unblinded Data Review Committee may decide to also include patients with eGFR ≥ 20 to < 30 mL/min/1.73 m^2.

7 UACR at screening: spot urine sample analysed at local laboratory ≥ 30 mg/g (3 mg/mmol) and < 3000 mg/g (300 mg/mmol) for participants on SGLT2i; spot urine sample analysed at local laboratory ≥ 50 mg/g (5 mg/mmol) and < 3000 mg/g (300 mg/mmol) for participants not on SGLT2i.

Note: The lower limit for participants not on SGLT2i may be increased to ≥ 60 mg/g (6 mg/mmol) in case high proportion of randomisation failures due to UACR (eg, if > 50% of participants fail due to UACR < 30 mg/g [3 mg/mmol]) at the discretion of the Sponsor.

Weight

8 Body mass index less than 40 kg/m^2.

Sex

9 Male or female of non-childbearing potential.

Reproduction

10 Female patients must be of non-childbearing potential.

Women of non-childbearing potential are defined as women who are either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomisation without an alternative medical cause. The following age-specific requirements apply:

(a) Women < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and FSH levels in the postmenopausal range.

(b) Women ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.

11 Male patients must be surgically sterile or using, in conjunction with their female partner, a highly effective method of contraception for the duration of the study (from the time they sign consent) and for 3 months after the last dose of study drug to prevent pregnancy in a partner. Male study participants must not donate or bank sperm during this same time period.

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 ICF and in this protocol.

13 Provision of signed and dated, written ICF prior to any mandatory study specific procedures, sampling, and analyses.

NOTE: For the optional pre-screening visit there is a separate informed consent. Refer to Section 4.1.1.

14 Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of samples for optional genetic research that supports Genomic Initiative.

Participants are eligible to be randomised in the study only if all of the following criteria apply at randomisation (Visit 3):

15 eGFR ≥ 30 mL/min/1.73 m^2 (by CKD-EPI formula at central laboratory) based on results from pre-randomisation Visit 2.

Note: Recruitment will start with patients who have eGFR ≥ 30 mL/min/1.73 m^2. During the study, the Safety Unblinded Data Review Committee may decide to also include patients with eGFR ≥ 20 to < 30 mL/min/1.73 m^2

16 UACR ≥ 30 mg/g (3 mg/mmol) and < 3000 mg/g (300 mg/mmol) based on central laboratory samples collected at pre-randomisation Visit 2. Refer to Section 8.1.1.

17 Serum/plasma K^+ level ≥ 3.5 and < 5.0 mmol/L within 10 days prior to randomisation (Visit 3) from local laboratory.

18 Serum/plasma sodium (Na^+) level within normal reference values within 10 days prior to randomisation (Visit 3) from local laboratory.

19 Systolic BP ≥ 90 and < 150 mmHg (or < 180mmHg if the patient is already receiving 3 or more antihypertensive drugs) at randomisation (Visit 3), with no change to antihypertensive treatments in previous 3 weeks. Antihypertensive drugs include, but are not limited to, a diuretic, ACEI, ARB, beta-blocker and calcium channel blocker.

5.2 Exclusion Criteria

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

Medical Conditions

1 Primary glomerulopathy, vasculitic renal disease (including ANCA-associated vasculitis), prior dialysis or unstable rapidly progressing renal disease, autosomal dominant or autosomal recessive polycystic kidney disease, lupus nephritis or ANCA-associated vasculitis.

2 Patients with currently decompensated HF requiring hospitalisation for optimisation of HF treatment and are not on stable HF therapy at the time of enrolment.

3 HF due to cardiomyopathies that would primarily require specific other treatment such as cardiomyopathy due to amyloidosis or infiltrative diseases, primary hypertrophic cardiomyopathy, cardiomyopathy related to current toxic or infective conditions (ie, ongoing chemotherapy, infective myocarditis, septic cardiomyopathy).

4 High output HF (eg, due to hyperthyroidism or Paget's disease).

5 HF due to pericardial disease, congenital heart disease or clinically significant uncorrected primary cardiac valvular disease or planned cardiac valve repair/replacement.

6 Patients with uncontrolled diabetes mellitus (HbA1c > 10%).

7 Patients with T1DM.

8 Intermittent or persistent 2nd or 3rd degree atrioventricular block, sinus node dysfunction with clinically significant bradycardia or sinus pauses, not treated with a pacemaker.

9 Known congenital long QT syndrome or history of QT prolongation associated with other medications.

10 History of any life-threatening cardiac dysrhythmia (continuous or paroxysmal) or uncontrolled ventricular rate in patients with atrial fibrillation or atrial flutter.

11 Acute coronary syndrome and/or elective/non-elective percutaneous cardiac interventions within 3 months prior to randomisation (Visit 3) or is planned to undergo any of these procedures during the study.

12 Any major cardiovascular (eg, open chest coronary artery bypass grafting or valvular repair/replacement) or major non-cardiovascular surgery as judged by the investigator within 3 months prior to randomisation (Visit 3) or is planned to undergo any of these procedures during the study.

13 Heart transplantation or left ventricular assist device at any time or if these are planned.

14 Kidney or any organ transplantation or if these are planned.

15 Addison's disease (a medical conditions associated with development of hyperkalaemia).

16 History or ongoing allergy/hypersensitivity, as judged by the investigator, to SGLT2i (eg, dapagliflozin, empagliflozin).

17 Any clinically significant disease or disorder (eg, cardiovascular, gastrointestinal, liver, renal, neurological, musculoskeletal, endocrine, metabolic, psychiatric, major physical impairment) which, as judged by the investigator, might put the patient at risk because of participation in the study, or probable alternative primary reason for patient's symptoms in judgement of investigator, including but not limited to:
   (a) Isolated pulmonary arterial hypertension (defined as mean PAP ≥ 25 mmHg at rest) or right ventricular failure; in the absence of left-sided HF.
   (b) Anaemia defined as haemoglobin level < 100 g/L or < 10 g/dL at time of screening (Visit 1a).
   (c) Severe chronic obstructive pulmonary disease or other lung disease including but not limited to pulmonary fibrosis requiring chronic oxygen therapy, regular nebuliser use or oral steroid therapy.
18 Stroke, transient ischaemic attack, carotid surgery, or carotid angioplasty within previous 3 months prior to randomisation (Visit 3).
19 Active malignancy requiring treatment (except for basal cell or squamous cell carcinomas of the skin).
20 Hepatic disease, including hepatitis and/or hepatic impairment (Child-Pugh class A-C), AST or ALT >2 × ULN; or TBL > 2 × ULN at time of screening (Visit 1a). An isolated increase in bilirubin in patients with known Gilbert's syndrome is not a reason for exclusion.
21 Prior or ongoing drug or alcohol abuse.
22 Patients treated with strong or moderate CYP3A4 inhibitor or inducer (Appendix H).
23 Patients with newly detected pathological laboratory values or an ongoing disease condition requiring investigation and/or initiation or adjustment of current treatment (in the opinion of the investigator).
24 Any condition outside the renal and cardiovascular disease area, such as but not limited to malignancy, with a life expectancy of less than 2 years based on investigator´s clinical judgement.
25 Any of the following signs or confirmation of COVID-19 infection:
   (a) Optional in case RT-PCR is available at the site with an appropriate turnaround time: Patient has a positive test result for SARS-CoV-2 at Visit 2 before randomisation at Visit 3.
   (b) Clinical signs and symptoms consistent with COVID-19 (eg, fever, dry cough, dyspnoea, sore throat, fatigue) or confirmed infection by appropriate laboratory test within the last 4 weeks prior to screening (Visit 1a) or at randomisation (Visit 3).
   (c) Patient has been previously hospitalised with COVID-19 infection and did not fully recover their previous health status.

Prior/Concomitant Therapy

26 Prior medical treatment with an MRA where the medication was taken within 90 days prior to screening (Visit 1a).

27 Treatment with MRA and other prohibited concomitant medications during run-in. Note: Prohibited medications are listed in Section 6.5.1.

28 Current or prior treatment within 6 months prior to screening (Visit 1a) with cytotoxic therapy, immunosuppressive therapy, or other immunotherapy.

29 Participation in another clinical study with an investigational product administered in the last 3 months prior to randomisation (Visit 3).

Other Exclusions

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

31 Judgement 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.

32 Previous randomisation in the present study.

33 Plasma donation within 1 month of the visit at the clinic or any blood donation/blood loss > 500 mL during the 3 months prior to any visit at the clinic.

Genetic Sampling (Optional)

Exclusion from this genetic research may be for any of the exclusion criteria specified for the main study or any of the following:

34 Previous allogeneic bone marrow transplant.

35 Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Patients should fast prior to the collection of blood samples for FPG and lipids, on the days specified in the SoA. Fasting is defined as no caloric intake for at least 8 hours prior to the collection of the sample.

There are no other specific meals and dietary restrictions.

Study medications should be taken at approximately the same hour each morning, and the time recorded by the participant in the diary card (see Section 6.4).

On days when participants will attend the study site for a study visit and assessments, they will be asked to **not** take their study medications prior to attending the study visit. The

participant will take the study medication at the site after completing all predose procedures and provided they are permitted to continue in the study following assessments.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but fail to be eligible to start Run-in. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the eGFR and/or K^+ inclusion/exclusion criteria for participation in the study at screening (Visit 1a) and/or pre-randomisation Visit 2, may have their eGFR and/or serum/plasma K^+ retested later upon investigator's discretion.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Only 1 rescreening is allowed in the study. Rescreened participants should be assigned the same participant number as for the initial screening.

6 STUDY INTERVENTION

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

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

After screening, eligible participants currently on treatment with a SGLT2i other than dapagliflozin should stop taking the SGLT2i and start on dapagliflozin 10 mg once daily. Participants on dapagliflozin treatment will continue on treatment but the medication will be provided. Participants will then undergo a 4 to 5-week run-in period to ensure washout of forbidden medications and stable doses of allowed background medications.

For participants eligible after screening not on treatment with a SGLT2i, treatment with dapagliflozin 10 mg once daily will be initiated. Participants will then undergo a 6 to 7-week run-in period to ensure washout of forbidden medications and stable doses of allowed background medications.

Participants will be randomly assigned with a 1:1:1:1 ratio to receive once daily administration of one of the following study treatments:

- AZD9977 15 mg + dapagliflozin 10 mg
- AZD9977 50 mg + dapagliflozin 10 mg
- AZD9977 150 mg + dapagliflozin 10 mg
- Dapagliflozin 10 mg

To ensure blinding to treatment allocation and the AZD9977 dose, daily dosing will consist of 1 open label dapagliflozin 10 mg tablet and 3 AZD9977 capsules containing respectively AZD9977 150 mg or placebo, AZD9977 50 mg or placebo, and AZD9977 15 mg or placebo See Table 5 and Section 4.1.

Table 5 Investigational Products

	AZD9977			Dapagliflozin
Intervention Name	AZD9977 15 mg or placebo	AZD9977 50 mg or placebo	AZD9977 100 mg or placebo	Dapagliflozin 10 mg
Type	Drug	Drug	Drug	Drug
Dose Formulation	Pellets in capsule (size 3)	Pellets in capsule (size 0)	Pellets in capsule (size 0)	Film-coated tablet
Unit Dose Strength(s)	15 mg	50 mg	100 mg	10 mg
Dosage Level(s)	**15 mg:** 1 AZD9977 15 mg capsule + 1 placebo size 0 capsule + 1 placebo size 0 capsule			10 mg tablet
	50 mg: 1 AZD9977 50 mg capsule + 1 placebo size 3 capsule + 1 placebo size 0 capsule			
	150 mg: 1 AZD9977 50 mg capsule + 1 AZD9977 100 mg capsule + 1 placebo size 3 capsule			
Route of Administration	oral	oral	oral	oral
IMP and NIMP	IMP	IMP	IMP	IMP, NIMP [a]
Sourcing	AZD9977, dapagliflozin, and matching placebo treatments will be supplied centrally through AstraZeneca.			
Packaging and Labelling	For each strength, AZD9977 and matching placebo will be provided in bottles containing 32 capsules.			Dapagliflozin will be supplied in HDPE bottles containing 35 tablets.
	All bottles will be labelled in accordance with GMP Annex 13 and per country regulatory requirement.			

GMP=Good Manufacturing Practice; HDPE=high-density polyethylene; IMP=investigational medicinal product; NIMP=non-investigational medicinal product.

[a] Dapagliflozin is NIMP during the run-in and safety follow-up, but IMP during the treatment phase.

6.1.2 Medical Devices

1 No AstraZeneca manufactured medical devices (or devices manufactured for AstraZeneca by a third party) are provided for use in this study.

2 Other medical devices (not manufactured by or for AstraZeneca) provided for use in this study are as follows.
   – dECG device: GE MAC 2000 ECG Analysis System (510k and CE marked)
3 All medical device deficiencies (including malfunction, use error and inadequate labelling) will be documented and reported by the investigator throughout the clinical investigation (see Section 8.3.10) and appropriately managed by the sponsor.

6.2 Preparation/Handling/Storage/Accountability

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 Study Drug Handling Instructions.

6.3 Measures to Minimise Bias: Randomisation and Blinding

All participants will be centrally assigned to randomised study intervention using an IRT/RTSM. Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information and directions for the RTSM will be provided to each site.

Study intervention will be dispensed at the study visits summarised in SoA.

Unused returned study intervention must not be re-dispensed to the participants.

The IRT/RTSM will provide to the investigator(s) or pharmacists the kit identification numbers to be allocated to the participant at the dispensing visit.

Routines for this will be described in the IRT/RTSM 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 IRT/RTSM 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.

The PK samples will be analysed at Labcorp Drug Development bioanalytical laboratory only for patients on active treatment. The bioanalytical laboratory will, therefore, have access to the treatment codes but will not share the codes with the sponsor or others involved in the study until the blinding is broken for the study after closure.

6.4 Study Intervention Compliance

Participants will take treatment at the site on visit days and at home between visits.

When participants are dosed at the site, they will receive study treatments directly from the investigator or designee, under medical supervision, after checking treatment was not taken at home before coming to the study site. The date, and time of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF.

When participants self-administer study treatments at home, compliance with study treatment will be assessed at each visit. Diary Cards will be given to the patients at the randomisation visit (Visit 3) and the patients will be asked to fill in the dose intake information (date and time) at home. The diary cards will be checked by study site personnel at the study visits and data transferred to the eCRF.

Compliance will be assessed by direct questioning and counting returned tablets/capsules during the site visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of dapagliflozin tablets and AZD9977/placebo capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays will also be recorded in the eCRF. If treatment was taken at home before coming to the study site, no new dose should be administered, and the date and time of the dose administered at home should be recorded in the eCRF.

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 screening (Visit 1a) 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

Participants may be enrolled and or continue in the study regardless of their choice to be vaccinated or not. COVID-19 vaccine received prior to or during the study entry must be recorded including the type of vaccine.

The Study Physician should be contacted if there are any questions regarding prior or concomitant therapies.

6.5.1 Prohibited Medications

The medications and supplements listed below are prohibited from at least start of run-in and for the duration of the study. Patients taking any of these medications at the start of the run-in period cannot be included into the study.

- Potassium-sparing diuretics (eg, amiloride, triamterene)
- MRAs or aldosterone antagonists (eg, eplerenone, spironolactone)
- ACEI and ARB taken in combination
- Direct renin inhibitor (eg, Aliskiren)
- Cyclosporin or tacrolimus
- Strong or moderate CYP3A4 inhibitors or inducers (see Appendix H)
- K^+ supplements or dietary salt alternatives containing K^+ such as Lo-Salt (prohibited during run-in unless if serum $K^+ < 3.5$ mmol/L, and can be started during the study as a corrective action if hypokalaemia is confirmed)

- NSAIDs (The use of acetylsalicylic acid as antiplatelet agent is allowed prior and during the study as well as the intermittent use of topical NSAIDs if prescribed for a medical condition)
- Potassium binders (prohibited at screening/randomisation but can be started as a corrective action during the study)

Medical treatment with an MRA is exclusionary if the medication was taken within 90 days prior to screening (Visit 1a). Cytotoxic therapy, immunosuppressive therapy, and other immunotherapy for primary or secondary renal disease are prohibited within 6 months prior to screening (Visit 1a) and for the duration of the study.

6.5.2 Background Medications

Background treatment for HF, hypertension, or renal disease should be stable for at least 3 weeks prior to randomisation (see inclusion criterion #4) and remain stable during the study.

Patients with HF and LVEF ≤ 40% should receive background standard of care for HFrEF and be treated according to locally recognised guidelines with both drugs and devices, as appropriate.

Guideline-recommended medications should be used at recommended doses unless contraindicated or not tolerated: an ACEI, or ARB or sacubitril/valsartan and a beta-blocker. It is advised that other guideline recommendations for management of cardiovascular disease and CKD are also followed (except for strong or moderate CYP3A4 inhibitors or inducers).

Patients who are on 10 mg dapagliflozin at screening should remain on the therapy as indicated throughout the treatment period of the study. Patients who are on another SGLT2i (eg, canagliflozin or empagliflozin) will be switched to 10 mg dapagliflozin starting at the start run-in (Visit 1b) after confirmed eligibility and will remain on the therapy throughout the treatment period of the study. Patients who are not on a SGLT2i will be started on 10 mg dapagliflozin at the start run-in (Visit 1b) after confirmed eligibility and will remain on the therapy throughout the safety follow-up period.

Glycaemic control should be performed according to local guidelines.

It is preferable that any background medical therapy (eg, HF, antihypertensive therapy as well as therapy with statins) will not be changed during study drug treatment, ie, between the screening visit and the last dose of study drug. However, if this is necessary, the participant does not need to be withdrawn from study drug.

6.5.3 Medications Inducing Hypoglycaemia

Participants using medications that can cause hypoglycaemia in T2DM patients, including

insulin or SU, may be required to reduce insulin by 10 to 20% (total daily dose) and SU by 25 to 50%. In addition, more frequent blood glucose monitoring may be considered in participants receiving insulin and/or SU and with baseline HbA1c ≤ 7% at randomisation.

6.6 Dose Modification

No dose modifications are allowed during the study.

6.7 Intervention After the End of the Study

Following the EOT visit, participants will stop study drug and continue on open label dapagliflozin 10 mg during the safety follow-up period. After the safety follow-up visit, participants should return to their usual treatments at the discretion of the investigator.

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 (definitive discontinuation) study intervention.

Participants may be discontinued from study intervention in the following situations:

- Participant decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment
- An AE that, in the opinion of the Investigator or AstraZeneca, warrants discontinuation from further dosing
- Severe non-compliance with the CSP
- Safety reasons as judged by the investigator and/or sponsor where continued treatment may put participant at undue risk

Participants will be discontinued from study intervention in the following situations:

- If the participant becomes pregnant during the course of the study
- Protocol-defined hyperkalaemia: Study treatments must be discontinued in case of confirmed (ie, 2 consecutive samples) serum/plasma $K^+ > 6.0$ mmol/L, or confirmed serum/plasma $K^+ > 5.5$ mmol/L (at investigator's discretion), or serum/plasma $K^+ > 5.5$ mmol/L with repeat value > 6 mmol/L (see Appendix F 1 for details on the monitoring and management of hyperkalaemia)
- Protocol-defined deteriorating renal function: Study treatments must be discontinued in case of confirmed eGFR reduction from baseline > 50% and/or any confirmed decrease below 15 mL/min/1.73 m^2 (see Appendix F 2 for details on the monitoring and management of deteriorating renal function)
- There have been reports of ketoacidosis, including DKA, in patients with T2DM taking dapagliflozin and other SGLT2 inhibitors in previous studies. Patients with T2DM on investigational treatment who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise and shortness of breath should be assessed for ketoacidosis, even if blood glucose levels are < 14 mmol/L (250 mg/dL). If ketoacidosis is suspected, discontinuation or temporary interruption of the investigational treatment should be considered and the patient should be promptly evaluated.

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from

the study.

If study interventions are permanently discontinued, the participant will remain in the study for the ET visit and the safety follow-up visit. The participant may continue on open-label dapagliflozin during the safety follow-up period as judged by the Investigator taking in consideration the reason for the permanent discontinuation of the study intervention.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Temporary Discontinuation and Rechallenge

Temporary discontinuation of study treatments may be considered if hyperkalaemia is observed and repeat tests are required to confirm protocol-defined discontinuation criteria (see Appendix F 1).

Temporary discontinuation of dapagliflozin should be considered if DKA is suspected and the patient should be promptly evaluated:

- If DKA is confirmed, study treatments should be discontinued permanently.
- If DKA is not confirmed, dapagliflozin may be restarted.

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 ET visit should be conducted, as shown in the SoA. See SoA for data to be collected at the ET visit.
  - The participant will discontinue the study intervention and be withdrawn from the study at that time. The 4-week safety follow-up after last dose will not be performed.
- 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 out 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.

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.
- 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, echocardiography) 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.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 400 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

8.1.1 Primary/Secondary Variable: Urinary Albumin to Creatinine Ratio (UACR)

The UACR is calculated as follows:

- UACR (mg/mmol) = 10 × urine albumin (mg/dL) / urine creatinine (mmol/L)

Urine samples for the determination of albumin and creatinine and calculation of UACR will be collected at the timepoints described in the SoA:

- After consent at screening (Visit 1a), a container to collect the spot urine sample will be dispensed to the participants. The spot urine sample will be collected at this visit.
- Collection of triplicate urine sampling will start at Visit 2. At Visit 1b and at subsequent visits, containers to collect the urine samples will be dispensed to the participants prior to the visits described in the SoA. Investigators will perform a phone call prior to the visit to remind the participants to collect the first morning void samples. Participants will collect first morning void urine samples at home on 3 consecutive days (ideally day of visit and

preceding 2 days [refrigerated overnight] which will be returned on the day of visit). Samples will be analysed centrally. At each visit, the geometric mean of the triplicate measurements will be computed centrally and used for all analyses of UACR.

Note: The samples collected on visit days will also be used for the determination of exploratory urinary parameters (see Section 8.5.2.1 and 8.6.2).

8.1.2 Exploratory Variables – Not Applicable

8.2 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA.

8.2.1 Physical Examinations

Physical examination, and measurement of weight and height will be conducted as outlined in the SoA.

- For weight and height measurements, the participant will be allowed to wear indoor, daytime clothing with no shoes and no coats/jackets and removal of heavy objects from pockets.
- A complete physical examination will be performed and include assessments of general appearance, respiratory, cardiovascular, abdominal, and neurological systems, the skin, lymph nodes, and an assessment of the presence and extent of peripheral (ankle/leg) oedema.

For information on how AEs based on physical examination findings should be recorded and reported, see Section 8.3.5.

8.2.2 Vital Signs

Blood pressure and pulse rate will be assessed at the study site, as outlined in the SoA, prior to blood collection for laboratory tests with the patient resting in a supine position using a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones) and will consist of 1 pulse and 3 BP measurements (3 consecutive BP readings will be recorded at intervals of at least 1 minute). The average of the 3 BP readings will be recorded on the eCRF.

For information on how AEs based on vital sign results should be recorded and reported, see Section 8.3.5.

8.2.3 Electrocardiograms

Single 12-lead ECG will be obtained after the patient has been resting in a supine position for at least 10 minutes, at the visits outlined in the SoA. A dECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals will be used. Interpretation of the clinical safety dECG findings will be reviewed and confirmed by the investigator and recorded in the eCRF. Digital ECGs will be collected, cleaned, and stored by ERT.

Investigators will assess patients' eligibility according to the ECG report of Visit 1a. Any abnormal finding in the ECG tracing will be evaluated by the investigator and will be specifically documented and registered in the CRF. Throughout the study, clinically relevant new findings or worsening of a pre-existing finding in the ECGs (parameters or abnormal findings in the tracing) must be considered an AE and must be recorded in the AE CRF form.

For information on how AEs based on ECG results should be recorded and reported, see Section 8.3.5.

8.2.4 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the visits indicated in the SoA.

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The clinical chemistry, haematology, and urinalysis will be performed at a local laboratory for screening, and at a central laboratory at baseline and subsequent visits, as indicated in the SoA.

Measurement of electrolytes (Na^+ and K^+) and creatinine at local laboratories may be done on either plasma or serum samples, depending on their capabilities, while these measurements at the central laboratory will be done on serum samples. In addition, K^+ levels will be measured in plasma samples at the central laboratories for exploratory analysis.

The participant's eGFR (mL/min/1.73 m^2) will be calculated based on the standard BSA-adjusted CKD-EPI formula using serum/plasma creatinine concentration alone (Levey et al 2009) as measured at a local laboratory and using both serum creatinine and serum cystatin C concentrations (Inker et al 2012)at a central laboratory. Note that for eGFR calculation based on creatinine levels, the calibrated methods provide equivalent results for plasma and serum sample types.

eGFR calculation using standard BSA-adjusted CKD-EPI formula using serum/plasma

creatinine concentration (Levey et al 2009):

$$eGFR\ (mL/min/1.73m^2) = 141 \times min\ (SCr/\kappa,1)^{\alpha} \times max\ (SCr/\kappa,1)^{-1.209} \times 0.993^{Age} \times [1.018\ if\ female] \times [1.159\ if\ black]$$

κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1.

eGFR calculation using standard BSA-adjusted CKD-EPI formula using both serum creatinine and serum cystatin C concentrations (Inker et al 2012):

$$eGFR\ (mL/min/1.73m^2) = 135 \times min(SCr/\kappa, 1)^{\alpha} \times max(SCr/\kappa, 1)^{-0.601} \times min(Scys/0.8, 1)^{-0.375} \times max(Scys/0.8, 1)^{0.711} \times 0.995^{Age} \times 0.969\ [if\ female] \times 1.08\ [if\ black]$$

SCr (serum creatinine) = mg/dL, Scys (standardised serum cystatin C) = mg/L, κ = 0.7 (females) or 0.9 (males), α = -0.248 (females) or -0.207 (males), min(SCr/κ or 1) = indicates the minimum of SCr/κ or 1, max(SCr/κ or 1) = indicates the maximum of SCr/κ or 1, min(Scys/0.8, 1) = indicates the minimum of Scys/0.8 or 1, max(Scys/0.8, 1) = indicates the maximum of Scys/0.8 or 1, age = years

The following laboratory variables will be measured:

Table 6 Laboratory Safety Variables

Haematology/Haemostasis (whole blood) [a]	**Clinical Chemistry (serum or plasma)** [a]
White blood cell (WBC) count	Na^+ [b]
Red blood cell (RBC) count	K^+ [b, c]
Haemoglobin (Hb)	Blood urea nitrogen (BUN)
Haematocrit (HCT)	Serum creatinine [b d]
Neutrophils absolute count [f]	Uric acid [f]
Lymphocytes absolute count [f]	Albumin
Monocytes absolute count [f]	Calcium
Eosinophils absolute count [f]	Phosphate
Basophils absolute count [f]	Alkaline phosphatase (ALP)
Platelets	Alanine aminotransferase (ALT)
International normalised ratio (INR) [e]	Aspartate aminotransferase (AST)
MCV [f]	Total bilirubin (TBL)
MCHC [f]	Glutamate dehydrogenase (GLDH) [f]
RBC distribution width [f]	Creatine kinase (CK) [f]
HbA1c	Bicarbonate (HCO_3^-) [f]
Urinalysis (urine) [a]	Chloride (Cl^-) [f]
Protein	Magnesium (Mg^+) [f]
Glucose	Glucose
Blood	Total cholesterol, direct HDL-C, triglycerides, LDL-C [g], VLDL-C [g] (fasting, see Section 5.3.1) [f]
Leukocyte esterase	**Other assessments**
Specific gravity [f]	Cystatin C [d, h]
pH [f]	RT-PCR test for SARS-CoV-2 (optional, at pre-randomisation visit)
Microscopic examination of the sediment if blood or leukocyte esterase are positive on dipstick [f]	Follicle stimulating hormone (FSH) (for confirmation of postmenopausal status of women < 50 years old only [women who are permanently sterilised are exempted], at screening)

Note: In case a participant shows an AST **or** ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN please refer to Appendix E. Actions required in cases of increases in liver biochemistry and evaluation of Hy's law cases, for further instructions.
BSA=body surface area; CKD-EPI=chronic kidney disease epidemiology collaboration; eGFR=estimated glomerular filtration rate; HbA1c=glycated haemoglobin; HDL-C= high density lipoprotein cholesterol; K^+=potassium; LDL-C=low density lipoprotein cholesterol; MCHC=mean corpuscular haemoglobin concentration; MCV=mean corpuscular volume; Na^+=sodium; RT-PCR=reverse transcriptase polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SoA=schedule of activities; ULN=upper limit of normal; VLDL-C= very low density lipoprotein cholesterol

[a] Local laboratory at screening and pre-randomisation (if applicable per SoA) and central laboratory at subsequent visits, unless specified otherwise.
[b] At the local laboratories, electrolytes (Na^+ and K^+) and creatinine may be measured in plasma samples instead of serum samples depending on their capability.
[c] Central laboratory measurements for K^+ levels will be with serum and plasma samples.
[d] eGFR (mL/min/1.73 m^2) will be calculated using the BSA-adjusted CKD-EPI formula and including both serum creatinine and serum cystatin C for central laboratory assessments; and with serum/plasma creatinine alone for local laboratory assessments.
[e] The post-randomisation INR measurements may be done at a local laboratory if the necessary material provided by the central laboratory is not available; and the measurements may be omitted if the local laboratory is not capable of doing the measurements. Refer to Laboratory Manual for details.
[f] These tests are not required at screening or pre-randomisation.
[g] Per Friedewald equation.
[h] Central laboratory for all cystatin C measurements.

Instructions for the collection and handling of the samples will be provided in the study specific Laboratory Manual.

8.3 Adverse Events and Serious Adverse Events

The PI 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 will be collected from randomisation (Visit 3) throughout the treatment period and including the follow-up period.

Serious AEs will be recorded from the time of signing of the full ICF for the study (Visit 1a). No AE or SAE information will be collected after just signing of the optional pre-screening ICF.

If the investigator becomes aware of a SAE, with a suspected causal relationship to at least 1 of the IMP, 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 AE assessment or other assessment/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)
- Date and time when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the investigational products (yes or no)
- Action taken with regard to investigational products
- 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) and/or other medication
- Description of AE

8.3.3 Causality Collection

The investigator should assess causal relationship between each of the investigational products 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: 'Have you had any health problems since the previous visit?' 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

The results from the protocol-mandated laboratory tests and vital signs will be summarised in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, ECG parameters and echocardiography findings 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.

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 $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ 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 during the course of the study, then investigators or other site personnel inform the appropriate AstraZeneca representatives within one 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 AEs 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 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 a SAE to the appropriate AstraZeneca representative by telephone.

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

For further guidance on the definition of a SAE, see Appendix B.

The reference document for definition of expectedness/listedness is the Investigator's Brochure for both study treatments.

8.3.8 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except when the pregnancy is discovered before the study participant has received any study drug.

8.3.8.1 Maternal Exposure

There is no information about effects that AZD9977 could have on the development of the foetus in humans. Pre-clinical studies have shown that AZD9977 is not genotoxic, however formal pre-clinical reproductive toxicology studies have not yet been completed.

Dapagliflozin must not be used in the second and third trimesters of pregnancy. In the time period corresponding to second and third trimester of pregnancy with respect to human renal maturation, maternal exposure to dapagliflozin in rat studies was associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny. There are no adequate and well-controlled studies of dapagliflozin in pregnant women.

Women of childbearing potential are not allowed to be included in this study. Should a pregnancy still occur, the investigational products 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 anomaly/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 anomaly) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs during 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 (see Section 8.3.8) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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

8.3.8.2 Paternal Exposure

It is important that women of childbearing potential, who are the partners of male participants, do not become pregnant during the study and for a total period of 3 months after the male study participant has received his last dose of IMP.

All male participants should avoid fathering a child by either true abstinence or use together with their female partner/spouse a highly effective method of contraception (see definition below), starting from the time of IMP administration until 3 months after the last dose of IMP.

For male participants whose partner is already pregnant, the man should use a condom for the duration of the study and for 1 week afterwards.

Male participants should not donate sperm for the duration of the study and for at least 3 months after the study follow-up visit.

Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered highly effective birth control methods such as:

- Combined (oestrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progesterone-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion of female partner
- Male vasectomy
- True sexual abstinence: True abstinence refers to: When this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptom-thermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.

If the partner of a male participant becomes pregnant during the study, this should be reported to the investigator. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a participant's partner is subsequently found to be pregnant after the study participant is included in the study, then consent will be sought from the partner and if granted any pregnancy will be followed and the status of mother and/or child will be reported to the sponsor after delivery.

8.3.9 Medication Error

If a medication error occurs during 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 (see Section 8.3.9) and within 30 days for all other medication errors.

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

8.3.10 Medical Device Deficiencies

In this study any deficiency observed with a third party medical device will be collected and reported to the manufacturer.

A medical device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Medical device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

The AstraZeneca (Appendix I), or manufacturer's where available, medical device complaint report will be used to collect the deficiency.

8.4 Overdose

Dapagliflozin has been well tolerated at doses up to 500 mg/day in single dose testing in healthy volunteers and up to 100 mg/day in repeat dose testing for 14 days in healthy volunteers and patients with type 2 diabetes. Only suspected single intake of more than 500 mg dapagliflozin or repeated intake of more than 100 mg dapagliflozin should be reported on the eCRF overdose module.

Presently there is no information regarding overdose of AZD9977 in man. For this study, any dose of AZD9977 greater than 150 mg within 24 hours will be considered an overdose.

If an overdose is suspected, monitoring of vital functions as well as treatment should be performed as appropriate.

- 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 during 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 (PK) samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - Pharmacokinetic samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

8.5.1 Pharmacokinetics

- Blood samples will be collected for measurement of plasma concentrations of AZD9977 and dapagliflozin, including predose samples from all participants and optional postdose samples from participants who consent, at the visits and timepoints specified in the SoA.
- Samples may be collected at additional timepoints 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.
- Samples collected for analyses of AZD9977 and dapagliflozin plasma concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during the study.
- Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentration in plasma will be assayed by Labcorp Drug Development on behalf of AstraZeneca, using appropriately validated bioanalytical methods. Full details of the analytical methods used will be described in a separate Bioanalytical Report.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Incurred sample reproducibility analysis or additional assay development work, 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 Pharmacodynamics

Urinary and serum/plasma parameters will be measured during the study for the evaluation of the exploratory endpoints:

- NT-proBNP, aldosterone, renin, ACTH, cortisol, copeptin, and FPG (per the SoA)

The following parameters will be measured from the blood samples collected for safety and analysed centrally (see Section 8.2.4):

- Bicarbonate (HCO_3^-), Na^+, K^+, creatinine, uric acid, BUN (at Visits 3 to 11) as part of clinical chemistry
- Haematocrit (at Visits 3 to 11) and MCV, MCHC, RBC distribution width, erythrocyte count (at Visits 3, 8, and 10), as part of haematology

8.5.2.1 Collection of Samples

Urine Samples

Urine samples will be collected and analysed at a central laboratory for the determination of the exploratory urinary parameters at the timepoints specified in the SoA.

The urine samples collected on visit days for the analysis of UACR (see Section 8.1.1) will be split, so that it can also be used for the determination of Na^+, K^+, uric acid, urea, osmolality, glucose and cortisol levels.

Blood Samples

Blood samples will be collected at the timepoints specified in the SoA and analysed at a central laboratory for the determination of the following parameters:

- NT-proBNP, aldosterone, active renin, ACTH, cortisol, and copeptin
- FPG (for fasting conditions, see Section 5.3.1)

In addition, blood samples will be collected at screening and analysed locally for the determination of NT-proBNP to confirm eligibility criteria.

Samples will be collected, labelled stored and shipped as detailed in the Laboratory Manual.

For storage, re-use and destruction of pharmacodynamic samples see Section 8.5 and Appendix C.

8.6 Human Biological Sample Biomarkers

8.6.1 Collection of Mandatory Samples for Biomarker Analysis

By consenting to participate in the study the participant consents to the mandatory research components of the study. Mandatory collection of samples for biomarker research is part of this study.

- Serum/plasma samples for cardiovascular biomarker research will be collected from all participants in this study as specified in the SoA. These samples will be used for the determination of cardiovascular biomarkers (including but not limited to hsTnT, PIIIP3, GDF-15, ST2, ADMA, SDMA, L-Arg, ICAM, NGAL) by a central laboratory.

8.6.2 Collection of Optional Biomarker Samples

Collection of optional samples for biomarker research is also part of this study as specified in the SoA and is subject to participant's optional consent:

- Serum, plasma, and urine samples will be collected for future use aimed at exploring biomarkers involved in PK, pharmacodynamics, safety and tolerability related to AZD9977 and dapagliflozin or related to cardiorenal diseases.

For storage, re-use and destruction of biomarker samples see Section 8.5.

8.7 Optional Genomics Initiative Sample

Collection of optional samples for Genomics Initiative research is also part of this study as specified in the SoA and is subject to participant's optional consent in the ICF addendum.

Blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

See Appendix D for information regarding the Genomics Initiative genetic sample. Details on processes for 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 Medical Resource Utilisation and Health Economics

Not Applicable.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary hypothesis for this study is that AZD9977 in combination with dapagliflozin will induce a greater reduction of albuminuria than with dapagliflozin alone, as assessed by the percent change from baseline in UACR at 12 weeks.

9.2 Sample Size Determination

A total of 119 evaluable participants per arm will provide 80% power to detect a 30% difference in a AZD9977 dose group combined with dapagliflozin 10 mg compared to dapagliflozin 10 mg alone in percent change from baseline in UACR at 12 weeks, assuming a SD of 1.0 on the natural log-scale and alpha = 0.05. To account for approximately 5% drop-out from the study, approximately 500 participants will be randomly assigned to study intervention (125 participants per group) such that approximately 476 evaluable participants (119 per group) complete the study.

Patients randomised according to CSP versions 1.0 to 5.0 (before dropping placebo and AZD9977 150 mg monotherapy arms) will be considered as part of Cohort 1, while patients randomised subsequently will be included in Cohort 2. The primary analysis for the remaining 4 treatment groups will combine data from both cohorts, while the accrued data from discontinued treatment groups will be analysed descriptively.

9.3 Populations for Analyses

The following populations are defined:

Table 7 Populations for Analysis

Population/Analysis set	Description
Enrolled	All participants who sign the main ICF.
Full Analysis Set (FAS)	All participants who are randomised and either receive or do not receive any study intervention. Participants are evaluated according to the treatment assigned at randomisation. The FAS will be used for all analyses of demographic baseline characteristics and efficacy data.
Per Protocol Set (PPS)	A subset of the FAS consisting of all participants who do not violate the terms of the protocol in a way that may affect the primary efficacy endpoint significantly. All decisions to exclude participants from the per protocol analysis set will be made and documented prior to the unblinding of the study.
Safety Set (SS)	All participants who are randomised and receive any study intervention. Participants are evaluated according to the actual treatment they received. If a participant received a different treatment dose than randomised throughout the study, they will be analysed according to the treated dose, not the randomisation dose. If a participant received study drug from the wrong kit for only part of the treatment duration, they will be analysed according to their randomisation dose. The SS will be used for all safety analyses.

Additional analysis sets, such as PK population may be defined the SAP for exploratory analyses.

9.4 Statistical Analyses

The SAP will be finalised prior to database lock for the interim analysis 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

All results will be presented by treatment group and overall, with descriptive statistics appropriate to the nature of the variables.

Demographic and baseline characteristics as well as prior and concomitant medication will be presented. For continuous variables, the number of non-missing observations, mean, SD, median, first and third quartiles, minimum, and maximum will be presented. For categorical variables: counts (n) and percentages (%) (where specified) will be presented. These

summaries will be provided by timepoint of assessment as appropriate.

When change from baseline will be described, the baseline value will be, in general, the last non-missing value prior to administration of the first dose of each treatment period. Further details will be described in the SAP.

The SAS® version 9.4 or later will be used for the data analysis.

In general, there will be no imputation of missing data for the safety analyses. Additional details will be provided in the SAP.

Deviations from the protocol will be assessed as "important" or "not-important". Important deviations from the protocol may lead to the exclusion of participants from any of the study analysis sets. Deviations will be defined before database hard lock. Important deviations will include the following:

- Violation of inclusion and/or exclusion criteria
- Administration of prohibited concomitant medications that are expected to influence the measurement of the primary endpoint.

All protocol deviations will be discussed at the data review meeting prior to database hard lock in order to define the analysis sets for the study. All the important protocol deviations will be listed by participants. Further details will be described in the SAP.

9.4.2 Efficacy

The analysis of all efficacy variables will be performed on the FAS. In addition, the primary efficacy endpoint will also be analysed using the PPS, as a sensitivity analysis.

9.4.2.1 Primary Endpoint

The primary efficacy endpoint for this study is the percent change from baseline in UACR at 12 weeks.

Baseline for UACR will be defined as the geometric mean of 3 UACR values derived from samples collected at consecutive days prior to the first dose of study treatment.

As UACR is assumed to follow a log-normal distribution, it will be log transformed for statistical analysis purposes. The mean log percent changes in UACR at 12 weeks for each of the 3 doses of AZD9977 combined with dapagliflozin 10 mg and dapagliflozin 10 mg alone will be estimated in a mixed model for repeated measures (Visits 7, 8, 9, and 10). The values will be back-transformed onto the original scale to give the geometric mean relative percent change from baseline at 12 weeks.

Patients randomised according to CSP versions 1.0 to 5.0 (before dropping placebo and AZD9977 150 mg monotherapy arms) will be considered as part of Cohort 1, while patients randomised subsequently will be included in Cohort 2. The primary analysis for the remaining 4 treatment groups will combine data from both cohorts, while the accrued data from discontinued treatment groups will be analysed descriptively.

The analysis model will include UACR baseline value, treatment, and visit as fixed effect, and the stratifying factors (T2DM [yes/no] and eGFR [$\geq$ 20 to < 30 mL/min/1.73 m^2; or $\geq$ 30 to < 45 mL/min/1.73 m^2; or $\geq$ 45 mL/min/1.73 m^2]) as well as the Cohort variable (1 or 2) as covariates. Moreover, treatment-by-visit interaction will also be included in the model. The final analytical approach will be described in detail in the SAP. For the primary analysis, the main treatment comparisons to be evaluated are (in a fixed-sequence testing):

1 Overall comparison of the percentage changes from baseline in UACR at week 12 across all 4 treatment groups
2 Each of the 3 doses of AZD9977 in combination with dapagliflozin 10 mg versus dapagliflozin 10 mg in the following order:
    1. AZD9977 150 mg + dapagliflozin 10 mg versus dapagliflozin 10 mg
    2. AZD9977 50 mg + dapagliflozin 10 mg versus dapagliflozin 10 mg
    3. AZD9977 15 mg + dapagliflozin 10 mg versus dapagliflozin 10 mg

9.4.2.2 Secondary Endpoint

The dose-response relationship of percent change from baseline in UACR at 12 weeks will be assessed using data from dapagliflozin (10 mg) alone and 3 doses of AZD9977 (15, 50, or 150 mg) combined with dapagliflozin (10 mg).

More details of all these models will be provided in the SAP.

9.4.3 Pharmacokinetics

Plasma concentrations of AZD9977 and dapagliflozin will be listed and summarised by treatment groups, based on the PK Analysis Set.

9.4.4 Pharmacodynamics and Biomarkers

The following exploratory pharmacodynamic and biomarker endpoints will be summarised by treatment group based on the FAS:

- Change from baseline in serum NT-proBNP over time
- Change from baseline in blood uric acid, BUN, FPG, haematocrit, renin, ACTH, cortisol and copeptin levels over time
- Change from baseline in blood MCV, MCHC, RBC distribution width, erythrocyte count over time
- Change from baseline in urine Na^+, K^+, uric acid, urea, osmolality, glucose, creatinine, and cortisol levels over time
- Change from baseline in blood and urine biomarkers over time

The following analyses will not be part of the CSR:

- Dose/exposure of AZD9977 and dapagliflozin relative to safety and pharmacodynamic variables (eg, serum/plasma K^+, eGFR, aldosterone)
- Exploratory research into genes/genetic variation that may influence response to treatment

Analysis for these exploratory objectives will be described in a separate analysis plan and results will be presented separately from the main CSR.

9.4.5 Safety

Safety analyses will be performed using the SS. Safety data will be presented using descriptive statistics unless otherwise specified.

In general, the baseline value for statistical analysis is the last non-missing value prior to administration of the first dose of IMP. Details are described in the SAP.

9.4.5.1 Adverse Events

Adverse events will be coded using the most recent version of the MedDRA that will have been released for execution at AstraZeneca or designee.

AEs will be presented for each treatment group by SOC and/or PT covering number and percentage of patients reporting at least 1 event and number of events where appropriate.

Only AEs occurring with an onset date, or worsening, on or after first dose of IMP and within 28 days after last dose of IMP will be presented in summary tables. Serious AEs occurring prior to start of IMP will be included in data listings.

An overview of AEs will present for each treatment group the number and percentage of patients with any AE, AEs with outcome of death, SAEs, and AEs leading to discontinuation of IMP, as well as AEs leading to IMP dose interruptions, and AEs leading to withdrawal from study as well as the number of individual occurrences in those categories.

Separate AE tables will be provided taken into consideration relationship as assessed by the investigator, maximum intensity, seriousness, death, and AEs leading to discontinuation of IMP as well as other action taken related to IMP, other significant AEs, and timing of events.

An additional table will present number and percentage of patients with most common AEs. Most common (eg, frequency of > 5%) will be defined in the SAP.

In accordance with the requirements of the FDA, a separate table will present non-serious AEs occurring in more than 5% of patients in any treatment group.

Key patient information will be presented for patients with AEs with outcome of death, SAEs, and AEs leading to discontinuation of IMP.

An AE listing for the SS will cover details for each individual AE; an AE listing for patients who were not exposed to IMP is presented separately.

Full details of AE analyses will be provided in the SAP.

9.4.5.2 Vital Signs

Vital sign parameters will be presented for each treatment group. Summary statistics for continuous variables cover n, mean, SD, minimum, Q1, median, Q3, and maximum.

For each scheduled post-baseline visit, descriptive statistics for all vital sign parameters will be presented for observed values and change from baseline.

Key patient information will be presented for patients with treatment-emergent changes in vital sign parameters outside of predefined criteria (see Section 9.4.5.6).

Supportive vital sign listings cover observed values and changes from baseline as well as abnormalities.

Details of vital sign analyses including definition of abnormality criteria (eg, definition of low, normal, high; clinically significant) and project-specific predefined criteria for treatment-emergent changes in relevant vital sign parameters (eg, systolic and diastolic BP) will be provided in the SAP.

9.4.5.3 Laboratory

Laboratory parameters will be presented for each treatment group. Summary statistics for

continuous variables cover n, mean, SD, minimum, Q1, median, Q3, and maximum. Frequency tables cover number and percentage of patients in the respective category.

For each scheduled post-baseline visit, descriptive statistics for all clinical chemistry and haematology parameters will be presented for observed values and change from baseline.

A frequency table will present number of patients reporting at least one treatment-emergent change in laboratory parameters outside predefined criteria (see Section 9.4.5.6).

Elevation in liver parameters for assessment of Hy's law will be done and reported appropriately if potential cases have been identified during the course of the study.

Key patient information will be presented for patients with treatment-emergent changes in laboratory parameters outside of predefined criteria.

For urinalysis, a frequency table will present number of patients reporting at least 1 treatment-emergent increase in baseline category and/or a shift table will present the baseline assessment against the maximum on-treatment category.

Supportive laboratory listings cover observed values and changes from baseline for each individual patient as well as abnormalities.

Details of laboratory analyses including definition of abnormality criteria (eg, definition of low, normal, high; clinically significant) and project-specific predefined criteria for treatment-emergent changes in relevant laboratory parameters will be provided in the SAP.

9.4.5.4 Electrocardiograms

Descriptive statistics will be produced at each schedule assessment timepoint for all quantitative ECG parameters (heart rate, PR, RR, QRS, QT, and QTcF intervals) for both observed absolute values and changes from baseline.

Electrocardiogram findings will also be listed.

An analysis of potentially clinically significant ECG values on QT, QTcF, QRS and PR interval, and heart rate will be performed. The number and percentage of patients with potentially clinically significant ECG values will be tabulated across time and treatment group. The criteria based on severity will be defined in the SAP.

Outliers with respect to QTcF will also be tabulated for the following categories:

- Absolute value > 450 ms
- Absolute value > 480 ms
- Absolute value > 500 ms

- Increase from baseline > 30 ms
- Increase from baseline > 60 ms

9.4.5.5 Physical Examination

The listings of the physical examination will include date of examination and confirmation of assessment performed (Yes/No).

9.4.5.6 Safety Topics of Interest

Hyperkalaemia

Hyperkalaemia will be evaluated by the analysis of serum/plasma K^+ levels (eg, absolute values and change from baseline, values outside predefined ranges, values meeting protocol-defined discontinuation criteria for hyperkalaemia). Further details will be provided in the SAP.

Hypotension

Symptomatic hypotension/decreased blood pressure will be evaluated by the analysis of BP measurements (eg, values outside predefined ranges) and the analysis of pre-defined AE PTs related to hypotension, as well as discontinuations due to hypotension. Further details will be provided in the SAP.

Deteriorating Renal Function

Deteriorating renal function will be evaluated by analysis of serum creatinine and eGFR values (eg, percent change from baseline in eGFR, absolute values and change from baseline, values meeting protocol-defined discontinuation criteria for deteriorating renal function) and analysis of pre-defined AE PTs related to deteriorating renal function. Further details will be provided in the SAP.

9.5 Interim Analyses

An interim analysis will be performed when 300 patients have been treated for 12 weeks, unless the planned date of the interim analysis is too close to the expected data base lock date, for the complete study. The purpose of the interim analysis is to have the possibility to trigger Phase 3 activities; therefore, there will be no alpha spent. The conduct of the study will not be impacted by the results of the interim analysis. The decision to conduct an interim analysis will be documented.

The SAP will describe the planned interim analyses in greater details.

9.6 Data Monitoring Committee

A Safety Unblinded Data Review Committee will be set up for this study for ongoing safety monitoring. In addition to general safety/tolerability, the committee will focus on potential

risks related to hypotension, deteriorating renal function and hyperkalaemia. An Interim Unblinded Data Review Committee will be set up to review data from the pre-planned interim analysis and make recommendations on future clinical development.

For details on the review committee, refer to Appendix A 5.

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 CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/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 CRO, 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, IRB/IEC, and investigators.
- For all studies except those utilising medical devices investigator safety reports must be prepared for SUSARs 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 or state other documents] 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.
- A pre-screening ICF and/or a full ICF have to be signed before any study intervention will take place.
- 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, HIPAA 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.

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The investigator or authorised designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

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 and its research collaborators 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 and its research collaborators 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 Committees Structure

A Safety Unblinded Data Review Committee will be set up for this study to monitor general safety/tolerability, with a focus on hypotension, deteriorating renal function and hyperkalaemia.

An Interim Unblinded Data Review Committee will be set up to review data from the pre-planned interim analysis and make recommendations regarding future clinical development.

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the CSP and letters to investigators.

A 6 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 main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee, and its research collaborators, 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

non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

- The sponsor or designee, and its research collaborators are 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, CROs).
- 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 15 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 8 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 agreement and computerised data checklist for electronic source data.

A 9 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 is the first patient enrolled (ie, who signed consent) and 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 CRO(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.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 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 multi-centre studies only in their entirety and not as individual site data. In this case, a co-ordinating 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 AE is the development of any untoward medical occurrence in a participant or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (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 SAE is an AE occurring during any study period (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 anomaly 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 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. Below are some examples of events that may be considered medically important based on the investigator's judgement:

- Angioedema not severe enough to require intubation but requiring iv 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.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.
- 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 judgement. 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, for example, 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 IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

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

- Errors related to or resulting from IRT/RTSM – 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 UN 3373 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 Optional Genomics Initiative Sample

D 1 Use/analysis of DNA

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments, or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participant´s DNA, ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on AZD9977 and dapagliflozin or other AstraZeneca study treatments of the same classes or for these indications continues but no longer than 15 years or other period as per local requirements.

D 2 Genetic research plan and procedures

Selection of Genetic Research Population

- All participants will be asked to participate in this genetic research. Participation is voluntary and if a participant declines to participate there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

Inclusion Criteria

For inclusion in this genetic research, participants must fulfil all of the inclusion criteria described in the main body of the CSP and: Provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion Criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Withdrawal of Consent for Genetic Research:

- Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2 of the CSP.

Collection of Samples for Genetic Research

- The blood sample for this genetic research will be obtained from the participants at Visit 3, at or after randomisation. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the sample is not drawn at Visit 3, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

Coding and Storage of DNA Samples

- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples will be stored for a maximum of 15 years, from the date of last participant last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.
- An additional second code will be assigned to the sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).
- The link between the participant enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

- The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed Consent

- The genetic component of this study is optional, and the participant may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study the participant must sign and date both the consent form for the main study and the addendum for the Genomics Initiative component of the study. Copies of both signed and dated consent forms must be given to the participant and the original filed at the study centre. The PI is responsible for ensuring that consent is given freely, and that the participant understands that they may freely withdrawal from the genetic aspect of the study at any time.

Participant Data Protection

- AstraZeneca will not provide individual genotype results to participants, any insurance company, any employer, their family members, general physician unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a participant's identity and also have access to his or her genetic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

Data Management

- Data will be reported will be reported separately from the CSR.
- Any genetic data generated in this study will be stored at a secure system at AstraZeneca and/or designated organisations to analyse the samples.
- AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations, or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results, but they will not be able to see individual participant data or any personal identifiers.
- Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

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 TBL from a local laboratory.

The investigator will also review AE 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 HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IMP.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and 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 Aminotransferase (AST) or ALT ≥ 3 x ULN **together with** TBL ≥ 2 x 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 ≥ 3 x ULN **together with** TBL ≥ 2 x ULN, where no other reason, other than the IMP, 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 ≥ 3 x ULN
- AST ≥ 3 x ULN
- TBL ≥ 2 x 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)

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 CSP.

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 CSP process for SAE reporting
- For participants that met PHL criteria prior to starting IMP, 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 3 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 TBL) 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 DILI caused by the IMP, 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 Potential Hy's Law 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 IMP:

- 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 Potential Hy's Law, (report term now 'Hy's law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP 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 CSP 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 HBsAg IgM and IgG anti-HBc HBV DNA [a] IgG anti-HCV HCV RNA [b] 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 (CD-transferrin) [c]
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin [c] Transferrin saturation

CMV=cytomegalovirus; DNA=deoxyribonucleic acid; EBV=Epstein-Barr virus; GGT=gamma glutamyl transferase; 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; IgG=immunoglobulin G; IgM=immunoglobulin M; INR=international normalised ratio; LDH=lactate dehydrogenase; RNA=ribonucleic acid.
[a] HBV DNA is only recommended when IgG anti-HBc is positive
[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive
[c] CD-transferrin and Transferrin are not available in China. Study teams should amend this list accordingly

E 7 References

Aithal et al, 2011
Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

FDA Guidance for Industry, July 2009
FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'. Available from; https://www.fda.gov/regulatory-information/search-fda-

guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation

Appendix F Management of Hyperkalaemia and Deteriorating Renal Function

F 1 Hyperkalaemia

At all baseline and on-treatment visits (according to the SoA) K^+ will be measured in either serum or plasma samples at a local laboratory depending on the laboratory's capability and in serum samples at a central laboratory. Repeat samples should be sent for both central and local laboratory assessment.

Inappropriate sample handling/storage or lengthy transport time to the central laboratory may result in falsely elevated serum K^+ levels in the centrally analysed blood samples. It is expected that local laboratory results (from either serum/plasma samples) will be available prior to central laboratory results and expected to take priority for decision-making/monitoring:

- Serum/plasma K^+ >5.5 to ≤ 6 mmol/L (based on local laboratory samples) should be reassessed within 72 hours.
  - If the repeat local laboratory sample has serum/plasma K^+ > 6.0 mmol/L, study treatments must be discontinued permanently.
  - If the repeat local laboratory sample has serum/plasma K^+ > 5.5 to ≤ 6.0 mmol/L, consider corrective actions, including dietary changes and/or adjustment/discontinuation of non-essential medications that might have caused or contributed to hyperkalaemia and reassess within 72 hours:
    - If local serum/plasma K^+ remains > 5.5 mmol/L to ≤ 6 mmol/L, consider permanent discontinuation or continue monitoring at the discretion of the investigator. Permanently discontinue if repeat local and/or central samples have serum/plasma K^+ > 6.0 mmol/L.
- Serum/plasma K^+ > 6 mmol/L (based on local laboratory samples) should be reassessed immediately and study treatments should be discontinued temporarily while waiting for results:
  - If the repeat local laboratory sample has serum/plasma K^+ > 6.0 mmol/L, study treatments must be discontinued permanently.
  - If the repeat local laboratory sample has serum/plasma K^+ > 5.5 to ≤ 6.0 mmol/L and the central laboratory sample has serum K^+ is > 6.0 mmol/L, study treatments must be discontinued permanently.
  - If the repeat local laboratory sample has serum/plasma K^+ > 5.5 to ≤ 6.0 mmol/L and the central laboratory sample has serum K^+ ≤ 6.0 mmol/L, based on the discretion of the Investigator, consider corrective actions, including dietary changes and/or adjustment/discontinuation of non-essential medications that might have caused or

contributed to hyperkalaemia; and/or continuation with reassessment; or permanent discontinuation.

– If the repeat local laboratory sample has serum/plasma $K^+ \leq 5.5$ mmol/L, then study treatments can be resumed, even if the central laboratory sample has serum $K^+ > 6.0$ mmol/L.

If the investigator is aware of any change in the participant's clinical status that may influence serum electrolyte levels or fluid balance (eg, vomiting and/or diarrhoea > 1 day), it is recommended to reassess serum/plasma K^+ levels as soon as possible after the acute event. In case of permanent discontinuation, serum/plasma K^+ levels should be monitored until resolution or stabilisation.

F 2 Deterioration of Renal Function

Serum creatinine will be measured both at a local laboratory and a central laboratory at all baseline and on-treatment visits according to the SoA. Repeat samples should be sent for both central and local laboratory assessment. It is expected that local laboratory results will be available prior to central laboratory results. As local and central laboratories will calculate eGFR using different formulas, central eGFR values should always be compared to central eGFR values and local eGFR values should always be compared to local eGFR values. For local laboratories, the eGFR assessment at Visit 3 (prior to the start of study treatment) will be taken as the baseline eGFR value.

- If eGFR shows a 30-50% decline from baseline and an absolute value ≥ 15 mL/min/1.73 m^2 (based on local and/or central laboratory samples), eGFR should be reassessed within 1 week.
  - If persistent 30-50% decline stabilises upon weekly follow-ups, eGFR monitoring may return to the standard SoA, at investigator's discretion.
- If eGFR shows a >50% decline from baseline and/or decreases to an absolute value < 15 ml/min/1.73 m^2 (based on local and/or central laboratory samples), eGFR should be reassessed within 48 hours.
  - If eGFR shows a 30% to 50% decline from baseline and an absolute value ≥ 15 mL/min/1.73 m^2, eGFR should be reassessed within 1 week.
  - If eGFR again shows a >50% reduction from baseline and/or absolute value < 15 mL/min/1.73 m^2, study treatments must be discontinued immediately and eGFR should be followed up within a week and weekly until signs of improvement and stabilisation.

If an unexpected, acute decline in kidney function is observed, the patient should be promptly evaluated. Volume depletion, hypotension, inter-current medical problems, metabolic

derangements, and concomitant drugs may cause increases in blood creatinine. Urinary tract infection and urinary obstruction should be considered. Several drugs may cause a decline in kidney function, especially NSAID and certain antibiotics such as trimethoprim. If any drug is suspected of causing or contributing to worsening kidney function, their use should be reconsidered.

Appendix G COVID-19 Specifics

G 1 Background to COVID-19

There is currently an outbreak of respiratory disease (COVID-19) caused by a novel SARS-CoV-2 that was first detected in Wuhan City, Hubei Province, China in 2019. This new virus has rapidly spread across the globe causing the WHO to declare a pandemic situation on 12 March 2020. The countermeasures initiated by national and local governments worldwide and the recommendations issued by the health authorities have impacted current and new clinical studies. As the threat of pandemic burden including new outbreaks, locally or globally, will impact the further conduct of clinical studies, appropriate risk assessments and mitigation measures will need to be taken into consideration in all clinical studies to protect subjects, site staff, and society as a whole.

Both EMA and FDA as well as national health authorities in Europe have issued new guidelines that aim to provide recommendations for actions for conduct of clinical studies of medical products during COVID-19 pandemic. Since the pandemic situation is evolving, guidelines, recommendations, national laws, and local restrictions may change at high pace. Given the circumstances of potentially relapsing pandemic or epidemic situation with regard to the spread of COVID-19 in future, special attention will be paid to protect subjects participating in the study and site staff involved in the investigations against infection with SARS-CoV-2 as requested by the newly issued EMA guideline.

G 2 Risk Assessment for COVID-19 Pandemic

Risk of infection with SARS-CoV-2

The 2 study drugs with different mechanisms of action are unlikely to impact on the course of infection with SARS-CoV-2. Dapagliflozin is an anti-glycaemic agent and AZD9977 is a selective mineralocorticoid receptor modulator; neither is expected to cause immune suppression. Therefore, risk of the participants exposure to SARS-CoV-2 or to suffer from COVID-19 is expected to be similar to the background population with the same co-morbidities, in particular HF and CKD. The risk of exposure to infected people cannot be completely excluded as the participants may need to be in public areas (eg, commute to the site) and have additional human contact (eg, with site staff and other participants of the clinical study).

Measures to mitigate the additional risks caused by COVID-19 are:

- This study is going to start enrolling only when the Sponsor and CRO in collaboration deem it is safe to start the study. In addition, the study will not start until the local confinement measures or other safety restrictions linked to the COVID-19 pandemic imposed by the local authorities are compatible with safe conduct of the study.

- Current national laws and local recommendations for prevention of pandemic will be strictly adhered to.
- Participants will be closely monitored for any signs and symptoms of COVID-19, including fever, dry cough, dyspnoea, sore throat, and fatigue throughout the study during the pandemic. Once clinical signs of infection are reported by participants, the Investigator needs to determine whether samples can be collected, and safety data can be recorded on site. If not, AEs and concomitant medications will be obtained via phone calls. The decision to continue with dosing the participant with the study drugs in the event of him/her showing symptoms of COVID-19 infection will be per Investigator's discretion.
- The probability of virus transmission will be controlled as much as possible by:
  - Advice for participant to adhere to local requirements for reduction of the public exposure while ambulatory.
  - Confirmation of COVID-19 infection by optional laboratory assessment will be conducted based on availability (test capacity and turnaround time) of approved tests and on Investigator's discretion.
  - Requesting all participants are contacted by phone 1 day prior to every visit for assessing COVID-19 symptoms and signs and are asked not to attend the site in case of suspected reports. In addition, participants are asked for any contact with a person who has tested positive for SARS-CoV-2. If applicable, participants will be referred to the local health care system for further follow-up and treatment.
  - Physical distancing and person-to-person contact restrictions will be applied during site visits.
  - Where physical distancing is not possible, personal protective equipment will be used by study participants (surgical face mask, gloves) and staff (for example but not limited to masks, gloves, protectors, medical suits) if deemed appropriate by the Investigators and site staff and guided by local requirements.
  - Logistical improvements of the site and structural measures of the study site building will be implemented to further improve physical distancing.
- If site visits are not possible due to local restrictions, home nursing visits may be considered after discussion with and approval by the Sponsor.

Risk Related to COVID-19 vaccination

The 2 study drugs are predicted to have a low risk of influencing COVID-19 vaccine effectiveness and no additional safety concerns are anticipated. Clinical trial participant who have already taken the COVID-19 vaccine of any type are permitted to enrol in the study. Clinical trial participant who are not yet vaccinated should consider current/local guidelines, vaccine availability, and benefit-risk assessment of the COVID-19 vaccine. Ultimately, the

decision to vaccinate will be based on the judgment of the treating physician taking into account the participant's best interest.

G 3 Restrictions Related to COVID-19

During the COVID-19 pandemic, participants are advised to adhere to local requirements for reduction of the public SARS-CoV-2 exposure while ambulatory. If applicable, prior to screening (Visit 1a), potential participants should be called to confirm they are not experiencing any COVID-19 symptoms and signs and are asked not to attend the site in case of suspected infection. If appropriate, participants will be referred to the local health care system. Physical distancing and person-to-person contact restrictions will be applied and explained to participants while staying at the study site. Where physical distancing is not possible, study participants will be asked to use surgical face masks and/or gloves if deemed appropriate by the Investigator and site staff and guided by local requirements.

G 4 Data Quality Assurance Related to COVID-19

Monitoring visits at site will be limited to a minimum required as deemed appropriate during COVID-19 pandemic, per local regulations.

In addition, where possible, other measures for carrying out protocol related activities, such as but not limited to home nursing, may be employed as required.

G 5 References

Guidance on the Management of Clinical Trials during the COVID19 (Coronavirus) pandemic, EMA, Version 3 (28/04/2020). https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency, March 2020, Updated on June 03, 2020 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency

Appendix H Strong and Moderate Cytochrome P450 3A4 (CYP3A4) Inhibitors and Inducers

Strong or moderate CYP3A4 inhibitors or inducers are prohibited at least 3 weeks prior to randomisation (ie, start of run-in period) and for the duration of the study.

The following list (Table 8) is not intended to be exhaustive and a similar restriction will apply to other agents that are known to modulate CYP3A4 activity. Appropriate medical judgement is required. Please contact AstraZeneca with any queries you have on this issue.

Table 8 CYP3A4-Interacting Medication that are Prohibited During the Study

Medication	Rationale
Boceprevir, cobicistat, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, telithromycin, troleandomycin, voriconazole	Strong CYP3A4 inhibitors which may increase AZD9977 concentrations.
Apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort	Strong CYP3A4 inducers which may decrease AZD9977 concentrations.
Aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil	Moderate CYP3A4 inhibitors which may increase AZD9977 concentrations.
Bosentan, efavirenz, etravirine, phenobarbital, primidone	Moderate CYP3A4 inducers which may decrease AZD9977 concentrations.

H 1 Reference

FDA guidance – Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers (content current as of 10 March 2020). Available at https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers. Accessed on 9 June 2020.

Appendix I Clinical Study Medical Device / Device Constituent Report Form

1 .. Details of Patient

Study code: _____ Centre: _____ E-code: _____ Randomisation code: _____

Intial report ☐ Follow up report ☐

2 Details of Patient

Sex: ☐ Male Weight: _____ kg

☐ Female Height: _____ cm

If Patient was **not** a study participant, tick box ☐

3 Details of Device / Device Constituent (Brand/common name)	**Type** (device constituent or medical device)	**Serial number**	**Lot/ Batch number**	**Intended Use**	**Who is the manufacturer?**

4 ☐ Malfunction/Deficiency **without** any apparent associated AE (progress to 6)

☐ Malfunction/Deficiency **with potential associated AE** (continue with 5)

☐ Malfunction/Deficiency **with associated with AE** (continue with 5) Also fill in AE Module in CRF

5 Adverse Event description (use same wording as in CRF): Diagnosis of AE(s). If diagnosis is not known, give symptom(s)	**Serious?** If yes, provide criteria	**Start date** (Year-MM-DD)	**Stop date** (Year-MM-DD)	**or cont.**	**Outcome[1]**
				☐	
				☐	
				☐	

1)Outcome: 0 = Recovered/Resolved 1 = Recovering/Resolving 2 = Recovered/Resolved with sequelae 3 = Not recovered/Not resolved 4 = Fatal

6 Please provide any further relevant information regarding the malfunction/deficiency event
(About the AE/symptoms (if applicable), cause/reason, any treatments received, investigations carried out, information about relevant drugs, outcome etc.) Provide a comprehensive description of the incident, including (1) what went wrong with the device (if applicable) and (2) a description of the health effects (if applicable), i.e. clinical signs, symptoms, conditions as well as the overall health impact

7 Signature of Investigator: Date:

Name of AstraZeneca Representative: Country:

Date:

Clinical Study Device malfunction/deficiency Report Form
Version 2.0

Appendix J Abbreviations

Abbreviation or special term	Explanation
2D	2-dimensional
3D	3-dimensional
ABPM	ambulatory blood pressure monitoring
ACCF	American College of Cardiology Foundation
ACEI	angiotensin-converting enzyme inhibitor
ACTH	adrenocorticotropic hormone
ADMA	asymmetric dimethylarginine
AE	adverse event
AHA	American Heart Association
ALP	alkaline phosphatase
ALT	alanine transaminase
ANA	antinuclear antibody
ANCA	anti-neutrophil cytoplasm antibody
ARB	angiotensin II receptor blocker
ARNI	angiotensin receptor-neprilysin inhibitor
AST	aspartate transaminase
BP	blood pressure
bpm	beats per minute
BSA	body surface area
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CKD	chronic kidney disease
CKD-EPI	chronic kidney disease epidemiology collaboration
CMV	cytomegalovirus
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	Case Report Form
CRO	Contract Research Organisation
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CYP	cytochrome P450

Abbreviation or special term	Explanation
dECG	digital electrocardiogram
DILI	Drug-Induced Liver Injury
DKA	diabetic ketoacidosis
DNA	deoxyribonucleic acid
EBV	Epstein-Barr virus
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EDV	end diastolic volume
E/e’	ratio between early mitral inflow velocity and mitral annular early diastolic velocity
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOT	end of treatment
ET	early termination
ERT	eResearch Technology
ESRD	end-stage renal disease
ESV	end systolic volume
FAS	Full Analysis Set
FDA	US Food and Drug Administration
FPG	fasting plasma glucose
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GDF-15	growth differentiation factor-15
GFR	glomerular filtration rate
GGT	gamma glutamyl transferase
GLDH	gamma-lactone dehydrogenase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HbA1c	glycated haemoglobin
HBc	hepatitis B core
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus

Abbreviation or special term	Explanation
HCV	hepatitis C virus
HEV	hepatitis E virus
HSV	herpes simplex virus
HCO_3^-	bicarbonate
HDL-C	high density lipoprotein cholesterol
HDPE	high-density polyethylene
HF	heart failure
HFmrEF	heart failure mid-range ejection fraction
HFpEF	heart failure preserved ejection fraction
HFrEF	heart failure reduced ejection fraction
HIPAA	Health Insurance Portability and Accountability Act
HL	Hy's law
HR	heart rate
HRQOL	health-related quality of life
hsTnT	high sensitivity troponin T
IATA	International Airline Transportation Association
IC50	concentration required to inhibit 50% of the activity
ICAM	intercellular adhesion molecule
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	Investigational Medicinal Product
INR	international normalised ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
K^+	potassium
L-Arg	l-arginine
LAVI	left atrial volume index
LDH	lactate dehydrogenase
LDL-C	low density lipoprotein cholesterol
LV	left ventricular
LVEF	left ventricular ejection fraction
LV-GLS	left ventricular global longitudinal strain

Abbreviation or special term	Explanation
LVM	left ventricle mass
MAD	multiple ascending dose
Max	maximum
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
MIRACLE	MIneRAlocorticoid reCeptor moduLator and sodium-glucosE cotransporter-2-inhibitor in HF and CKD trial
MR	mineralocorticoid receptor
MRA	mineralocorticoid receptor antagonist
Na^+	sodium
NGAL	neutrophil gelatinase-associated lipocalin
NIMP	Non-Investigational Medicinal Product
NSAID	non-steroidal anti-inflammatory drug
NT-proBNP	N-terminal-pro-brain natriuretic peptide
NYHA	New York Heart Association
OGTT	oral glucose tolerance test
PAP	pulmonary artery pressure
PHL	potential Hy's law
PI	Principal Investigator
PIIIP3	procollagen type III N-terminal propeptide
PK	pharmacokinetic(s)
PPS	Per Protocol Set
PRO	patient-reported outcome
PT	Preferred Term
Q1	first quartile
Q3	third quartile
QTcF	QT interval corrected using Fridericia's formula
RAAS	renin-angiotensin-aldosterone system
RBC	red blood cell
RNA	ribonucleic acid
RT-PCR	reverse transcriptase polymerase chain reaction
RTSM	Randomisation and Trial Supply Management
SAE	serious adverse event

Abbreviation or special term	Explanation
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCr	serum creatinine
Scys	standardised serum cystatin C
SD	standard deviation
SDMA	symmetric dimethylarginine
SGLT2	sodium-glucose co-transporter-2
SGLT2i	sodium-glucose co-transporter-2 inhibitor
SoA	Schedule of Activities
SOC	System Organ Class
ST2	suppression of tumourigenicity 2 (biomarker)
SS	Safety Set
SU	sulfonylurea
SUSAR	suspected unexpected serious adverse reactions
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TAPSE	tricuspid annular plane systolic excursion
TBL	total bilirubin
TR Vmax	tricuspid regurgitation maximal velocity
UACR	urinary albumin to creatinine ratio
UGT	uridine diphosphate glycosyltransferase
ULN	upper limit of normal
VLDL-C	very low density lipoprotein cholesterol
WBC	white blood cell
WHO	World Health Organisation

Appendix K Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment, **Amendment 6**, is located directly before the Table of Contents.

Amendment 5 (20 December 2021)

This amendment was considered to be 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.

Overall Rationale for the Amendment

The previous Clinical Study Protocol (CSP) version, version 5.0, dated 15 July 2021 has been updated to adjust the design to heart failure treatment guidelines (ESC Guidelines 2021), by dropping the placebo and AZD9977 monotherapy arms to ensure all patients receive SGLT2i (dapagliflozin) during the study, as well as to reduce the burden of study assessments on study patients. The updates are summarised below.

Section Number and Name	Description of Change	Brief Rationale
Cover page Section 1.1 Synopsis Section 4 Study Design	Removal of the LVEF criterion below 55%	CSP title updated to not include any numbers for HF definition.
Cover page Section 1.1 Synopsis Section 1.2 Schema Section 3 Objectives and Endpoints Section 4.1 Overall Design Section 4.2 Scientific Rationale for Study Design Section 6.1.1 Investigational Products	Change of study design details 1) Treatment arms for AZD9977 150 mg and for placebo were removed. 2) Update of study duration 3) Inclusion of patients with or without SGLT2i treatment	To reflect recent changes in heart failure guidelines (European Society of Cardiology, 2021) and rapid evolving uptake and change in clinical practice to treat patients with SGLT2i in the population, adjustments have been made to the design by removal of the placebo treatment, thereby changing to active-controlled treatment.
Section 1.1 Synopsis Section 4.1 Overall Design	Change of targeted enrolment percentages of patients for the following cohorts 1. with eGFR $\geq$ 20 to $<$ 30 mL/min/1.73 m^2 and 2.eGFR $\geq$ 45 mL/min/1.73 m^2	1. To avoid recruitment hurdles that are not of clinical relevance. 2. A more appropriate cap based on patients randomised so far.

Section Number and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 9.1 Statistical Hypotheses	Update of the primary hypothesis	The primary hypothesis was adjusted according to the new study design.
Section 1.1 Synopsis Section 9.2 Sample Size Determination	Update for sample size and drop-out rate, also for an interim analysis	The sample size and the drop-out rate have been updated according to the new study design. The expected effect size was reduced due to the fact that the new comparator is an active drug (dapagliflozin 10 mg).
Section 1.2 Schema	Update of the figure concerning the study design	The figure was updated according to the new study design.
Section 1.3 Schedule of Activities	Time windows for Visits 2 and 5 to 10 were amended: Visit 2: -10 to -3 days Visit 5: ± 2 days Visits 6, 7, 8, 9 and 10: ± 3 days Visit 11: ± 4 days	To allow for flexibility in scheduling for sites and subjects and adjustment to fit with number of tablets in one dapagliflozin bottle for the safety follow-up.
Section 1.3 Schedule of Activities	Inclusion of central laboratory serum/plasma samples for K^+, creatinine including eGFR calculation at Visit 2	To have values from central laboratory closer to randomisation Visit 3.
Section 1.3 Schedule of Activities	Removal of PK sampling on Day 64	Reduction of sampling procedures and blood volume to lessen burden on sites and subjects.
Section 1.3 Schedule of Activities	Reduction of number of PD sampling visits (NT-proBNP, aldosterone, renin, ACTH, cortisol, copeptin, and FPG) from 9 to 5 visits (visits 3, 5, 7, 10, 11)	Reduction of sampling procedures and blood volume to lessen burden on sites and subjects.
Section 1.3 Schedule of Activities	Inclusion of dapagliflozin 10 mg treatment after the EOT visit	To do safety follow-up under the same standard of care (dapagliflozin) as during run-in.

Section Number and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities Section 3 Objectives and Endpoints Section 4.2 Scientific Rationale for Study Design Section 8.1.2.1 Transthoracic Echocardiography-derived Parameters	Removal of transthoracic echocardiography; removal of the applicable exploratory objective	Lessen the operational study complexity in order to reduce burden on sites and subjects. Extensive central echo protocol and needed to transfer data for central reading. In addition, local echocardiography is already being conducted at screening to confirm HF diagnosis.
Section 1.3 Schedule of Activities Section 3 Objectives and Endpoints Section4.2 Scientific Rationale for Study Design Section 8.1.2.2 Patient Reported Outcomes Appendix I Kansas City Cardiomyopathy Questionnaire Appendix J Kidney Disease and Quality of Life Appendix K Patient Global Impression of Severity – Heart Failure	Removal of patient-reported outcomes questionnaires KCCQ, KDQOL-36, and PGIS-HF	Lessen the operational study complexity in order to reduce burden on sites and participants.
Section 1.3 Schedule of Activities Section 3 Objectives and Endpoints Section 8.1.2.3 Bioimpedance Spectroscopy	Removal of bioimpedance spectroscopy; removal of weight measurements for bioimpedance at Visits 5 and 8, removal of applicable footnotes in Section 1.3 Schedule of Activities	Lessen the operational study complexity in order to reduce burden on sites and subjects.

Section Number and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities Section 3 Objectives and Endpoints Section 8.1.2.4 Home based Monitoring of Activity Section 9.3 Populations for Analyses	Removal of home-based monitoring of activity	Lessen the operational study complexity in order to reduce burden on sites and subjects.
Section 1.3 Schedule of Activities Section 3 Objectives and Endpoints Section 8.1.2.5 Ambulatory Blood Pressure Monitoring	Removal of ambulatory blood pressure monitoring in selected countries	Lessen the operational study complexity in order to reduce burden on sites and subjects.
Section 1.3 Schedule of Activities Section 3 Objectives and Endpoints Section 8.6.1 Collection of Mandatory Samples for Biomarker Analysis	Removal of collection of serum, plasma, and urine samples for exploratory biomarkers related to AZD9977 and dapagliflozin or related cardiorenal diseases	Correction of an error.
Section 1.3 Schedule of Activities Section 5.1 Inclusion Criteria	Inclusion of an informed consent for optional pre-screening	An optional pre-screening visit is introduced to reduce screen failures related to UACR and all patients who undergo the additional visit needs to sign a separate informed consent.
Section 1.3 Schedule of Activities Section 8.6.1 Collection of Mandatory Samples for Biomarker Analysis	Alignment with number of visits for PD markers (Visit 3 [Day 1], Visit 7 [Day 22], Visit 10 [Day 85], Visit 11 [Day 113])	Reduction of sampling procedures and blood volume to lessen burden on sites and subjects.
Section 1.3 Schedule of Activities Section 8.6.2 Collection of Optional Biomarker Samples	Removal of blood samples for RNA expression analysis and information regarding unused samples of serum, plasma, and urine. Addition of information regarding collection of serum, plasma, and urine samples for future use	Reduction of sampling procedures and blood volume to lessen burden on sites and subjects. Description of exploratory biomarker research moved to the correct section.

Section Number and Name	Description of Change	Brief Rationale
Section 2.2.1.4 Sodium-glucose Co-transporter 2 Inhibitors in Heart Failure and Chronic Kidney Disease	Inclusion of an additional literature reference	To provide the correct literature reference to a statement in this section.
Section 2.2 Background	Inclusion of additional literature references	To add more background to the study.
Section 2.3.1 Risk Assessment	Inclusion of data from completed combination toxicology study	To reflect new data in the drug development program.
Section 4.1 Overall Design	Addition of an optional pre-screening including timelines	In some clinics UACR is not part of clinical practice, introducing an optional pre-screening visit for UACR within the protocol will facilitate identifying eligible patients.
Section 4.1 Overall Design Section 9.2 Sample Size Determination	Update of numbers of participants	Based on new statistical calculations for the 4-arm study.
Section 4.3 Justification for Dose	Inclusion of further information from studies with dapagliflozin	Updated to reflect recent regulatory approvals of dapagliflozin 10 mg for the treatment of CKD, which is of relevance to the patient population being studied.
Section 5.1 Inclusion Criteria	Change of the LVEF criterion below 55% to below 60%	To broaden patient population by allowing additional patients who fall into the HFpEF category to enrol into the study in order to increase recruitment.
Section 5.1 Inclusion Criteria	Reduction of NT-proBNP threshold from 600 pg/mL to 300 pg/mL for sinus rhythm patients and from 900 pg/mL to 600 pg/mL for atrial fibrillation/flutter patients	To broaden the eligible HF population, taking into account this is an exploratory phase study.
Section 5.1 Inclusion Criteria	Removal of UACR values from the criterion for eGFR	To have UACR and eGFR as separate inclusion criteria.
Section 5.1 Inclusion Criteria	Update of the criterion for UACR at Visit 2	To have UACR from Visit 2 performed at the central laboratory to confirm eligibility for randomisation.
Section 5.1 Inclusion Criteria	Inclusion of a separate paragraph regarding randomisation with all applicable criteria for Visit 3	To explain what is required to be eligible for randomisation.

Section Number and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion Criteria Section 6.5.2 Background Medications	Inclusion of a separate paragraph regarding the run-in period with all applicable criteria for Visit 2	To explain the addition of open label dapagliflozin to all patients during run-in.
Section 5.1 Inclusion Criteria Section 8.2.4 Clinical Safety Laboratory Assessments	Addition of UACR measurement at screening including value ranges for participants who are either on SGLT2i or not on SGLT2i	The lower UACR limit at screening will be higher for patients naïve to SGLT2i treatment since UACR is expected to decrease during run-in in these patients and the UACR limits for eligibility to be randomised are the same for all patients.
Section 5.2 Exclusion Criteria Section 6.5.1 Prohibited Medications	Removal of SGLT2i from prohibited prior/ concomitant therapy	Increasingly difficult to recruit SGLT2i naïve patients due to change in HF guidelines and rapid inclusion of SGLT2i's in SoC for HF treatment.
Section 6.1.2 Medical Devices	Removal of ABPM device, bioimpedance spectroscopy device, activity tracker, and sleep analyser	Simplification for sites and participants.
Section 6.3 Measures to Minimise Bias: Randomisation and Blinding Section 8.5.1.1 Determination of Drug Concentration	Replacement of Covance with Labcorp Drug Development for PK samples	Legal entity change.
Section 6.5.2 Background Medications	Additional information regarding the start for treatment with dapagliflozin 10 mg for participants being on treatment with SGLT2i or not	According to new study design.
Section 6.7 Intervention After the End of the Study	Clarification on the use of dapagliflozin during the safety follow-up period after the blinded randomised treatment period in the study	All patients will be on open label dapagliflozin during run-in up to randomisation and after the blinded study treatment period during the safety follow-up.
Section 7.1 Discontinuation of Study Intervention	Updated text on DKA events	To be aligned with other AstraZeneca study protocols involving dapagliflozin.
Section 8 Study Assessments and Procedures	The maximum amount of blood collected from each participant over the duration of the study, was re-calculated and updated from 500 mL to 400 mL.	To reflect simplification of blood sampling and reduced burden to patients.

Section Number and Name	Description of Change	Brief Rationale
Section 8.1.1 Primary/Secondary Variable: Urinary Albumin to Creatinine Ratio (UACR)	Inclusion of details regarding procedures	For clarification on procedures.
Section 8.2.4 Clinical Safety Laboratory Assessments	Addition of formulas for the calculation of eGFR	To provide clarification on the calculation.
Section 9.3 Populations for Analyses Section 9.4.5.1 Adverse Events	Replacement of Safety Analysis Set (SAF) by Safety Set (SS)	SS is the new AZ standard.
Section 9.4.2.1 Primary Endpoint	Removal of AZD9977 alone and introduction of dapagliflozin 10 mg as active comparator	The primary endpoint was updated according to the comparison with the active comparator.
Section 9.4.2.2 Secondary Endpoint	Removal of AZD9977 150 mg alone	The dose response relationship was modified due to the drop of the placebo and AZD9977 alone arm.
Section 9.4.2.3 Exploratory Endpoints	Removal of exploratory endpoints	The exploratory endpoints have been updated according to the removed related exploratory variables.
Section 9.4.4 Pharmacodynamics and Biomarkers	Removal of MR-related gene transcription	Reduction of sampling procedures and blood volume to lessen burden on sites and subjects.
Section 9.5 Interim Analyses Section 9.6 Data Monitoring Committee	Change in size of interim analysis study population	Change in size of interim analysis population due to the updated sample size of the new study design.
Section 11 REFERENCES	Addition of literature references	To support the updated study design.

Amendment 4 (15 July 2021)

This amendment is considered to be 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.

Overall Rationale for the Amendment

The previous CSP version, version 4.0, dated 19 March 2021 was updated to implement patient-centric measures and improve recruitment. The updates are summarised below.

Section Number and Name	Description of Change	Brief Rationale
Cover page	Provided the full form of the study acronym, MIRACLE.	For clarity.
Section 1.1 Synopsis Section 4.1 Overall Design	The study will now be conducted at approximately 210 sites in approximately 20 countries as a change from the previously planned 170 sites in approximately 18 countries.	To increase potential participant pool.
Section 1.2 Schema Section 1.3 Schedule of Activities Section 5.1 Inclusion Criteria Section 5.2 Exclusion Criteria	Time window between Visits 2 and 3 was widened from −5 to −1 days to −7 to −1 days. Consequently, text in some of the inclusion and exclusion criteria was updated to align with this change in the time window.	To relieve operational burden without compromising participant safety or study data quality.
Section 5.1 Inclusion Criteria Section 5.2 Exclusion Criteria	Moved selection criteria regarding use of prior and concomitant medications from the section on Inclusion criteria to the section on Exclusion criteria.	Corrected because the content is appropriate under exclusion criteria rather than inclusion criteria.
Section 5.1 Inclusion Criteria	Clarification that 50% of adjustment of loop diuretics is allowed	To clarify and improve recruitment without compromising participant safety or study data quality.
Section 5.1 Inclusion Criteria	Change in inclusion criterion of lower limit of systolic BP from ≥ 100 mmHg to ≥ 90 mmHg.	To improve recruitment without compromising participant safety or study data quality.
Section 5.1 Inclusion Criteria	The criterion NT-proBNP ≥ 900 pg/mL applies to patients with atrial fibrillation/flutter either at screening “or in medical history”.	Clarification that medical history is included in this criterion.
Section 5.1 Inclusion Criteria Section 6.5.1 Prohibited Medications	The time period during which prior treatment with an MRA or SGLT2i is not allowed was updated from “for > 90 days to 12 months prior to screening” to be “within 90 days prior to screening”.	To improve recruitment without compromising participant safety or study data quality.
Section 5.2 Exclusion Criteria	The exclusion criterion of prolonged QT interval (QTcF > 470 ms) on ECG at screening (Visit 1) was removed.	To improve recruitment without compromising participant safety or study data quality.

Section Number and Name	Description of Change	Brief Rationale
Section 5.4 Screen Failures	Clarification that individuals who do not meet the inclusion/exclusion criteria regarding eGFR and K^+ levels may have these blood tests redone once after Visit 1 and/or Visit 2 upon investigator's discretion.	Clarification for transparency.
Section 1.3 Schedule of Activities Section 6.1.2 Medical Devices Section 8.1.2 Exploratory Variables Section 9.4.2.3 Exploratory Endpoints Appendix A 4 Data Protection	Cancellation of plans to use Eko DUO device (stethoscope and integrated single-lead electrocardiogram [ECG]). Consequently, related text on these electrocardiograms and phonocardiograms in various sections was updated.	Operational issues in providing the device to all sites.
Section 6.1.2 Medical Devices	Clarification that wearable devices of activity tracker and sleep analyser should be optional and based on the participants' consent.	Participant-centric approach.
Section 1.1 Synopsis Section 4.1 Overall Design Section 8.1.2.4 Home-based Monitoring of Activity Section 9.3 Populations for Analyses	The requirement of selecting approximately 200 participants for home-based monitoring of activity was removed.	As use of wearable devices is no longer mandatory for the participants, the final sample size for this subgroup is uncertain.
Section 6.5 Concomitant Therapy Appendix G 2 Risk Assessment for COVID-19 Pandemic	Added that COVID-19 vaccination is not likely to impact the study treatments and that the study treatments are not likely to impact COVID-19 vaccination. Participants may be enrolled and or continue in the study regardless of their choice to be vaccinated or not.	Participant-centric approach and transparency.
Section 6.5.1 Prohibited Medications	Clarification that dietary K^+ supplements or alternatives that are prohibited at screening/randomisation can be started during the study as a corrective action if hypokalaemia is confirmed.	Participant-centric approach and transparency.
Section 1.3 Schedule of Activities Section 8.1.1 Primary/Secondary Variable: Urinary Albumin to Creatinine Ratio (UACR)	Clarification that the first morning void urine sample should be a full sample and not a spot sample.	To ensure that adequate sample is available for the various analyses.

Section Number and Name	Description of Change	Brief Rationale
Section 8.1.2.2 Patient-Reported Outcomes	Clarified that 2 questions from the Kansas City Cardiomyopathy Questionnaire will not be applicable in this study.	For clarity.
Section 1.3 Schedule of Activities Section 8.1.2.3 Bioimpedance Spectroscopy	Addition of body weight measurement at visits that include bioimpedance spectroscopy.	The bioimpedance spectroscopy device used in this study does not measure body weight (required for the analysis).
Section 8.1.2.5 Ambulatory Blood Pressure Monitoring	Participants will be allowed to visit the study site in case required for adjusting or fitting the ABPM device.	Participant-centric approach.
Section 1.3 Schedule of Activities Section 8.2.4 Clinical Safety Laboratory Assessments Appendix F 1	Data on levels of electrolytes (potassium and sodium) and creatinine provided by local laboratories may be based on plasma or serum samples.	To adapt the study design to local laboratory capabilities without compromising data quality. Data on serum levels of electrolytes (potassium and sodium) and creatinine will be provided by the central laboratory.
Section 8.2.4 Clinical Safety Laboratory Assessments	The post-randomisation INR measurements may be done at a local laboratory if the necessary material provided by the central laboratory is not available; and the measurements may be omitted if the local laboratory is not capable of doing the measurements.	To adapt the study design to the central and local laboratory capabilities.
Section 8.2.4 Clinical Safety Laboratory Assessments	Clarification that microscopic examination of urine sample sediments will be performed depending on the local laboratory's capability.	To adapt the study design to local laboratory capabilities without compromising data quality.
Section 1.3 Schedule of Activities Section 8.2.4 Clinical Safety Laboratory Assessments	Collection of a plasma sample for K^+ measurement at the central laboratory.	Clarification that a separate plasma sample should be collected for the purpose of exploratory pharmacodynamic analysis.
Section 8.5.1 Pharmacokinetics	Clarification that samples collected for PK assessments may be used, if necessary, for safety or efficacy assessments only during the study and not after the study.	Correction of an error.

Section Number and Name	Description of Change	Brief Rationale
Section 8.6.2 Collection of Optional Biomarker Samples	Added text to clarify that unused samples of serum, plasma, and urine samples may be stored and used for future exploratory analyses if participant consents.	To clarify exploratory biomarker sample collection and use.
Section 8 Study Assessments and Procedures	The maximum amount of blood collected from each participant over the duration of the study, was re-calculated and updated from 400 mL to 500 mL.	For transparency.
Section 1.1 Synopsis Section 4.1 Overall Design	Addition of a table to present the study treatment groups.	To improve clarity and readability.
Section 1.2 Schema Section 1.3 Schedule of Activities Section 3 Objectives and Endpoints	Addition of a note that Visits at Week 7 and Week 13 (Visits 8 and 10) correspond to visits after completion of 6 weeks and 12 weeks of study treatment, respectively.	To provide a clarification and align with the explanation provided in the Statistical Analysis Plan.
Section 1.2 Schema Section 3 Objectives and Endpoints	Language updated to clarify that at "12 weeks" and other similar usage indicates "at the end of 12 weeks" ie, in Week 13.	For clarity.
Section 1.1 Synopsis Section 4.1 Overall Design	Change in stratification based on eGFR in (mL/min/1.73 m^2) from: ≥ 30 to ≤ 45; or > 45 to: ≥ 30 to < 45; or ≥ 45.	Correction of an error.
Section 1.1 Synopsis Section 4.1 Overall Design Appendix F 2	Updated language describing eGFR-based participant stratification	For clarity
Throughout the document, wherever applicable.	Units of eGFR were corrected to mL/min/1.73 m^2 consistently throughout the document.	Correction of an error.
Section 5.1 Inclusion Criteria Section 8.2.4 Clinical Safety Laboratory Assessments	Pregnancy test and lactation status that were mentioned for menopausal women were deleted.	Correction of an error.
Section 8.2.4 Clinical Safety Laboratory Assessments	The CKD-EPI formula was mentioned as "non-BSA adjusted", which was corrected to "BSA-adjusted".	Correction to align with the standard CKD-EPI formula.
Throughout the document, wherever applicable.	Minor language changes.	To improve readability.

Amendment 3 (19 March 2021)

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.

Overall Rationale for the Amendment

Revised CSP, Final 3.0, dated 26 January 2021 was updated to 19 March 2021.

Section Number and Name	Description of Change	Brief Rationale
Protocol Amendment Summary of Changes	Correction of rationale for change relating to Eko DUO device	Eko DUO device is site-based not home-based
	Correction of typo in description of change for exclusion criterion 6 for HBA1c (<10% corrected to >10%)	Correction of typo
Section 2.3.1 Risk Assessment	Mitigation strategy for patients with uncontrolled diabetes mellitus corrected in line with change to inclusion criterion 6 made at Protocol Amendment 2 (HbA1c changed from >12% to >10%)	Alignment with change to definition of uncontrolled diabetes mellitus made in previous amendment
Section 6.3 Measures to Minimise Bias: Randomisation and Blinding	Clarified that unused returned study intervention must not be re-dispensed to the participants	In response to Regulatory Authority in Slovakia request
Section 8.1.2.6 Digital Cardiac Auscultation and Electrocardiogram	Clarified that the Eko DUO device will be used in clinic not at home	Eko DUO device is site-based not home-based
Section 8.3.5	Going forward, any new or aggravated clinically relevant abnormal medical finding will be reported as an AE regardless of relationship to the disease under study.	Condition that medical findings unequivocally related to disease under study did not need to be reported as an AE was removed in response to Regulatory Authority in Germany request
Section 8.3.8.1 Maternal Exposure	Correction to align with mandated template text	Aligned with template
Section 9.4.2.3 Exploratory Endpoints	Respiratory rate was removed from the exploratory endpoint, Change from baseline in activity, heart rate, respiratory rate, body fluid retention, and sleep patterns over time	Respiratory rate was included in error; it is not collected in the study as per Schedule of Activities.

In addition, the following administrative changes were made:

- Tables of Contents updated.
- Minor editorial changes.

Amendment 2 (26 January 2021)

This amendment is considered to be 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.

Overall Rationale for the Amendment

Revised CSP, Final 2.0, dated 06 October 2020 was updated to 26 January 2021.

Section Number and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 4.1 Overall Design Section 8.1.2.4 Home-based Monitoring of Activity	Added text to describe secondary randomisation for Home-based Monitoring of Activity subgroup	To clarify randomisation of subgroups
Section 1.1 Synopsis Section 9.4.2.1 Primary Endpoint	Added text to analysis model on stratifying factors as covariates	To clarify the analysis model
Section 1.1 Synopsis Section 4.1 Overall Design, Section 9.4.2.1 Primary Endpoint	Lower limit of eGFR was changed from "<30 mL/min" to "≥20 to <30 mL/min"	To clarify that the lower limit of eGFR is 20 mL/min in this study
Section 1.3 Schedule of Assessments Section 5.1 Inclusion Criteria Section 8.2.4 Clinical Safety Laboratory Assessments (including Table 5)	Added text on FSH testing and adjusted table layout; text on LH was removed	To clarify tests regarding female reproductive status
Section 1.3 Schedule of Assessments; Section 8.1.2.3	Added text to exclude participants with pacemakers or other implanted devices from the bioimpedance assessment	The use of bioimpedance devices is contraindicated for patients with pacemakers or other electronic implanted devices
Section 1.3 Schedule of Assessments	Added text on hypertension medication; cross-references added	To clarify that hypertension treatment can be adjusted if needed at the screening visit

Section Number and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Assessments Section 3 Objectives and Endpoints Section 6.1.2 Medical Devices Section 8.1.2.6 Digital Cardiac Auscultation and Electrocardiogram Section 8.3.10 Medical Device Deficiencies Section 9.4.2.3 Exploratory Endpoints Appendix A4 Data Protection Appendix A7 Data Quality Assurance	Added text on the Eko DUO device and dECG device; new sections added (Section 8.1.2.6 and Section 8.3.10), other applicable sections updated, SoA revised accordingly, cross-references added as appropriate	To describe addition of new device to the protocol for site-based ECG monitoring
Section 2.2 Background Section 2.2.1.4 Sodium-glucose Co-transporter 2 Inhibitors in Heart Failure and Chronic Kidney Disease Section 2.3 Benefit/Risk Assessment (Table 2) Section 2.3.2 Benefit Assessment Section 11 References	Updated introductory text according to revised Investigator's Brochure of dapagliflozin; redundant reference was deleted	To include findings from recent clinical trials with dapagliflozin that suggest it has an additive treatment effect when given concomitantly with MRAs (DAPA-HF trial) and to further describe the dapagliflozin risk and benefit in patients with chronic kidney disease (DAPA-CKD trial)
Section 3 Objectives and Endpoints Section 9.4.2.3 Exploratory Endpoints	Corrected typo in alignment with Schedule of Assessments	To clarify that the KCCQ must be completed at 6 and 12 weeks, not at 8 and 12 weeks

Section Number and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion Criteria	Added "flutter" to criterion 5; added timepoints to criterion 6; revised the timepoint wording at criterion 11; corrected the cross-reference at criterion 12; added age-specific requirements to criterion 16 and revised text according; systolic BP inclusion criterion 9 clarified and diastolic BP inclusion criterion 10 removed	To clarify eligibility criteria
Section 5.2 Exclusion Criteria	Revised the timepoint wording in criteria 11 and 18; definition of uncontrolled diabetes mellitus changed from HBA1c >12% to >10% in criterion 6; any major cardiovascular surgery planned or within 3 months added as new criterion 12; COVID-19 criterion 25 (c) clarified	To clarify eligibility criteria
Section 6.5.1 Prohibited Medications	Revised list and added text in alignment with Section 5.1 Inclusion Criteria	To clarify medication restrictions
Section 6.7 Intervention After the End of the Study	Edited text	To clarify when patients should return to their usual treatments
Section 7.2 Participant Withdrawal from the Study	Added text on ET and safety follow-up visits	To clarify procedures upon participant withdrawal
Section 8 Study Assessments and Procedures	Added text on procedures performed at another facility	To clarify time frames for procedures performed at another facility than the study site
Section 8.1.2.4 Home-based Monitoring of Activity Section 8.1.2.5 Ambulatory Blood Pressure Monitoring Section 8.1.2.6 Digital Cardiac Auscultation and Electrocardiogram	Added text on outcomes of the monitoring procedures	To clarify availability of results and handling of health-related issues
Section 8.4 Overdose	Added text on dose limit in terms of number of capsules	To clarify overdose definition whilst maintaining the study blinding

Section Number and Name	Description of Change	Brief Rationale
Section 8.3.10 Medical Device Deficiencies Appendix L	New section added and Clinical Study Medical Device / Device Constituent Report Form included as an appendix	Required for studies in which a medical device is provided for use in the study
Section 9.3 Populations for Analyses Section 9.4.2 Efficacy	Added text in alignment with the SAP	To further describe statistical considerations of the study

In addition, the following administrative changes were made:

- A duplicate scanned page was removed from Appendix J (Kidney Disease and Quality of Life).
- Protocol amendment history for previous amendment was moved to a new Appendix (Appendix N).
- Tables of Contents and the List of Abbreviations were updated.
- Minor editorial changes were made throughout.

Amendment 1 (06 October 2020)

This amendment is considered to be 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.

Overall rationale for the Amendment

The original CSP, Final 1.0, dated 25 August 2020, was updated to include modifications to the number of sites and countries and updates to laboratory parameters for clarity. Minor editorial updates were made throughout.

Section Number and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 4.1 Overall Design	Update of number of sites and countries	To increase potential participant pool
Section 4.1 Overall Design	Update of eGFR strata for randomisation	To fix inconsistencies between protocol summary and Section 4.1
Section 8.1.1 Primary/Secondary Variable Urinary Albumin to Creatinine Ratio (UACR)	Correction of typo in Urinary Albumin to Creatinine Ratio unit	To fix a typo

Section Number and Name	Description of Change	Brief Rationale
Section 8.2.4 Clinical Safety Laboratory Assessments	Update of local laboratory requirements to make Glutamate dehydrogenase, RBC distribution width, and Bicarbonate at screening dependent on local capabilities	To account for the fact that some countries are not able to perform these tests locally
Section 9.2 Sample Size Determination	Addition of alpha value	To align with FDA comments
Section 9.3 Populations for Analyses	Clarification of the Full Analysis Set including participants who both receive and do not receive study intervention	To align with FDA comments

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