Clinical Study Report Synopsis	
Drug Substance	AZD9977 (balcinrenone) and dapagliflozin
Study Code	D6402C00001
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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

Study dates: First participant enrolled: 26 January 2021
Last participant last visit: 22 September 2023
Date of premature stop of recruitment: 18 April 2023
The study was terminated early due to recruitment challenges.
The analyses presented in this report are based on a clinical data lock date of 20 October 2023

Phase of development: Therapeutic exploratory (II)

Study Sponsor: AstraZeneca AB

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study site(s)

A total of 160 sites in 22 countries participated (ie, enrolled [consented] participants) into this study.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 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

Study design

This was a Phase IIb, multi-centre, randomised, double-blind, active-controlled parallel group, study that assessed the efficacy, safety and tolerability of AZD9977 and dapagliflozin combination administered for 12 weeks in participants with heart failure (HF) and chronic kidney disease (CKD).

The study was conducted in 160 sites in North America, Asia/Pacific, and European countries.

The study consisted of an optional pre-screening visit, a 1-week screening period, an up to 7 week run-in period, a 12-week treatment period (including 6 visits), the end of treatment visit, and a 4-week safety follow-up after last dose (including 1 visit).

At screening, participants who were on 10 mg dapagliflozin remained on the therapy as indicated throughout the treatment period of the study until the safety follow-up. Participants who were on another sodium-glucose co-transporter-2 inhibitor (SGLT2i) (eg, canagliflozin or empagliflozin) were required to switch to 10 mg dapagliflozin starting at the run-in (Visit 1b) after confirmed eligibility and remained on the therapy throughout the treatment period of the study until the safety follow-up. Participants who were not on a SGLT2i were to start on 10 mg dapagliflozin at the run-in (Visit 1b) after confirmed eligibility and remained on the therapy throughout the safety follow-up period.

According to clinical study protocol (CSP) Versions 1 to 5, participants were randomised to receive one of the 6 study treatments. Due to the change in study design at CSP Version 6, participants were randomly assigned in a 1:1:1:1 ratio to receive once daily administration of one of the 4 study treatments (excluding placebo and AZD9977 150 mg monotherapy arm). To ensure blinding, the study treatment was administered in the form of 3 oral capsules and 1 oral tablet (double-dummy).

Target subject population and sample size

The study target population was 21 years of age or older patients with HF (left ventricular ejection fraction [LVEF] below 60%) and CKD estimated glomerular filtration rate (eGFR) ≥ 30 and ≤ 60 mL/min/1.73 m^2). The intention was to expand the eGFR range to ≥ 20 to ≤ 60 mL/min/1.73 m^2 later in the study to have 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.

Approximately 500 participants were planned to be randomly assigned to study intervention (125 participants per treatment arm) such that approximately 476 evaluable participants (119 participants per treatment arm) would complete the study. However, due to persistent recruitment challenges, the study participant recruitment was prematurely stopped and the targeted inclusion of 119 evaluable participants per treatment arm could not be achieved. With the premature stop of recruitment, the expansion of the eGFR range or the target proportion of eGFR subgroups were never implemented.

Investigational product and comparator(s): dosage, mode of administration

A summary of the study treatment arms is provided below:

Table S2 Study Treatments Arms

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 m g	Placebo	Dapagliflozin 10 mg
AZD9977 150 mg + Dapagliflozin 10 mg	Placebo	AZD9977 50 m g	AZD9977 100 mg	Dapagliflozin 10 mg
Dapagliflozin 10 mg alone	Placebo	Placebo	Placebo	Dapagliflozin 10 mg
AZD9977 150 mg [a]	Placebo	AZD9977 50 mg	AZD9977 100 mg	Placebo
Placebo [a]	Placebo	Placebo	Placebo	Placebo

[a] Initially participants were assigned to one of the 6 treatment arms. There was a change in study design and thereafter participants were assigned to one of the 4 treatment arms ie, AZD9977 15/50/150 mg + dapagliflozin 10 mg and dapagliflozin 10 mg monotherapy arm (excluding placebo and AZD9977 150 mg monotherapy arms).

A summary of the study treatment dosage, mode of administration, and batch numbers is provided in the table below:

Table S3 Study Treatments

	AZD9977 (Balcinrenone)			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 Strengths	15 mg	50 mg	100 mg	10 mg
Dosage Levels	**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 were supplied centrally through AstraZeneca.			

	AZD9977 (Balcinrenone)	Dapagliflozin
Packaging and Labelling	For each strength, AZD9977 and matching placebo was provided in bottles containing 32 capsules.	Dapagliflozin was supplied in HDPE bottles containing 35 tablets.
	All bottles were labelled in accordance with GMP Annex 13 and per country regulatory requirement.	
Batch/Lot Number(s):	Provided separately in the CSR Appendices	

[a] Dapagliflozin was NIMP during the run-in and safety follow-up, but IMP during the treatment phase.
Note: Refer to the first table above for the study treatment arm details.
Abbreviations: GMP = Good Manufacturing Practice; HDPE = high-density polyethylene; IMP = investigational medicinal product; NA = not applicable; NIMP = non-investigational medicinal product.

Duration of treatment

The study consisted of a 12-week treatment period (including 6 visits).

Statistical methods

The primary hypothesis for this study was that AZD9977 in combination with dapagliflozin would induce a reduction of albuminuria greater than with dapagliflozin alone, as assessed by the percent change from baseline in urinary albumin to creatinine ratio (UACR) at 12 weeks.

A total of 119 evaluable participants per arm were to provide 80% power to detect a 30% difference in a AZD9977 dose arm 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 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 were to be randomly assigned to study intervention (125 participants per arm) such that approximately 476 evaluable participants (119 per arm) would complete the study.

Participants randomised according to CSP Versions 1.0 to 5.0 (before dropping placebo and AZD9977 150 mg monotherapy arms) were considered as part of Cohort 1, while participants randomised subsequently were considered part of Cohort 2. The primary analysis for remaining 4 treatment arms combined data from both cohorts, while the accrued data from discontinued treatment arms were analysed descriptively.

The primary efficacy endpoint for this study was 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 was estimated in a mixed model for repeated measures (Visits 7, 8, 9, and 10). The values were back transformed onto the original scale to give the geometric mean relative change from baseline at 12 weeks. The analysis model included UACR baseline value, treatment, and visit as fixed effect, and the stratifying factors (Type 2 diabetes mellitus [yes/no] and eGFR $\geq$ 30 to

< 45 mL/min/1.73 m^2; or ≥ 45 mL/min/1.73 m^2]) as well as the Cohort variable (1 or 2) as covariates. Moreover, treatment-by-visit interaction was also included in the model. The final analytical approach was described in detail in the Statistical Analysis Plan.

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

1 Overall comparison of the percentage changes from baseline in UACR at week 12 across all 4 treatment arms
2 Each of the 3 doses of AZD9977 in combination with dapagliflozin 10 mg versus dapagliflozin 10 mg in the following order:
   (a) AZD9977 150 mg + dapagliflozin 10 mg versus dapagliflozin 10 mg
   (b) AZD9977 50 mg + dapagliflozin 10 mg versus dapagliflozin 10 mg
   (c) 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 was assessed using data from dapagliflozin (10 mg) alone and 3 doses of AZD9977 (15, 50, or 150 mg) combined with dapagliflozin (10 mg).

Study population

On 18 April 2023, due to recruitment challenges, AstraZeneca decided to stop the study participant recruitment earlier than originally planned. The study has therefore randomised 153 participants instead of 500 planned participants.

Majority of study participants were white, males, overweight or obese who had median LVEF of 46%, median eGFR of 39.72 mL/min/1.73 m^2, and a median UACR of 103.35 mg/g (11.67 mg/mmol). The study population was considered representative of the target population for the treatment combination under evaluation.

There were no major imbalances across the treatment arms with regard to withdrawals from study, demographics and baseline disease characteristics.

Summary of efficacy results

- The smaller than planned number of participants reduced the power in the statistical comparisons and increased the variability of the results.
- In the primary analysis, all AZD9977 15/50/150 mg + dapagliflozin 10 mg doses resulted in a numerical reduction in UACR compared to dapagliflozin 10 mg monotherapy from baseline to 12 weeks, not reaching statistical significance.

Summary of pharmacokinetic results

- Pre-dose AZD9977 levels increased dose proportionally and were stable over time, indicating stationary pharmacokinetics of AZD9977.
- Dapagliflozin concentration levels were as anticipated and similar in all AZD9977 15/50/150 mg + dapagliflozin 10 mg and dapagliflozin 10 mg monotherapy arms showing that AZD9977 does not affect the pharmacokinetics of dapagliflozin.

Summary of pharmacodynamic results

- AZD9977 15/50/150 mg + dapagliflozin 10 mg were associated with numerical reductions in N-terminal-pro-brain natriuretic peptide (NT-proBNP) levels compared to dapagliflozin 10 mg monotherapy at Week 12 (Visit 10).
- Increased aldosterone levels were seen after start of treatment for all AZD9977 15/50/150 mg + dapagliflozin 10 mg arms but not with dapagliflozin 10 mg monotherapy (no formal statistical comparison), supporting target engagement in arms with AZD9977.

Summary of safety results

- AZD9977 15/50/150 mg + dapagliflozin 10 mg combinations and dapagliflozin 10 mg monotherapy were well tolerated in study participants with stable symptomatic HF and CKD, and no new safety concern was identified.
- The most commonly reported AEs were nasopharyngitis, CKD, diarrhoea, hyperkalaemia, nausea, fall, urinary tract infection, and urinary tract infection bacterial. In general, AEs were consistent with the underlying disease of the study population. Most of the AEs were mild or moderate in intensity.
- Three deaths occurred during the study (sudden cardiac death, coronavirus disease 2019 (COVID-19), and cardiac failure) whereof one was during safety follow-up. None was assessed as possibly related to study intervention by the investigator.
- The number of SAEs and AEs leading to treatment discontinuation was low.
- AEs related to the safety topics of interest (hyperkalaemia, deteriorating renal function, and hypotension) were few and none were serious.
- The number of participants with serum K^+ values > 5.5 mmol/L was numerically higher in the AZD9977 150 mg + dapagliflozin 10 mg arm compared to all other arms. Mean serum K^+ showed numerically higher increases from baseline in the AZD9977 50/150 mg + dapagliflozin 10 mg arms compared to the lowest combination dose and dapagliflozin 10 mg monotherapy arms.
- Small mean decreases from baseline were seen in eGFR in all treatment arms, with a numerically larger decrease in the AZD9977 150 mg + dapagliflozin 10 mg compared to the other arms.
- Small reductions in systolic and diastolic BP were seen in all combination treatment arms (AZD997715/50/150 mg + dapagliflozin 10 mg) compared to dapagliflozin 10 mg monotherapy arm.

- No safety concerns were raised with regard to vital signs, clinical laboratory tests, or ECG.

Conclusion(s)

- The smaller than planned number of participants reduced the power in the statistical comparisons and increased the variability of the results.
- In the primary analysis, all AZD9977 15/50/150 mg + dapagliflozin 10 mg doses resulted in a numerical reduction in UACR compared to dapagliflozin 10 mg monotherapy from baseline to 12 weeks, not reaching statistical significance.
- Pre-dose AZD9977 concentration levels increased dose proportionally and were stable over time indicating stationary pharmacokinetics of AZD9977.
- Dapagliflozin concentration levels were as expected and similar in all AZD9977 15/50/150 mg + dapagliflozin 10 mg and dapagliflozin 10 mg monotherapy arms showing that AZD9977 does not affect the PK of dapagliflozin.
- AZD9977 15/50/150 mg + dapagliflozin 10 mg were associated with numerical reductions in NT-proBNP levels compared to dapagliflozin 10 mg monotherapy at Week 12 (Visit 10).
- Increased aldosterone levels were seen after start of treatment for all AZD9977 15/50/150 mg + dapagliflozin 10 mg doses but not with dapagliflozin 10 mg monotherapy (no formal statistical comparison), supporting target engagement in arms with AZD9977.
- AZD9977 15/50/150 mg/dapagliflozin 10 mg and dapagliflozin 10 mg monotherapy were well tolerated in the study participants with stable symptomatic HF and CKD, and no new safety concern was identified.
- AEs related to the safety topics of interest (hyperkalaemia, deteriorating renal function, and hypotension) were few and none were serious.