Received: 18 February 2022 | Revised: 23 May 2022 | Accepted: 13 July 2022

DOI: 10.1111/cts.13377

ARTICLE

Effect of AZD9977 and spironolactone on serum potassium in heart failure with preserved or mildly reduced ejection fraction, and renal impairment: A randomized trial

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Funding information
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Abstract

This phase Ib study compared the effects of AZD9977, a selective mineralocorticoid receptor modulator with predicted low hyperkalemia risk, with spironolactone on serum potassium (sK^+) in patients with heart failure (HF) with preserved or mildly reduced ejection fraction (EF; ≥40%), and renal impairment. Patients with HF with EF greater than or equal to 40% and estimated glomerular filtration rate of 40–70 ml/min/1.73 m^2 were randomized to once-daily AZD9977 100 mg or spironolactone 25 mg for 14 days, up-titrated to AZD9977 200 mg or spironolactone 50 mg for another 14 days. The primary end point was relative change (%) in sK^+ for AZD9977 versus spironolactone (baseline to day 28). Serum/urinary electrolytes, fractional excretion (FE) of Na^+/K^+, plasma aldosterone, cortisol, and renin, and safety were also assessed. Sixty-eight patients were randomized (AZD9977, $n = 33$; spironolactone, $n = 35$). Mean (SD) age was 73.0 (8.5) years, 51.5% men. Mean sK^+

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change from baseline to day 28 was 5.7% (AZD9977) and 4.2% (spironolactone), and 1.5% and 4.2% at day 14. Relative change (95% confidence interval) in sK^+ with AZD9977 versus spironolactone was −0.3% (−5.3% to 4.4%; day 28), and 3.4% (−0.8% to 7.5%; day 14). Median increase from baseline in plasma aldosterone at day 28 was 89.8 pmol/L for AZD9977 and 67.4 pmol/L for spironolactone. Median FE of K^+ was 12.9% (AZD9977) and 10.1% (spironolactone). AZD9977 was well-tolerated. No discontinuations due to hyperkalemia occurred with either treatment. Evidence of target engagement for AZD9977 with a favorable safety profile, supports further evaluation of AZD9977 in patients with HF and renal impairment.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Activation of the mineralocorticoid receptor (MR) promotes cardiac and renal disease in heart failure (HF), and blockade with MR antagonists (MRAs) presents a means to improve outcomes. However, use of available MRAs require caution due to a risk of hyperkalemia and renal impairment.

WHAT QUESTION DID THIS STUDY ADDRESS?

What is the effect of AZD9977, a selective MR modulator with predicted low hyperkalemia risk, on serum potassium (sK^+) and safety in patients with HF with mildly reduced or preserved ejection fraction and renal impairment, versus spironolactone?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

It is difficult to clearly establish effects on sK^+ in a small cohort of patients with renal disease and concomitant use of renin-angiotensin-aldosterone system inhibitors and loop diuretics. However, evidence of a pharmacodynamic effect for AZD9977 was observed in this study with a favorable safety profile that warrants further evaluation of AZD9977 in patients with HF and renal impairment.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

The study findings of clear MR engagement (based on aldosterone elevation) along with a numerical difference in fractional excretion of potassium with AZD9977 versus spironolactone support our nonclinical data that AZD9977 has a modulator effect on the MR rather than pure antagonism. If this can be validated in additional larger trials, then MR modulation may offer a way to prevent endogenous MR activation with a reduced risk of hyperkalemia.

INTRODUCTION

Morbidity and mortality from heart failure (HF) remain high worldwide.[1] As such, there is a significant unmet need for new therapies to improve quality of life and life expectancy in patients with HF. Activation of the mineralocorticoid receptor (MR) is one promising therapeutic target, as an independent and powerful mediator of deterioration of cardiac and renal function in HF.[2] Blockade of this pathway using MR antagonists (MRAs) is an effective therapeutic intervention in patients with HF with reduced ejection fraction (HFrEF).[2,3] Robust data from large randomized controlled trials (RCTs) have shown improved outcomes with MRAs, including spironolactone[4] and eplerenone,[5] in patients with HFrEF. Recently, the MRA finerenone was found to reduce the incidence of the composite cardiovascular outcome (time to first onset of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for HF) in patients with diabetic kidney disease.[6] Although the therapeutic benefit of MRAs is yet unproven in patients with HF and preserved EF (HFpEF) or mildly reduced EF (HFmrEF),[7,8] a benefit has been suggested in subpopulations in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial of spironolactone.[9–11] In this context, there is widespread interest among clinicians regarding the potential use of MRAs in HFpEF and HFmrEF.

Despite improved cardiovascular and renal outcomes in clinical trials, MRAs are used somewhat cautiously in

patients with HF and chronic kidney disease due to perceived and actual risks of hyperkalemia and worsening renal impairment. Even in well-controlled RCTs, for example, the "Americas cohort" from the TOPCAT trial, spironolactone use was associated with a three-fold increased risk of hyperkalemia compared with placebo (hazard ratio 3.21, 95% confidence interval [CI] 2.46–4.20, $p < 0.001$).[8] A reduced estimated glomerular filtration rate (eGFR; ≤60 ml/min) is a risk factor for developing hyperkalemia in HF.[12] Severe hyperkalemia is associated with increased cardiovascular and all-cause mortality, and hyperkalemia is a common reason for discontinuation of MRAs or dose reduction in HF.[8] However, in the TOPCAT trial, discontinuation of spironolactone was associated with a worsened outcome/less clinical benefit, and other studies have shown that dose reduction was associated with higher 180-day mortality compared with maintained doses.[12,13] Overall, the concern surrounding the risk of hyperkalemia limits the use of MRAs in clinical practice, particularly in patients with HF and impaired kidney function, but discontinuation of indicated MRA therapy leads to worse clinical outcomes.[2,12–15]

AZD9977 is a non-steroidal, selective MR modulator in clinical development, predicted to have a low hyperkalemia risk based on preclinical data.[16] Unlike the MRA eplerenone, AZD9977 is a partial MRA due to its unique interaction pattern with MR, which results in a distinct recruitment of co-factor peptides when compared with eplerenone.[16] In preclinical studies, AZD9977 resulted in a dose-dependent reduction in albuminuria and improved kidney histopathology in uni-nephrectomized db/db mice, and also in uni-nephrectomized rats on a high-salt diet and aldosterone infusion; thus providing organ protection.[16] However, in contrast to eplerenone, AZD9977 has no effects on urinary electrolyte balance in preclinical models, and plasma potassium elevation was reduced compared with eplerenone after potassium challenge in mice subjected to 5/6 nephrectomy,[17] in line with a potential lower risk of hyperkalemia. These preclinical results suggest that AZD9977 may have the potential to address an important unmet need for MR modulation, providing organ protection with a reduced hyperkalemia risk in patients with HF and reduced renal function who are at risk of hyperkalemia.

We evaluated the effect of AZD9977 compared with spironolactone on serum potassium (sK^+) in patients with HF (ejection fraction [EF] ≥40%) and renal impairment (eGFR range 40–70 ml/min/1.73 m^2).

METHODS

This was a phase Ib, open-label, randomized, parallel-group, multicenter study designed to assess the effect of pharmacologically equipotent doses of AZD9977 and spironolactone on sK^+ in patients with HF (HFpEF or HFmrEF) and eGFR in the range of 40–70 ml/min/1.73 m^2.

This study (NCT03682497; ClinicalTrials.gov) was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonization Good Clinical Practice Guidelines, applicable regulatory requirements and the AstraZeneca policy on Bioethics. The study protocol was approved by the ethics committee or institutional review board at each site (18 centers across 4 countries: Bulgaria, Czech Republic, Poland, and the United Kingdom). All patients were required to provide written, informed consent.

Patients

Eligible patients were adults greater than or equal to 18 years (women of non-childbearing potential) with a body mass index less than 40 kg/m^2, a clinical diagnosis of HF based on signs and symptoms, left ventricular ejection fraction (LVEF) greater than or equal to 40% based on transthoracic echocardiogram measurement within the past 12 months, eGFR of 40–70 ml/min/1.73 m^2 (Chronic Kidney Disease Epidemiology Collaboration formula), two measures of plasma N-terminal pro-B type natriuretic peptide (NTproBNP) greater than or equal to 125 pg/ml, baseline sK^+ 3.5–4.8 mmol/L, on stable dose of a loop diuretic, plus either an angiotensin receptor blocker or angiotensin converting enzyme inhibitor, for greater than or equal to 4 weeks prior to randomization.

Exclusion criteria included documented LVEF less than 40% at any time, acute decompensation of HF requiring hospital admission or escalation in therapy, primary cardiomyopathy, high output HF, other medical conditions likely to impact on the study results, and hyponatremia (serum Na^+ [sNa^+] < 135 mmol/L at enrollment) (see Table S1 for further information).

Study design and treatments

All patients were centrally assigned to randomized study treatment using an interactive voice/web response system. Randomization was produced by PAREXEL Informatics using the AstraZeneca randomization solution (AZRand) and stratified for the presence of type 2 diabetes mellitus to ensure equal distribution between treatment groups. Patients were randomized 1:1 to receive AZD9977 100 mg once daily (50 mg capsule) or spironolactone 25 mg (25 mg tablet) once daily for the first 14 days (predicted to be equipotent doses in terms of average receptor occupancy). If sK^+ was less than or equal to 4.8 mmol/L after 14 days of treatment, the dose was then uptitrated to AZD9977 200 mg

once daily or spironolactone 50 mg once daily for an additional 14 days of treatment (study design; Figure S1).

Patients were requested to take their study drug orally each day, in the morning between ~08:00–10:00 a.m. Patients remained at the study site until continuation in the study was confirmed by the investigator following assessment of their willingness to continue, protocol compliance, and evaluation of safety. Patients with confirmed sK^+ greater than or equal to 5.6 mmol/L or reduction in eGFR greater than or equal to 25% from baseline had their study medication discontinued and were asked to remain in the study until follow-up was completed. Patients were advised to avoid potassium-rich foods, drinks, and dietary supplements throughout the study; site staff were provided with a low-potassium dietary advice sheet for use. Caffeine, alcohol, and tobacco were to be avoided for at least 8 h prior to sampling of blood and urine; all patients were to avoid conception either through abstinence or use of an effective method of contraception throughout the study and until 3 months after the final dose.

Schedule of assessments

A full schedule of assessments is provided in Table S2. Briefly, assessments were scheduled at day (±1 relative to first dose): −14 to 0 (visit 1, screening), 1 (visit 2, baseline), 7 (visit 3), 14 (visit 4), 21 (visit 5), 28 (visit 6, end of trial), and 34 (visit 7, follow-up). Samples for efficacy measures were collected at all visits up to day 28, and samples for exploratory variables were collected on days 1, 14, and 28 (except for transthoracic echocardiography, which was performed at screening or randomization, and days 1 and 28). Plasma samples for pharmacokinetic (PK) assessment were collected at all visits up to day 28 (except at screening). Safety was assessed at all clinic visits. A laboratory manual was provided to sites that provided instructions on blood sample collection. In brief, blood samples for serum electrolytes were collected with the tourniquet loosened and were then handled carefully (on ice as appropriate). Plasma was separated at each study site according to site procedures. If hemolysis was suspected, sampling could be repeated. All measures were performed by a central laboratory (Covance) except for laboratory safety parameters determined by local laboratories.

Outcomes

The primary end point was relative change (%) from baseline to day 28 in sK^+ for AZD9977 compared with spironolactone; calculated as:

$$\left\{1-\left(\frac{\text{AZD9977}_{\text{Day28}}/\text{AZD9977}_{\text{baseline}}}{\text{spironolactone}_{\text{Day28}}/\text{spironolactone}_{\text{baseline}}}\right)\right\}\cdot 100\%$$

Secondary end points were the relative change (%) in sK^+ from baseline to day 14 (using the above equation) between equipotent doses of AZD9977 and spironolactone, and PKs of AZD9977 and spironolactone based on trough plasma concentrations (C_{trough}).

Safety and tolerability were assessed in terms of adverse events (AEs), vital signs (supine blood pressure [BP], pulse rate), 12-lead digital electrocardiogram (ECG), physical examination, and laboratory safety (hematology, clinical chemistry, and urine chemistry).

Exploratory assessments

Exploratory assessments included the effect of AZD9977 and spironolactone on serum and urinary Na^+, K^+, urea and creatinine levels, the fractional excretion of Na^+ (FE-Na) and FE-K by the kidneys, plasma aldosterone (target engagement marker) and renin, the proportion of patients uptitrated to a higher dose of AZD9977 or spironolactone, change in eGFR, urinary albumin, urinary albumin to creatinine ratio (uACR), cortisol, the proportion of patients experiencing confirmed hyperkalemia ($sK^+ \geq 5.6$ mmol/L), and markers of cardiovascular efficacy (e.g., plasma NTproBNP levels, and echocardiographic measures of filling pressure and left ventricular systolic and diastolic function).

Pharmacokinetic assessments

To quantify C_{trough} plasma concentrations of AZD9977 and spironolactone (based on canrenone, the active metabolite of spironolactone), blood samples were taken before the next dose at all visits after the screening visit up to the end of treatment.

Statistical methods

A sample size of 25 patients per treatment was estimated to provide 90% power to detect a 9.1% relative change in sK^+ for AZD9977 (based on the above equation relating to the primary end point), compared with spironolactone, from baseline to day 28, using a two-sided, two-sample *t*-test with a significance level of 0.05. The target value for the primary end point of 9.1% was established by applying the primary end point equation to an assumed common baseline value of 4.3 mmol/L,[18] and an increase of

0.43 mmol/L for spironolactone,[19] and no increase for AZD9977.

The Mixed Model Repeated Measures method was used with baseline measures (last measurement prior to the first study drug administration [for each parameter]) as covariate, and diabetes status, visit, treatment, and the interaction between visit and treatment as fixed factors. An unstructured covariance structure was used, with Kenward-Roger correction for degrees of freedom approximation (significance level of 0.05 and a 2-sided test).

Primary and secondary end point (sK^+) data were evaluated on the full analysis set; defined as all randomized patients who received at least one dose of study drug. Serum K^+ levels were assumed to be log-normally distributed, all calculations were performed on log scale and then back transformed, with relative changes in sK^+ reported as least squares means (LSmean). PK end points were evaluated on the PK analysis set; defined as all patients who received at least one dose of study drug and who had at least one PK sample taken during the study.

Analysis of data for AEs, clinical laboratory measures, vital signs, and ECG were completed on the safety analysis set; defined as all randomized patients who received at least one dose of study drug. Results are described descriptively.

RESULTS

Patients

In total, 139 patients were enrolled into the study between November 2018 and March 2020 at 18 centers in four countries: Bulgaria (3 centers), Czech Republic (7 centers), Poland (5 centers), and the United Kingdom (3 centers). Of these, 68 patients were randomized and received AZD9977 ($n = 33$) or spironolactone ($n = 35$; Figure 1). All randomized patients received at least one dose of their assigned treatment and were included in the full analysis set and safety population. A total of 64 patients ($n = 31$ in the AZD9977 group and $n = 33$ in the spironolactone group) were included in the PK analysis set; each patient providing one to four samples.

Patients were generally well matched between the two treatment groups in terms of baseline characteristics and demographics (Table 1). Disease-related medical history was as expected for the study population; hypertension (97%), dyslipidemia (75%), atrial fibrillation (54%), coronary artery disease (46%), and type 2 diabetes (40%). As there was no predefined inclusion criteria cutoff for baseline uACR, the variability was high and with a tendency toward a between-group difference (Table 2); the number of patients with uACR at baseline of less than 30, 30 to less than or equal to 300, and greater than 300 mg/g was

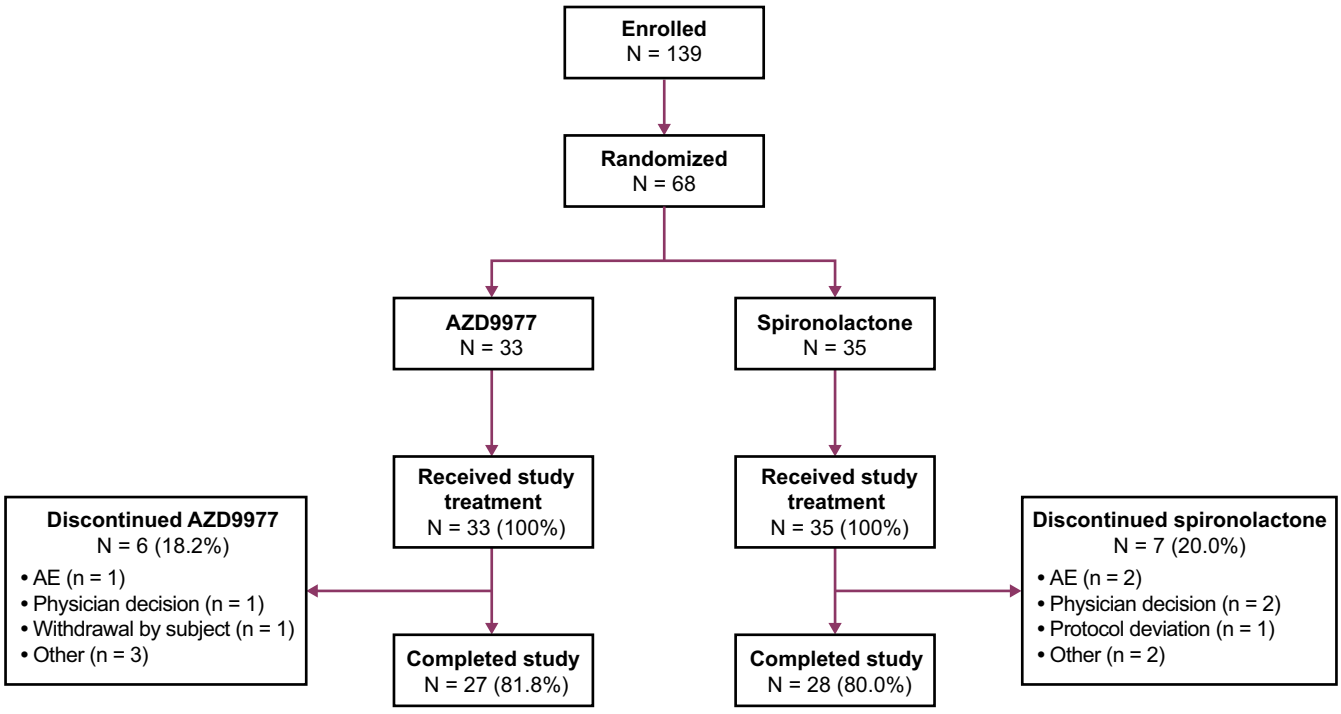

FIGURE 1 Patient disposition. A total of 71 patients were enrolled but not randomized due either to screen failure ($n = 64$), subject withdrawal ($n = 6$), or other reason ($n = 1$, coronavirus disease 2019 [COVID-19]). AE, adverse event; N, number of subjects in treatment group.

TABLE 1 Patient demographics and characteristics

Demographics or characteristic	AZD9977 (*N* = 33)	Spironolactone (*N* = 35)	Total (*N* = 68)
Mean age, years (SD)	73.0 (9.1)	73.0 (7.0)	73.0 (8.5)
Age group (years), *n* (%)			
50–64	6 (18.2)	5 (14.3)	11 (16.2)
65–84	23 (69.7)	28 (80.0)	51 (75.0)
≥85	4 (12.1)	2 (5.7)	6 (8.8)
BMI, kg/m^2, *n* (%)	82 (54–120)	89 (60–129)	85.5 (54–129)
Sex, *n* (%) male	15 (45.5)	20 (57.1)	35 (51.5)
Race, *n* (%) White	33 (100)	35 (100)	68 (100)
sK^+, mmol/L, mean (SD)	4.44 (0.48)	4.54 (0.36)	4.49 (0.42)
LVEF (%), mean (SD)	56.3 (8.3)	55.1 (6.9)	55.7 (7.6)
eGFR (ml/min/1.73 m^2), mean (SD)	59 (12)	57 (15)	58 (14)
Medical history, *n* (%)			
Hypertension	32 (97.0)	34 (97.1)	66 (97.1)
Angina pectoris	11 (33.3)	10 (28.6)	21 (30.9)
Atrial fibrillation	19 (57.6)	18 (51.4)	37 (54.4)
Atrial flutter	3 (9.1)	1 (2.9)	4 (5.9)
Cardiac valve disease	11 (33.3)	11 (31.4)	22 (32.4)
Coronary artery disease	13 (39.4)	18 (51.4)	31 (45.6)
Coronary artery stenosis	6 (18.2)	10 (28.6)	16 (23.5)
Myocardial infarction	8 (24.2)	11 (31.4)	19 (27.9)
Ventricular arrhythmia	3 (9.1)	1 (2.9)	4 (5.9)
Dyslipidemia	24 (72.7)	27 (77.1)	51 (75.0)
Type 2 diabetes mellitus	13 (39.4)	14 (40.0)	27 (39.7)

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; N, number of subjects in treatment group; SD, standard deviation; sK^+, serum potassium.

21, six and two in the AZD9977 group, and 22, seven, and one in the spironolactone group (albumin measures were not available for 9 patients [AZD9977, $n = 4$ and spironolactone, $n = 5$]).

Similar proportions of patients underwent dose uptitration at day 14: 24 patients (72.7%) for AZD9977 and 26 patients (74.3%) for spironolactone ($p = 1.0$). Four patients in the AZD9977 group and three patients in the spironolactone group were not uptitrated due to an sK^+ value of greater than 4.8 mmol/L and remained on the lower dose of study drug for the rest of their participation in the study. One patient in the spironolactone group had an sK^+ value of 4.8 mmol/L at day 14 but was not uptitrated at the discretion of the investigator.

Efficacy

At baseline, mean (SD) sK^+ levels were 4.44 (0.48) mmol/L for AZD9977 and 4.54 (0.36) mmol/L for spironolactone. At day 28, these values were 4.63 (0.51) mmol/L and 4.72 (0.37) mmol/L, respectively. Figure 2a shows the change from baseline in sK^+ over time during treatment with AZD9977 or spironolactone.

Primary end point

The relative change (LSmean, 95% CI) in sK^+ from baseline to day 28 between AZD9977 and spironolactone was −0.3% (−5.3% to 4.4%) and not statistically significant ($p = 0.888$). The geometric mean (95% CI) change in sK^+ from baseline to day 28 was 5.73% (1.89%–9.73%) for AZD9977 and 4.21% (0.41%–8.15%) for spironolactone (Figure 2a); equivalent to mean (SD) increases of 0.26 (0.41) and 0.19 (0.45) mmol/L, respectively. The observed increase in sK^+ levels with spironolactone was smaller than anticipated (less than half) and the change with AZD9977 was not zero, invalidating the primary assumption on sK^+ and rendering the statistical analysis of the primary end point inconclusive.

TABLE 2 Change from baseline and relative change between AZD9977 and spironolactone for exploratory parameters (at day 28)

	AZD9977 ($n = 33$)		Spironolactone ($n = 35$)		Relative change from baseline (95% CI), AZD9977 vs. spironolactone	p value
	Baseline	Δ at day 28	Baseline	Δ at day 28		
sNa^+ (mmol/L)	141.8 (3.0)	−2.2 (2.5)	141.6 (2.4)	−1.7 (2.3)	1.00 (0.99–1.00)	0.31
Serum urea (mmol/L)	7.48 (1.9)	+0.64 (2.4)	7.27 (2.8)	+0.83 (2.5)	0.98 (0.85–1.13)	0.77
Urine urea (mmol/L)	246.9 (135.5)	−36.3 (107.4)	198.3 (108.6)	15.3 (109.0)	0.81 (0.59–1.12)	0.20
Serum creatinine (μmol/L)	98.3 (20.0)	+6.2 (14.3)	105.2 (27.2)	+4.0 (20.9)	1.00 (0.91–1.09)	0.92
Urine albumin (mg/L)	144.4 (457.7)	−45.2 (264.5)	54.4 (158.4)	−10.3 (24.5)	1.20 (0.66–2.18)	0.54
Cortisol (μmol/L)	356.41 (119.8)	+8.43 (114.66)	356.9 (119.8)	+47.9 (144.4)	0.93 (0.78–1.10)	0.39
Plasma renin (pmol/L)	0.20 (0.1, 4.6)	+0.42 (−0.7, 4.0)	0.46 (0.10, 22.9)	+0.42 (−20.9, 15.2)	0.85 (0.45–1.60)	0.61
Plasma aldosterone (pmol/L)	127.8 (100.2, 207.4)	+89.8 (24.8, 145.1)	156.5 (105.3, 250.5)	+67.4 (3.96, 148.9)	1.10 (0.82–1.48)	0.51
eGFR (ml/min/1.73 m^2)	59 (12)	−3 (8)	57 (15)	−4 (14)	0.99 (0.89–1.10)	0.85
uACR (g/mol)	185.5 (600.9)	−40.7 (108.9)	62.8 (163.7)	−4.4 (13.3)	13.1 (6.8–25.2)	0.23
Weight (kg)	83.6 (14.8)	−1.2 (4.6)	89.6 (15.4)	−1.2 (2.5)	0.09 (−1.98–2.16)	0.93
Cardiovascular efficacy						
NTproBNP (pmol/L)	129.7 (115.1)	−13.1 (52.3)	139.8 (163.1)	−26.5 (72.6)	1.02 (0.76–1.36)	0.91
Echocardiography						
E/A ratio[a]	0.9 (0.6)	+0.1 (0.7)	0.8 (0.7)	+ <0.1 (0.3)	0.15 (−0.14–0.44)	0.30
E/é ratio[b]	11.6 (5.8)	−1.7 (5.0)	10.6 (5.3)	−0.6 (4.1)	−0.35 (−2.81–2.11)	0.77
Left ventricular global longitudinal strain (%)	−14.7 (4.5)	+1.3 (3.3)	−15.8 (3.1)	+0.7 (3.3)	0.81 (−1.07–2.70)	0.39

Note: n-values vary for each parameter.

All values are mean (SD) except for renin and aldosterone, which are median (minimum, maximum) and median (IQR), respectively; p value for relative change based on LSmean.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LSmean, least squares means; NTproBNP, plasma N-terminal pro-brain natriuretic peptide; SD, standard deviation; sNa^+, serum sodium; uACR, urinary albumin to creatinine ratio.

[a]Ratio peak velocity blood flow from left ventricular relaxation in early diastole (E wave) to peak velocity flow in late diastole due to atrial contraction (A wave).

[b]Ratio of transmitral early peak velocity (E) by pulsed wave Doppler to early diastolic mitral annulus velocity (e') estimated by tissue Doppler.

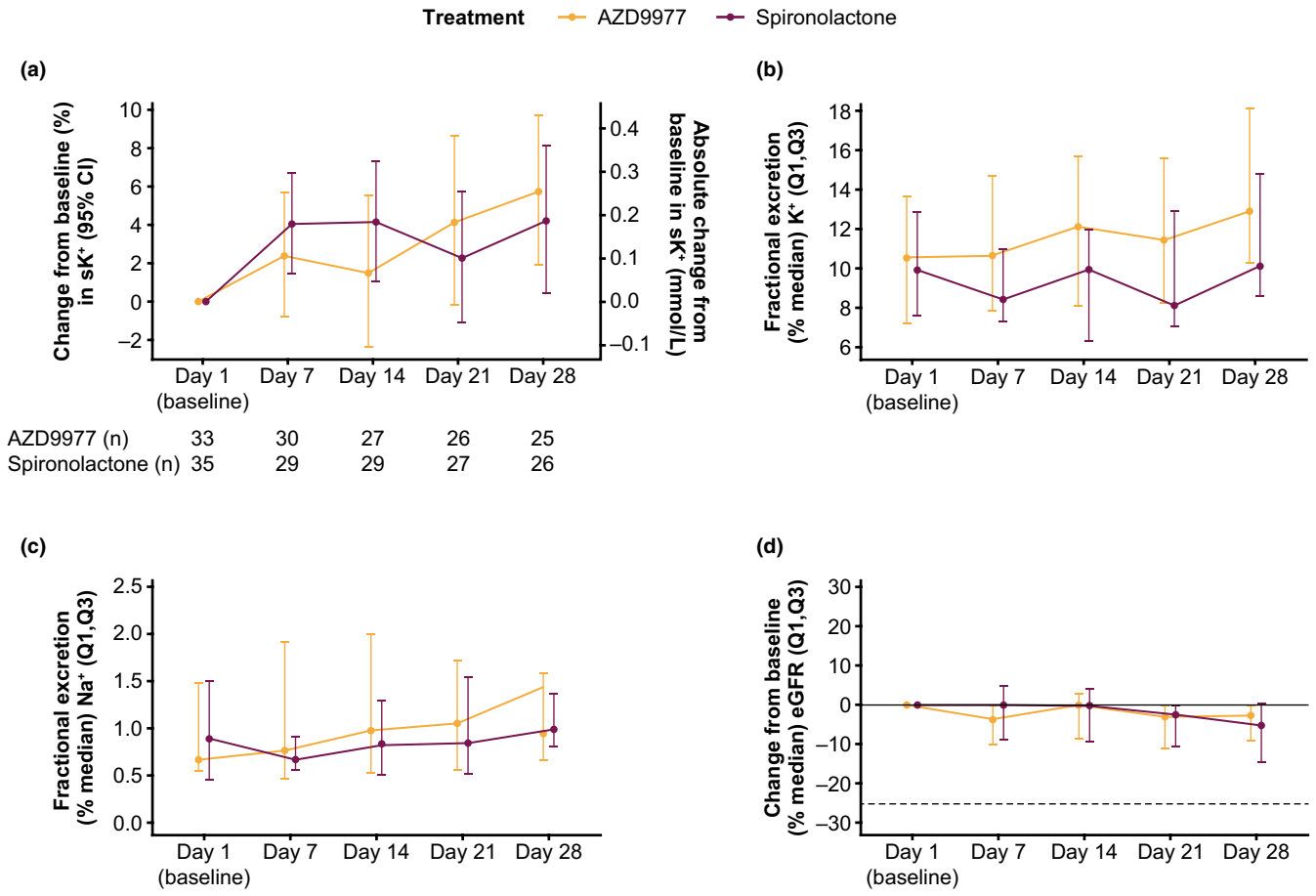

FIGURE 2 Analysis of laboratory parameters (a) change from baseline in sK^+, (b) fractional renal excretion of K^+, (c) fractional renal excretion of Na^+, and (d) change in eGFR during treatment with AZD9977 ($n = 33$) or spironolactone ($n = 35$) (full analysis set). Values are mean (95% CI) for sK^+. Values are median (IQR) for fractional renal excretion and eGFR. Dashed line: discontinuation criteria (change ≤25%). CI, confidence interval; eGFR, estimated glomerular filtration rate; IQR, interquartile range; sK^+, serum potassium.

Secondary end point

At day 14, the relative change (LSmean, 95% CI) in sK^+ from baseline between AZD9977 and spironolactone was 3.4% (−0.8% to 7.5%) and again not statistically significant ($p = 0.109$). The geometric mean (95% CI) change in sK^+ from baseline was 1.49% (−2.41% to 5.55%) for AZD9977 and 4.15% (1.02%–7.38%) for spironolactone; equivalent to mean (SD) changes of 0.06 (0.49) and 0.19 (0.39) mmol/L, respectively.

Exploratory assessments

At day 28, the median (interquartile range [IQR]) FE-K was 12.9% (10.3–18.1) for AZD9977 and 10.1% (8.6–14.8) for spironolactone; the values being numerically higher for AZD9977 than for spironolactone throughout the study (Figure 2b). There was little difference evident between the treatment groups throughout the study for FE-Na; at day 28, median (IQR) FE-Na was 0.95% (0.67–1.59) for AZD9977 and 0.99% (0.81–1.37) for spironolactone (Figure 2c). Neither spironolactone nor AZD9977 was found to significantly alter cortisol levels compared with baseline although a greater numerical increase was seen for spironolactone at day 28 (Table 2).

Other laboratory parameters were generally comparable between the treatment groups at baseline with no significant changes evident during the study (Table 2). Median increase from baseline in plasma aldosterone at day 28 was similar between treatment groups, being 89.8 pmol/L for AZD9977 and 67.4 pmol/L for spironolactone. The relative change from baseline based on LSmean (95% CI) for AZD9977 versus spironolactone for aldosterone was 1.10 (0.82–1.48, $p = 0.507$; Table 2). A similar trend for increased plasma renin was observed (Table 2). These changes were generally consistent with the effects expected following administration of an MRA. Mean (SD) change from baseline in eGFR (ml/min/1.73 m^2) at day 28 was −2.5 (8) for AZD9977 and −4 (14) for spironolactone; these changes were generally small and not significantly different ($p = 0.851$; Table 2 and Figure 2d).

Baseline uACR values were low in both groups, and high variability was reported during the study with a trend toward reduction in both treatment groups of similar effect size. Microalbuminuria (30–300 mg/L, based on spot test) was observed at baseline in 15 patients (AZD9977, $n = 6$ [range 38–157 mg/L], and spironolactone, $n = 9$ [range 31–171 mg/L]). In relation to cardiovascular efficacy end points, there were no clinically significant changes in levels of plasma NTproBNP or in echocardiographic parameters with AZD9977, or differences compared with spironolactone, throughout the study.

Pharmacokinetic assessments

Steady-state plasma concentrations of AZD9977 and canrenone, the active metabolite of spironolactone, were reached within 1 week, with C_{trough} values within the expected range for the administered doses of AZD9977 and spironolactone.[20,21] The geometric mean (coefficient of variation %) C_{trough} for AZD9977 was 91.4 nmol/L (309%) and 243 nmol/L (238%) after 100 and 200 mg once daily dosing, respectively. C_{trough} values for canrenone following spironolactone 25 and 50 mg once daily dosing, were 132 nmol/L (163%) and 226 nmol/L (246%), respectively.

Safety and tolerability

A higher frequency of AEs was reported in the AZD9977 group (19 AEs in 13 patients [39.4%]) compared with the spironolactone group (11 AEs in 6 patients [17.1%]), but no clear pattern could be discerned towards the types of AE reported (Tables 3 and 4). Most AEs were mild in intensity with no severe AEs reported in either group. Five patients had AEs considered by the investigator as related to study treatment: three patients (9.1%) on AZD9977 had a total of five AEs considered related to study drug (single case reports of diarrhea, headache, hypotension, nausea, and pruritus); two patients (5.7%) on spironolactone had AEs considered related to study drug (one renal failure and one renal impairment).

One patient in the AZD9977 group experienced a serious AE (SAE) of syncope. This was considered not related to treatment and resolved without dose adjustment of study drug and following administration of fluids plus adjustment of concomitant medications. The patient completed the study with no further AEs.

Overall, three patients discontinued treatment due to an AE, one in the AZD9977 group (diarrhea), and two in the spironolactone group (renal failure, $n = 1$ and renal impairment, $n = 1$; Figure 1). No patients discontinued due to hyperkalemia ($sK^+ \geq 5.6$ mmol/L). Changes in eGFR were generally small. At around Day 28, a median decrease in eGFR of 3 ml/min/1.73 m^2 was seen for AZD9977 ($n = 26$) and of 7 ml/min/1.73 m^2 for spironolactone ($n = 27$), which showed improvement at follow-up/after last dose (follow-up visit, or unscheduled visit after last dose). In total, the number of patients who were either discontinued from study treatment due to a reduction in eGFR greater than or equal to 25% (day 1) compared with baseline, or who were identified as having a reduction in eGFR greater than or equal to 25% (day 1) compared with baseline but not discontinued as per protocol, was four for AZD9977 and six for spironolactone.

There were no clinically relevant trends suggestive of a safety concern for AZD9977 regarding laboratory safety measures, vital signs, ECG, and heart rate. In general, systolic BP and diastolic BP showed a decrease from baseline in both treatment groups; at around day 28 of treatment, a mean decrease in systolic BP of 9 mmHg was seen in the AZD9977 group ($n = 26$) and of 2 mmHg in the

TABLE 3 Number of subjects with AEs (any category, safety analysis set)

AE category	Number (%) of patients	
	AZD9977 ($N = 33$)	Spironolactone ($N = 35$)
Any AE	13 (39.4)	6 (17.1)
Mild	10 (30.3)	4 (11.4)
Moderate	3 (9.1)	2 (5.7)
Any AE with fatal outcome	0	0
Any SAE	1 (3.0)	0
Any AE leading to discontinuation of study drug	1 (3.0)	2 (5.7)
Any AE considered related to study drug	3 (9.1)	2 (5.7)

Note: Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.

Includes AEs with an onset date on or after the date of first dose.

Abbreviations: AE, adverse event; *N*, number of subjects in treatment group; SAE, serious AE.

TABLE 4 Adverse events by SOC/PT

AE preferred term	Number (%) of patients	
	AZD9977 (*N* = 33)	Spironolactone (*N* = 35)
Any AE	13 (39.4)	6 (17.1)
Cardiac disorders	2 (6.1)	0
Atrial fibrillation	1 (3.0)	0
Tachyarrhythmia	1 (3.0)	0
Gastrointestinal disorders	2 (6.1)	0
Diarrhea	1 (3.0)	0
Nausea	1 (3.0)	0
Vomiting	1 (3.0)	0
General disorders and administration site conditions	1 (3.0)	0
Edema peripheral	1 (3.0)	0
Infections and infestations	5 (15.2)	1 (2.9)
Lower respiratory tract infection	1 (3.0)	0
Nasopharyngitis	1 (3.0)	0
Upper respiratory tract infection	1 (3.0)	0
Urinary tract infection	1 (3.0)	0
Viral infection	1 (3.0)	1 (2.9)
Investigations	1 (3.0)	1 (2.9)
Alanine aminotransferase increased	1 (3.0)	0
Aspartate aminotransferase increased	1 (3.0)	0
Heart rate increased	0	1 (2.9)
Nervous system disorders	2 (6.1)	0
Headache	1 (3.0)	0
Syncope	1 (3.0)	0
Psychiatric disorders	0	1 (2.9)
Anxiety	0	1 (2.9)
Renal and urinary disorders	0	2 (5.7)
Renal failure	0	1 (2.9)
Renal impairment	0	1 (2.9)
Respiratory, thoracic, and mediastinal disorders	1 (3.0)	0
Dyspnea	1 (3.0)	0
Skin and subcutaneous tissue disorders	2 (6.1)	1 (2.9)
Dry skin	1 (3.0)	0
Pruritus	1 (3.0)	0
Skin swelling	0	1 (2.9)
Vascular disorders	1 (3.0)	1 (2.9)
Hypertension	0	1 (2.9)
Hypotension	1 (3.0)	0

Note: Subjects with multiple events in the same preferred term are counted only once in that preferred term. Subjects with events in more than one preferred term are counted once in each of those preferred terms.

Includes AEs with an onset date on or after the date of first dose.

Percentages are based on the number of subjects in the treatment group.

Abbreviations: AE, adverse event; N, number of subjects in treatment group; PT, preferred term; SOC, system organ class.

spironolactone group (n = 27). Reduction in systolic BP was numerically larger with AZD9977 than for spironolactone, and occurred from a different baseline systolic BP (AZD9977 144 mmHg; spironolactone 134 mmHg).

DISCUSSION

In this phase Ib study in patients with HF with mildly reduced mid-range or preserved LVEF and moderate renal impairment, the effect of spironolactone on sK^+ elevation was less than expected and not different from the effect observed with the selective mineralocorticoid receptor modulator AZD9977. In addition, AZD9977 was generally well tolerated at the doses investigated (once-daily AZD9977 100 mg, uptitrated to AZD9977 200 mg) and no discontinuations due to hyperkalemia occurred with either treatment.

Blockade of aldosterone-mediated urinary Na^+ reabsorption by MRAs, and consequent reduction in urinary K^+ excretion, is considered a key contributory factor for MRA-mediated elevation in sK^+. This predisposes patients to a subsequent risk for hyperkalemia and restricts the use of MRAs in patients with HF and renal impairment.[22] In the present study, changes in plasma renin and aldosterone levels were similar in both treatment groups and consistent with administration of an MRA, indicating effective target engagement.[16] The effects of AZD9977 and spironolactone on sK^+ and FE-K were numerically similar, with no statistically significant differences observed. In terms of nonsignificant trends, at day 14, when all randomized patients were receiving equipotent doses of spironolactone (25 mg daily) or AZD9977 (100 mg daily), we observed a numerically smaller increase in sK^+ in those patients receiving

AZD9977 compared with spironolactone, and a numerically greater effect on FE-K with AZD9977. This is in line with preclinical data and the proposed potential differential pharmacological effect consistent with the modulator mode of action of AZD9977 and a predicted lower risk of hyperkalemia.[16] However, larger trials of AZD9977 are required to determine whether these observations represent a real effect and can be reproduced. We also recognize that dietary Na^+ and K^+ intake were not tightly controlled in this study, which impacts any conclusions that can be drawn from the fractional urinary excretion data. Furthermore, the kidneys are not the only organ involved in potassium homeostasis in the human body. The gastrointestinal tract also plays an important role which was not explored in this study. Nevertheless, the findings are in line with the proposed mechanism of action of AZD9977 in the kidneys and supports further evaluation of AZD9977 in appropriately sized and designed clinical trials.

With regard to exploratory biomarkers of corticosteroid axis modulation, neither treatment resulted in a significant change in plasma cortisol and no statistically significant differences were observed between treatments. However, up to day 28, spironolactone treatment resulted in greater numeric increases in plasma cortisol with AZD9977 that appeared to be dose dependent. Secondary mineralocorticoid receptor activation, by spill-over of cortisol signaling, may potentially contribute to the observed difference in FE-K^+ seen between treatment with spironolactone and AZD9977, but this requires further study.[23] There were no clinically significant changes over time or differences between study drugs for other exploratory end points, including other biomarkers or echocardiographic measurements, which likely reflects the small cohort and short duration of the study. With regard to safety, AZD9977 was generally well tolerated in this study, with few discontinuations due to changes in renal function, few SAEs, and no patterns seen in the type of AE reported. We observed a numeric reduction in uACR in both treatment groups, with no statistically significant difference within or between the treatment groups.

Limitations

This was an open-label designed study comparing the effect of AZD9977 and spironolactone on sK^+ in patients with HF and renal impairment. Sample size was determined under the assumptions that we would see a mean increase in sK^+ of at least 0.43 mmol/L in the patients treated with 50 mg spironolactone at day 28. As this criterion was not met, the study would have required a larger sample size to yield a conclusion on the primary end point, and further studies will be needed to assess this in more detail. Given the variability of renal function over time, use of an average of screening and baseline eGFR values might have provided a more reliable estimate of instances of fall in eGFR greater than 25% during dosing of study treatments. The study was also terminated early due to the emergence of the coronavirus disease 2019 (COVID-19) pandemic and concern that patients may not be able to attend site visit, thus resulting in a small number of patients either in screening or recently randomized being discontinued from the trial. Patients more than halfway through the study were not affected by the early termination and were followed up as planned. Early termination of the trial is unlikely to have had any significant impact on our findings.

In summary, although a smaller than expected increase in sK+ was seen during spironolactone treatment, invalidating the primary assumption on sK^+ and rendering the statistical analysis of our primary end point inconclusive, this study demonstrated good target engagement for AZD9977 based on a similar increase in serum aldosterone concentration compared with spironolactone. The trend toward greater renal FE-K^+ with AZD9977 is consistent with the proposed MR modulator mode of action based on preclinical data; however, further studies are required to validate the findings and confirm the mode of action of AZD9977. The observation of a numerically greater reduction of systolic BP in the AZD9977 compared with the spironolactone group was interesting and possibly due to patients in the AZD9977 group being more hypertensive. If this finding is reproduced in future studies, this could represent a clinically beneficial effect for patients with cardiovascular/renal disease. AZD9977 was well tolerated with no safety concerns identified. Overall, this study supports further evaluation of AZD9977 in patients with HF and renal impairment.

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript. I.B.S., A.G., A.W., P.J.G., J.H.-G., J.H., S.J., A.R., J.S., K.B., and J.M. designed the research. I.B.S., A.G., A.R., J.M., J.S., A.W., J.H., and L.W. performed the research. A.G., J.H.-G., A.R., J.S., J.M., J.H., A.W., P.J.G., and S.J. analyzed the data.

ACKNOWLEDGMENTS

The authors would like to thank the patients, their families, and all investigators involved in this study. Medical writing support was provided by Shavonn Harper, PhD, and Carl V Felton, PhD, and editorial support was provided by Michelle Seddon, Dip Psych, of Paragon, UK/US, and was funded by AstraZeneca.

FUNDING INFORMATION

This study was funded by AstraZeneca.

CONFLICTS OF INTEREST

I.B.S. has received honoraria from Boehringer Ingelheim, Novartis, Merck, and Vifor for participation in educational events or advisory boards, and institution research funding from AstraZeneca, Boehringer Ingelheim, Merck, Novartis, and Vifor. A.G., P.J.G., L.W., J.H.-G., J.H., S.J., A.R., J.S., K.B., J.M., and A.W. are employees of AstraZeneca and may own stock or stock options.

DATA AVAILABILITY STATEMENT

Data underlying the findings described in this manuscript, and related information contained in the study protocol, may be obtained in accordance with AstraZeneca's data sharing policy described at: https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Squire IB, Gabrielsen A, Greasley PJ, et al. Effect of AZD9977 and spironolactone on serum potassium in heart failure with preserved or mildly reduced ejection fraction, and renal impairment: A randomized trial. *Clin Transl Sci*. 2022;00:1-12. doi:10.1111/cts.13377