NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Sodium zirconium cyclosilicate for treating hyperkalaemia [ID1293]

Contents:

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Pre-meeting briefing

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Key issues: treatment pathway and clinical effectiveness

- What serum potassium concentration needs treatment as an emergency in hospital?
- At what potassium concentration would sodium zirconium cyclosilicate (SZC) be started if used in a chronic setting?
- Will SZC avoid the need for a low potassium diet and change the management of drugs that raise potassium (i.e. RAASi) as company suggest?
- How long would maintenance treatment with SZC last?
- Is the placebo group of ZS-004 generalisable to people having current standard care after initial correction of hyperkalaemia?
  - In absence of trial data, is there observational evidence that a low potassium diet lowers the chance of having a subsequent hyperkalaemia event? Does low adherence to the diet affect this?
- 6% of people in the maintenance phase of ZS-005 had hypokalaemia (serum potassium <3.5 mmol/L). How would hypokalaemia in people taking SZC be monitored and managed? What are the risks of hypokalaemia?

Key issues: cost effectiveness

- Should the cost effectiveness of SZC in people with heart failure and chronic kidney disease be considered separately?
- The SZC trials only provide data on the surrogate outcomes of serum potassium and renin-angiotensin-aldosterone-system inhibitor (RAASi) use and not for the effect of SZC on survival. The company has modelled the effect of differences in these surrogate outcomes on clinical endpoints using observational data. What factors affect these relationships? How robust are these observational data and risk estimates?
- Company model does not include association between taking RAASi and increased serum potassium, potentially a bias in favour of SZC because more patients stay on RAASi. Are ERG estimates of 0.23 mmol/L or 0.1mmol/L higher serum potassium while taking RAASi appropriate?
- Company suggest that model overestimates treatment effect of standard care (because people in placebo arm of ZS004 had prior SZC) making the estimate of the relative benefit of SZC in reducing serum potassium pessimistic compared with standard care. Is this valid? Would a potential overestimation of effectiveness of standard care cancel out potential bias in favour of SZC from excluding RAASi- potassium level association?
- Company and ERG have different preferred assumptions for: management of RAASi for people taking SZC, utility values for chronic kidney disease health states, cost of managing RAASi and drug wastage. What does committee prefer?
- Is a 52 week time horizon in the acute setting appropriate? Is it appropriate to then assume that these patients are then managed in the chronic setting?

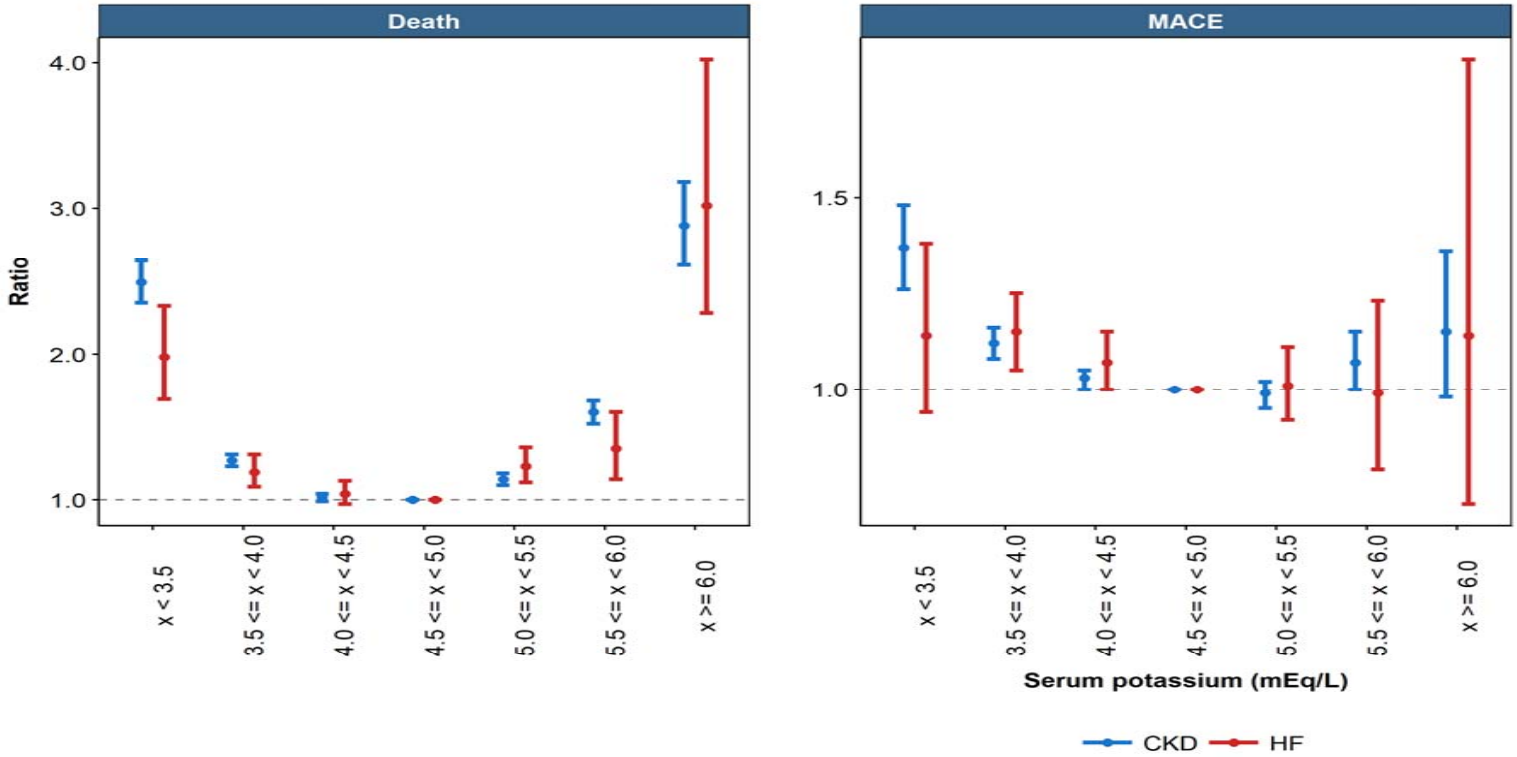
Hyperkalaemia

- **Hyperkalaemia:** high levels of potassium in the blood (normal range 3.5 to 5.0 mmol/L). Definitions of high moderate and mild levels vary.
  - Company definition of hyperkalaemia is >5.0 mmol/L and the company suggests hyperkalaemia needing treatment is >5.5 mmol/L
- **Symptoms** include muscle weakness, muscle stiffness or fatigue, however many people have no symptoms
- **Severe hyperkalaemia** can cause irregular heart beat, leading to cardiac arrest and death
- **Risk factors for hyperkalaemia include**:
  - Chronic kidney disease
  - Medicines, including those used to treat high blood pressure such as:
    - renin-angiotensin aldosterone system inhibitors (**RAASi**) including angiotensin-converting enzyme (**ACE**) inhibitors, angiotensin II receptor blockers (**ARB**), direct renin inhibitors (e.g. aliskerin)
    - aldosterone-receptor antagonists (e.g. spironolactone)
    - other potassium-sparing diuretics (e.g. amiloride)
    - beta-blockers (e.g. propranolol, metoprolol, atenolol – via inhibition of renin release)
  - Other medicines (heparin, NSAIDS, COX-2 inhibitors etc.)

Hyperkalaemia associated with increased risk of major acute cardiac events and death

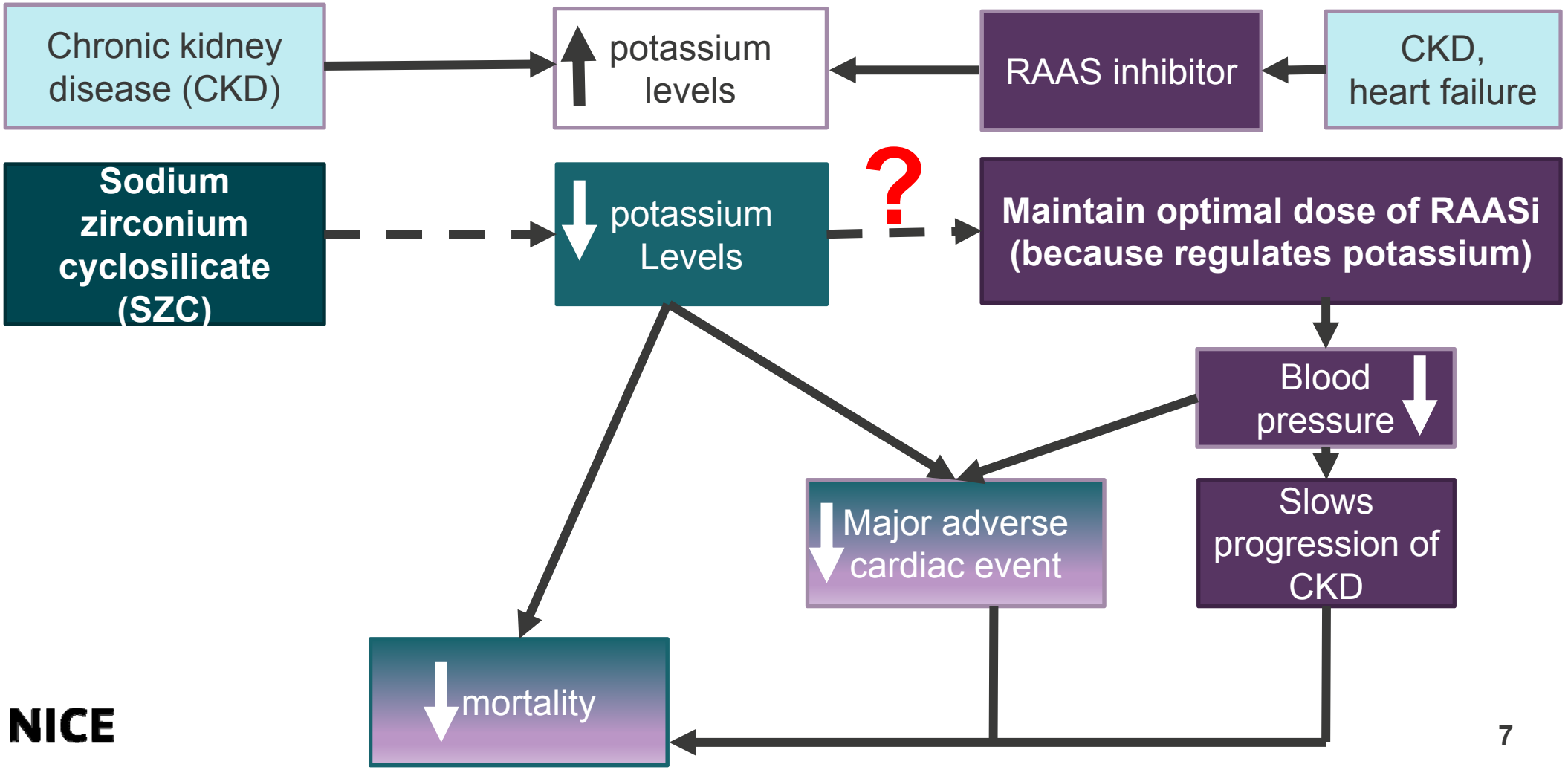
UK Clinical Practice Research Datalink risk equation study: adjusted incidence rate ratios for mortality and Major Adverse Cardiac Events (MACE) by levels of serum potassium in chronic kidney disease (blue, CKD) and heart failure (red, HF).

Risk of death increased if serum potassium high (hyperkalaemia) or low (hypokalaemia) . The normal range of serum potassium is considered to be ≥ 3.5 mmol/L and ≤ 5.0mmol/L)



Relationship between potassium levels, RAAS inhibitor use and mortality

Relationship between serum potassium and mortality complex with many interacting factors



Treatment options for hyperkalaemia

Low-potassium diet

Active treatments to reduce serum potassium

Stop medicines that cause hyperkalaemia

Potassium binding agents:

<u>Cation exchange</u>

- Sodium polystyrene sulphonate
- Calcium polystyrene sulphonate (calcium resonium)
- Patiromer*

<u>Potassium ion exchange</u>

Sodium zirconium cyclosilicate*

Treatments to increase uptake of potassium into cells

- Insulin glucose infusions ± salbutamol

Potassium-binding agents for hyperkalaemia

- Potassium-binding agents reduce excess levels of potassium ions by capturing potassium ions, allowing them to be excreted from the body
- Current potassium-binding options for hyperkalaemia are non-selective cation-exchange resins (e.g. calcium- or sodium-polystyrene sulfonate)
- Professional group statement (Renal Association) noted that calcium polystyrene sulfonate (Resonium) is the cation treatment used in UK
- Sodium zirconium cyclosilicate (SZC) is designed to mimic structure of potassium ion channels and is highly selective for potassium ions over other cations (e.g. calcium and magnesium ions)

Patient perspectives

- **Symptoms are dangerous and distressing**
  - "hyperkalaemia can make a person feel sick, shake have a racing heart and feel disorientated"
- **Current treatments are not adequate**
  - Extremely unpalatable and patients are looking forward to new treatment options
- **Dietary intervention not adequate and dietary restrictions not always effective**
  - A low potassium diet is very demanding especially as it restricts common items like bananas, coffee and chocolate and alongside other restrictions on dairy food if phosphate levels are too high accompanied by the very common liquid restriction of 500 ml/day
- **Living with someone who develops hyperkalaemia is difficult for partners/carers especially if they are struggling to work out what to buy and cook**
- **Groups of people who may have particular need:**
  - people on dialysis or with advanced chronic kidney disease (CKD 5), but not yet on dialysis. People cannot process potassium between dialysis days and are at risk of having a hyperkalaemia event
  - "for [people] on conservative care [being looked after in the community]... often reluctance to prescribe specialist drugs by non-specialists so patients can lose out"

Innovation: proposed benefits of sodium zirconium cyclosilicate (SZC)

Comments from the Royal College of Pathologists, Renal Association and company included:

- Company: represents a ‘step-change in the management of patients with HK’
- All agreed may allow people ‘to continue and optimise treatment on renin-angiotensin-aldosterone system inhibitor/ mineralocorticoid-receptor antagonist (RAASi/MRA) therapy’ although it was noted that the optimal management of RAASi in people with hyperkalaemia is not fully established
- Controls potassium levels ‘without the need to adopt a restrictive low-potassium diet’ (company). Renal Association suggested SZC would be used alongside diet restriction
- Renal Association and Royal College of Pathologists: may reduce unnecessary hospital admissions
- Company: ‘only potassium-binding agent with rapid onset of action (within 1 hour)’
- Renal Association: current potassium binding treatment with resonium is ineffective and poorly tolerated and has significant complications such as constipation, a major issue in chronic kidney disease

Decision problem (1)

	NICE scope	Company
Population	Adults with hyperkalaemia (HK)	Adults with hyperkalaemia in a comorbid patient population comprising chronic kidney disease (CKD) (stage 3–5) or heart failure (HF)
Comparator	Standard care. This includes a low potassium (K^+) diet with or without agents that reduce levels of potassium in the body	Acute setting: Intermittent use of calcium resonium (with some patients receiving a repeat dose of insulin-glucose) Chronic setting: no therapy administered
Rationale for difference from scope	All patients are managed with lifestyle interventions for the background maintenance of serum potassium (e.g. dietary intervention and modification of concomitant medications, such as RAASi)	

Abbreviations RAASi, Renin-angiotensin-aldosterone system inhibitor

Decision problem (2)

	NICE scope	Company
Outcomes	• Serum potassium level • Use of RAASi therapy • Mortality • Time to normalisation • AEs of treatment • Health-related quality of life	• Serum potassium level • Time to normalisation • Adverse events of treatment • Use of RAASi therapy (exploratory endpoint)
Rationale for difference from scope	Mortality was not an outcome in the clinical trial programme for SZC as this would be confounded by underlying comorbidities. HRQoL was not collected in the clinical trial programme for SZC.	
Subgroups to be considered	• People with acidosis • People with acute HK • People with CKD • People with HF	• Base case analysis includes adults with HK and comorbidity for CKD or HF • People with acute HK
Rationale for difference from scope	The clinical trial programme for SZC did not evaluate people with acidosis.	

Abbreviations: SZC sodium zirconium cyclosilicate; HK, hyperkalaemia; CKD, chronic kidney disease; HF, heart failure; RAASi, Renin-angiotensin-aldosterone system inhibitor; HRQoL health related quality of life

Sodium zirconium cyclosilicate (AstraZeneca)

Mechanism of action	Sodium zirconium cyclosilicate (SZC) is a non-absorbed, non-polymer inorganic powder with a uniform micropore structure that preferentially captures potassium in exchange for hydrogen and sodium cations.
Administration and dosage	SZC is a 5 g or 10 g powder for oral suspension **Correction phase (acute phase)** Recommended starting dose 10 g, 3 times daily. Normal potassium level typically achieved within 24-48 hours. Max treatment duration 72 hours. **Maintenance phase (chronic phase)** Recommended starting dose 5 g, once daily can be up titrated to 10 g, once daily or down titrated to 5 g, once every other day to maintain normal K+ level. Can be taken with/without food and along with other medications
Marketing authorisation	For “the treatment of hyperkalaemia in adult patients”
Cost	SZC 5 g = ****; SZC 10 g = **** **Treatment cost in the acute setting:** First HK event (over 28 days of treatment) = **** Subsequent HK event (over 28 days of treatment) = **** **Treatment cost in the chronic setting:** First HK event (over 28 days of treatment) = **** Subsequent HK event (over 52 weeks of treatment) = ****

Treatment pathway

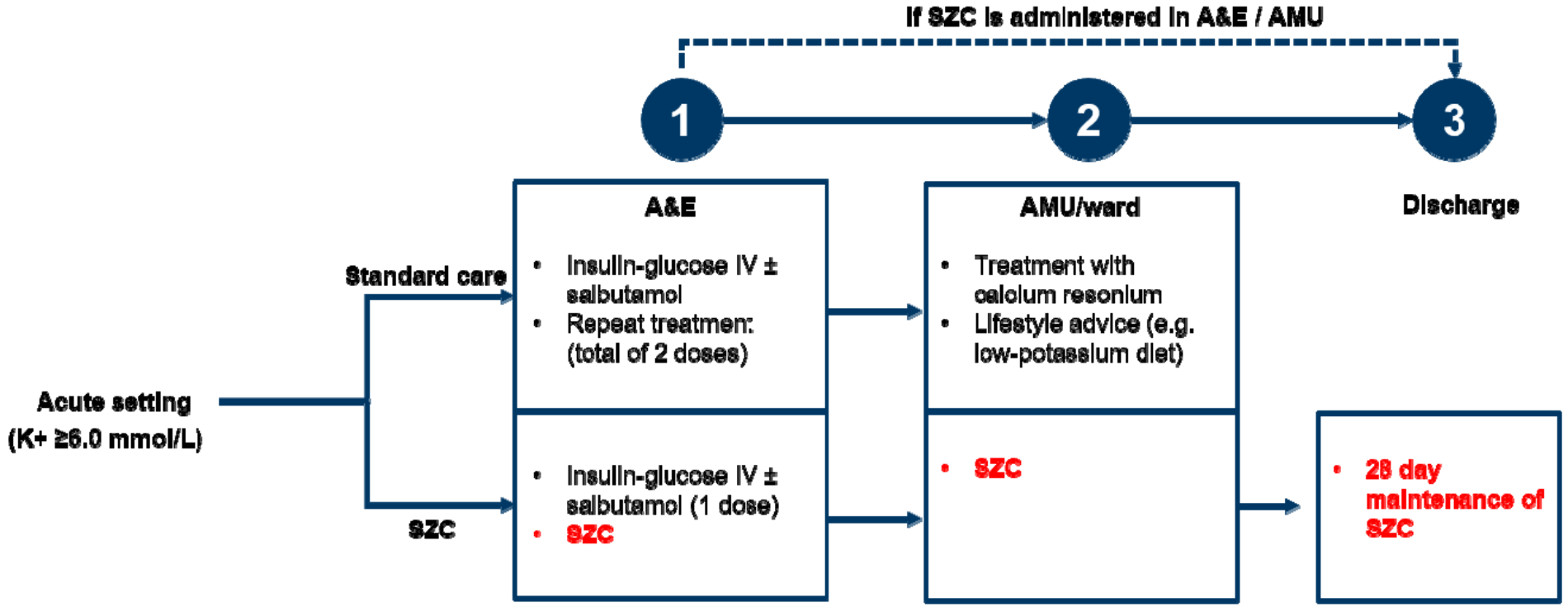
UK Renal Association guidelines for correction treatment of acute hyperkalaemia

- **Step 1**: **protect the heart**. Intravenous (IV) calcium salts (calcium chloride or calcium gluconate) should be given to in the presence of electrocardiogram evidence of hyperkalaemia
- **Step 2: shift potassium into cells**. Insulin-glucose by IV infusion should be used with salbutamol to treat moderate and severe hyperkalaemia (serum potassium ≥6.0 mmol/L)
- **Step 3: remove potassium from the body**. Cation-exchange resins such as calcium resonium should not used in the emergency management of severe hyperkalaemia, but may be considered in patients with mild-to-moderate hyperkalaemia (Serum potassium 5.5–6.4mmol/L). This is because they have a slow onset of action that limits their use in emergencies.
- **Step 4: monitor serum potassium (and blood glucose concentrations) closely** to assess efficacy of treatment and to look for rebound hyperkalaemia after the initial response to treatment wanes
- **Step 5: prevent recurrence of hyperkalaemia with the use of calcium resonium**

Treatment pathway: acute setting

Company:

- Presented the treatment pathway for people presenting in an **acute setting** and people presenting in a **chronic setting** separately **(see next slide)**
- Argue people presenting in acute setting (A&E) represent those with acute medical problems such as sepsis, dehydration/acute kidney injury, or pneumonia
- Suggest people presenting this setting have serum potassium (≥6.0 mmol/L) and need rapid reduction in serum potassium



Abbreviations: SZC sodium zirconium cyclosilicate; RAASi, Renin-angiotensin-aldosterone system inhibitor

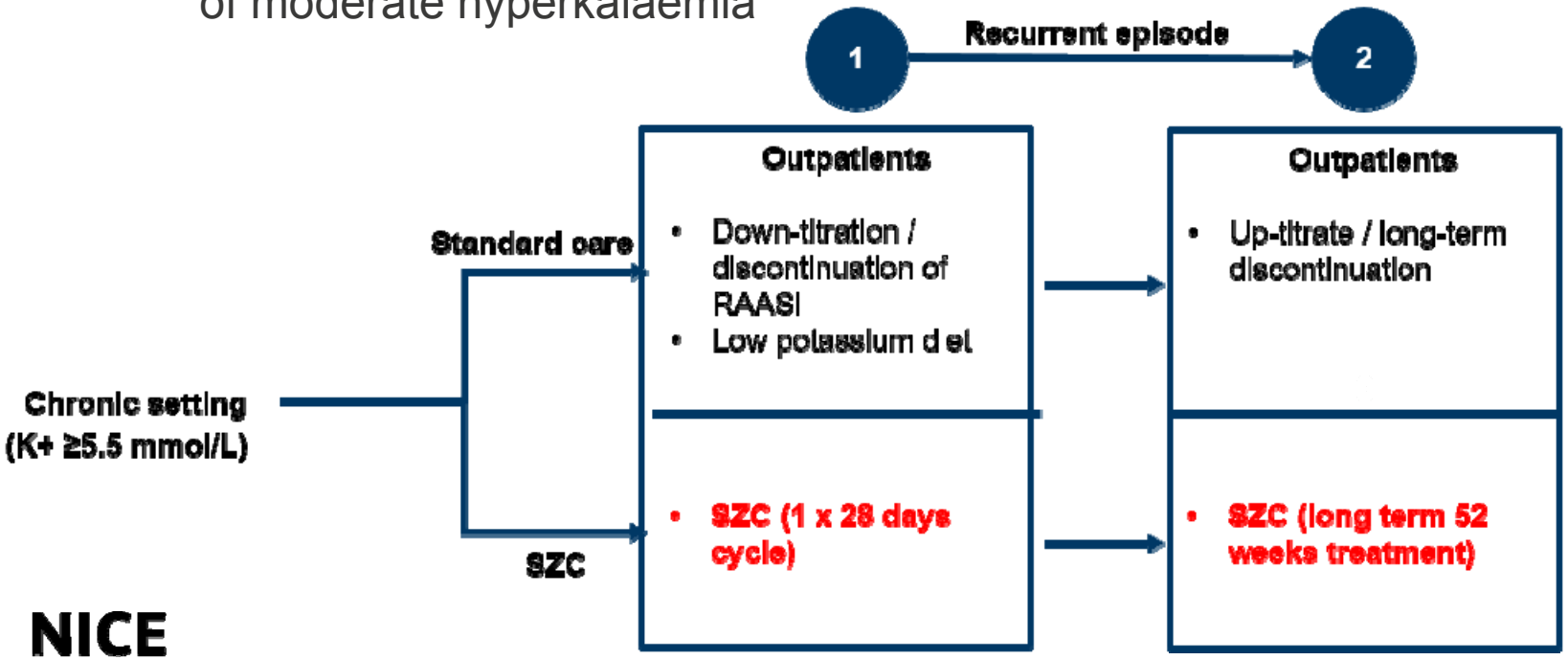
Treatment pathway: chronic setting

Company:

- People in chronic setting will have already been identified as having hyperkalaemia and will be regularly monitored in secondary care as outpatients
- People may start treatment if serum potassium ≥5.5 mmol/L

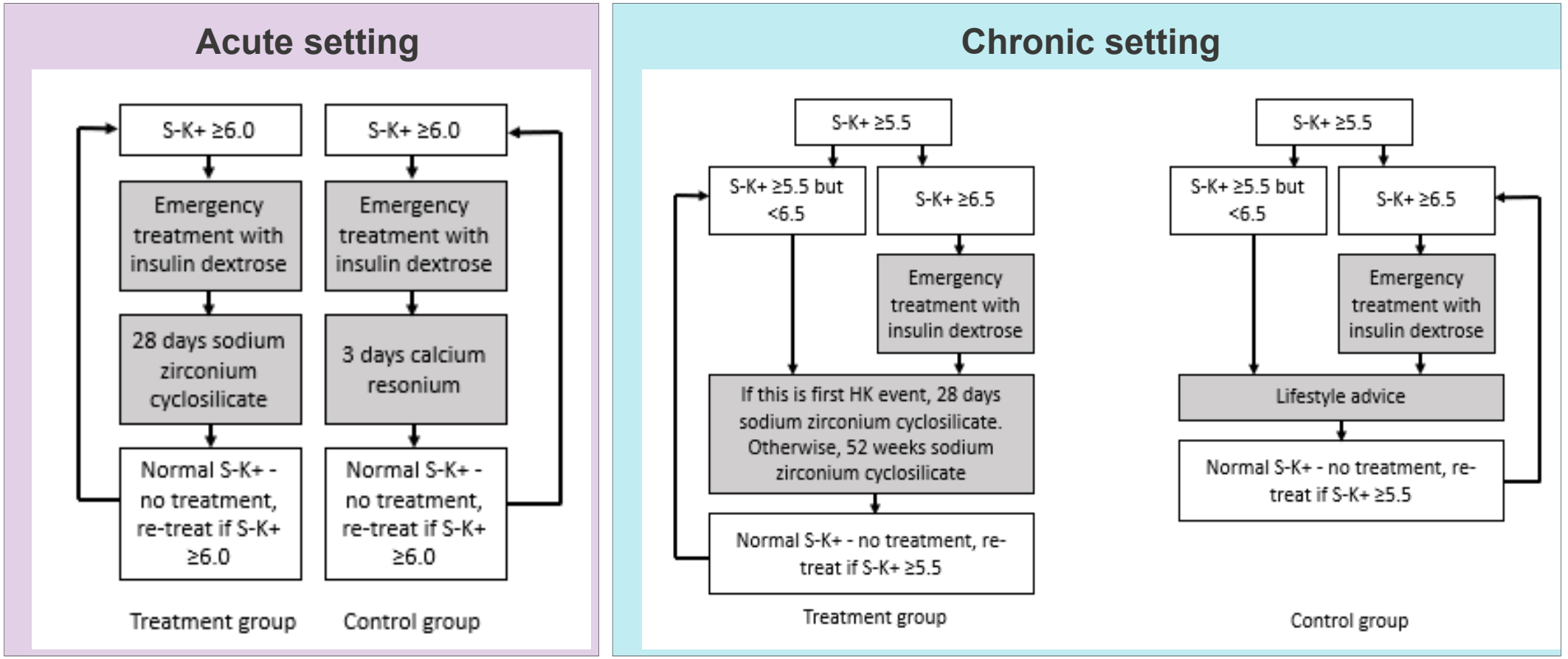
ERG:

- Clinical advice suggests that serum potassium level at which start treatment with SZC would vary by clinician and circumstances
  - possible that SZC would not be given until levels of >6.0 mmol/L unless RAASi treatment was being down-titrated or if patients were experiencing recurrent episodes of moderate hyperkalaemia



Abbreviations: SZC sodium zirconium cyclosilicate; RAASi, Renin-angiotensin-aldosterone system inhibitor

Treatment pathway and comparators in model - acute and chronic setting scenarios



- Clinical advice to Evidence Review Group (ERG): people with potassium >6.5 mmol/L but acutely unwell would also be admitted for emergency treatment, although they would usually require a shorter hospital stay
- ERG noted that populations are modelled separately, so that people initially treated in acute setting are not modelled as having maintenance treatment in the chronic (outpatient) setting

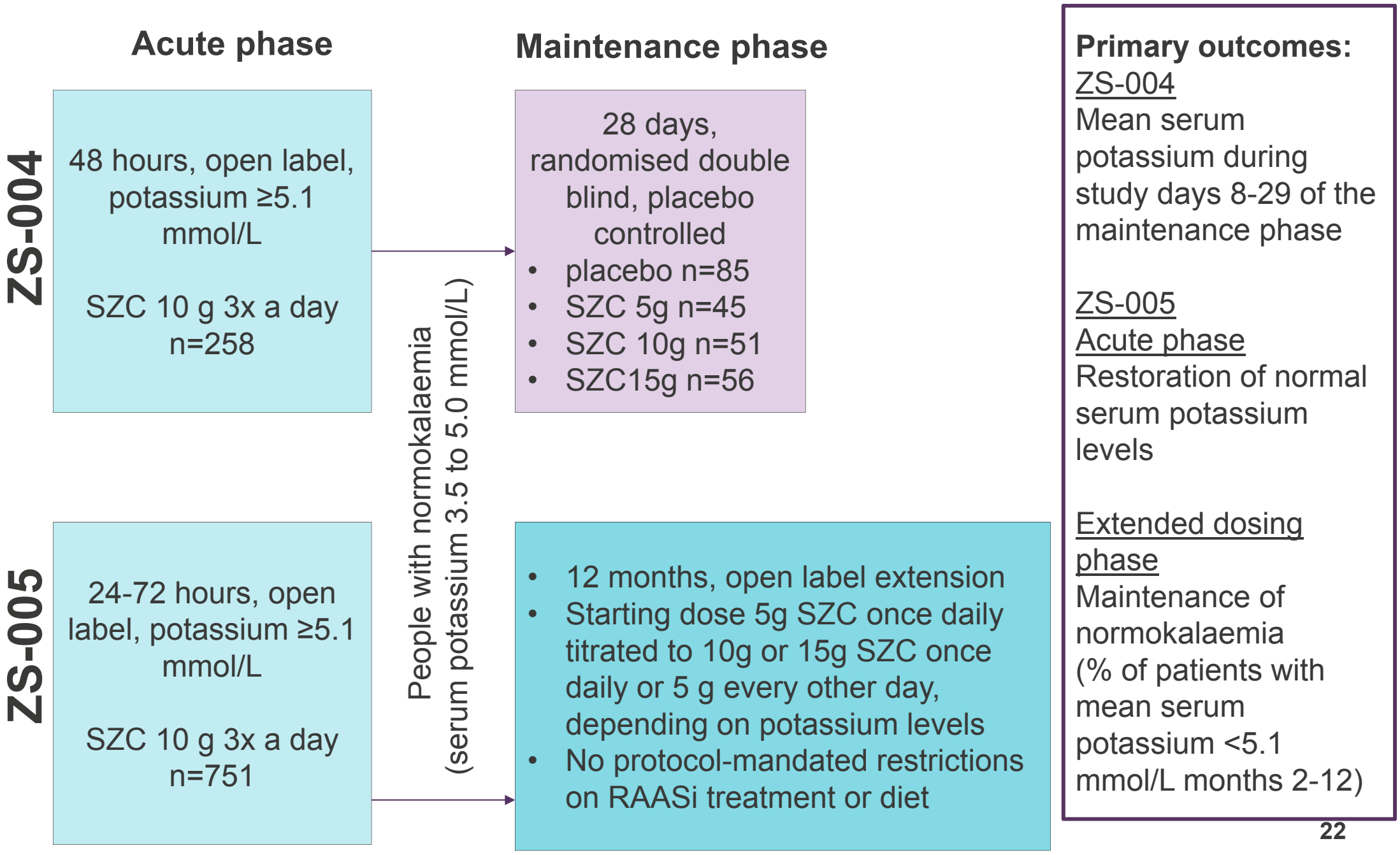
Use of renin-angiotenisin system inhibitors in people with hyperkalaemia

- People with chronic kidney disease and heart failure are offered renin-angiotensin–aldosterone system inhibitors (RAASi) which protect against mortality, worsening of chronic kidney disease and major adverse cardiac events
- The use of RAASi is carefully managed in people with hyperkalaemia because RAASi increase the retention of potassium

Company submission: clinical advice on RAASi management in clinical practice	NICE CG 182: chronic kidney disease in adults: assessment + management
Chronic setting (where people have serum potassium ≥5.5 mmol/L) • Don't start RAASi if ≥5.0 • 80% of people down titrate and 20% discontinue if ≥5.5 to 5.9 mmol/L • Stop RAASi if ≥6.0 mmol/L **Acute** setting (where people have serum potassium (≥6.0) • Stop RAASi	• Measure serum potassium before starting RAASi in people with CKD, repeat measurements after 1 to 2 weeks and after each dose increase • Do not routinely offer a RAASi to people with CKD if pretreatment serum potassium ≥5.0 mmol/L • Stop RAASi if serum potassium increases to ≥6.0 mmol/L

Clinical effectiveness

Clinical effectiveness evidence: trials used in model



Availability of comparative data

	Source of evidence	
	Correction phase	**Maintenance/extended phase**
Intervention	• SZ-004 + SZ-005 (sodium zirconium cyclosilicate (SZC) for 48 hrs or 24-72 hrs respectively)	• SZ-004 up to 28 days of treatment with SZC • SZ-005 up to 52 weeks treatment with SZC
Comparator	• No comparator in trials • No data from separate studies presented for insulin glucose because "these are administered earlier in the treatment pathway [than SZC] and have different mechanisms of action and the timepoints at which outcomes measured differed from SZ-004 and SZ-005 trials" • No data presented for calcium resonium because available published evidence is not for dose used in UK	• Placebo (for up to 28 days) • No comparative data for days 29-365 • No comparative data presented for SZC vs. dietary modifications or reduction in RAASi

ERG comments: timing of administration and different mechanism of action not valid reason for not formally comparing SZC with temporising agents. However, lack of comparable time points at which outcomes were measured is a valid reason for an indirect comparison not being feasible.

Generalisability of ZS-004 and ZS-005

Generalisability of data from ZS-004 and ZS-005

- The majority of patients in ZS-004 and ZS-005 were from the USA, Australia and South Africa
- 10 patients in ZS-005 were from the UK (one site)
- **Clinical advice to the ERG**: patients in the "acute" phase in the included studies are not fully representative of real-world patients with acute hyperkalaemia because trials were carried out in an outpatient setting

Heterogeneity of ZS-004 and ZS-005

Company:

- Considered a meta-analysis of ZS-004 and ZS-005 infeasible, stating the studies are too heterogeneous
- In particular the clinical trial design:
  - different lengths of treatment with SZC in acute phase of ZS-004 and -005
  - maintenance/extended phase of ZS-004 and ZS-005 differed in whether SZC dose titration was permitted
  - duration of maintenance/extended phase of ZS-004 (28 days) and ZS-005 (52 weeks) differed

ERG:

- Noted an inconsistency between the clinical and cost effectiveness section of the company submission regarding whether the treatments received in the acute phase of ZS-004 and ZS-005 were similar enough to pool data from this phase of the trials
- However, agreed that it is not possible to conduct a meta-analysis of ZS-004 and ZS-005 due to the lack of comparator arm in ZS-005

Baseline characteristics in ZS-004 & ZS005

Characteristic	ZS-004 SZC 10 g (acute phase) (n=258)	ZS-005 Overall SZC group (n=751)
Age, mean (SD)	64.0 (12.7)	63.6 (13.03)
Male, n (%)	149 (57.8)	448 (59.7)
Serum potassium baseline, n (%)		
<5.5	119 (46.1)	287 (38.2)
5.5 to <6.0	100 (38.8)	338 (45.0)
≥6.0	39 (15.1)	126 (16.8)
eGFR at baseline, n (%)		
<60 mL/min	179 (69.4)	552 (73.5)
≥ 60 mL/min	72 (27.9)	190 (25.3)
Comorbidities, n (%)		
Chronic kidney disease	169 (65.5)	513 (58.3)
Heart failure	94 (36.4)	285 (37.9)
Diabetes mellitus	170 (65.9)	471 (62.7)
Use of RAASi medication, n (%)	180 (69.8)	383 (51.0)

 Abbreviations: SZC sodium zirconium cyclosilicate; RAASi, Renin-angiotensin-aldosterone system inhibitor

ZS-005: restoration of normal serum potassium in the acute/correction phase

- Normal serum potassium defined as between 3.5 mmol/L and 5.0 mmol/L
- This was a primary outcome in ZS-005

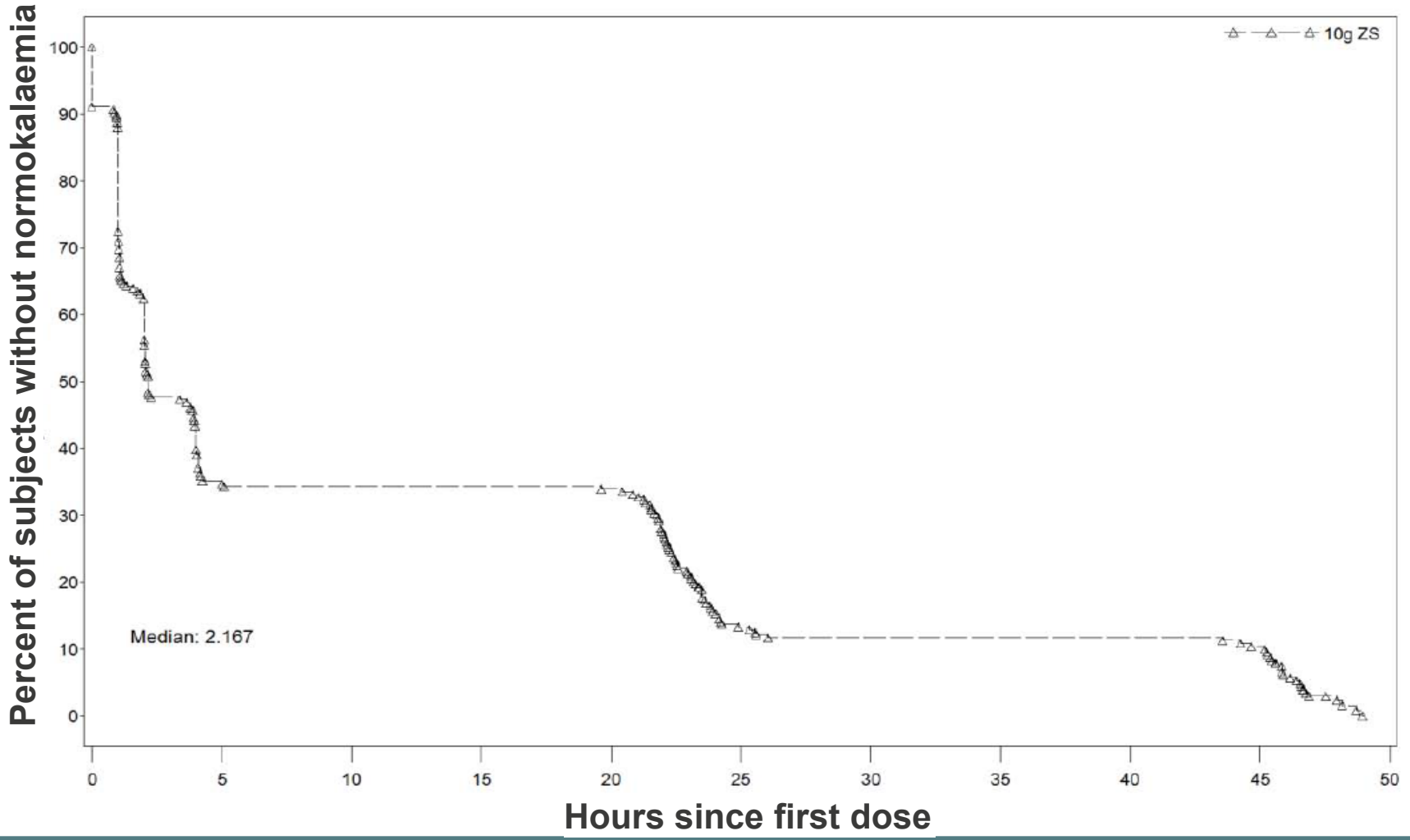
Acute phase ZS005	SZC 10 g 3 x daily (N=749)					
	Primary outcome definition of normal serum potassium			Wider definition of normal serum potassium		
	S-K 3.5–5.0 mmol/L inclusive			S-K 3.5–5.5 mmol/L, inclusive		
	n/N	Proportion	95% CI	n/N	Proportion	95% CI
24 hours	494/748	0.66	0.63 to 0.69	692/748	0.93	0.90 to 0.94
48 hours	563/748	0.75	0.72 to 0.68	732/748	0.98	0.97 to 0.99
72 hours/last	583/748	0.78	0.75 to 0.81	738/748	0.99	0.80 to 0.99

- For comparison in ZS-004: proportion with normalised serum potassium at:
  - 24 hrs: 66.1% (168/254)
  - 48 hrs: 88.0% (221/251)
- This was a secondary outcome in that study

 Abbreviations: SZC sodium zirconium cyclosilicate; S-K, serum potassium

ZS-004: time to serum potassium normalisation in acute/correction phase

Secondary outcome in ZS-004



Company:

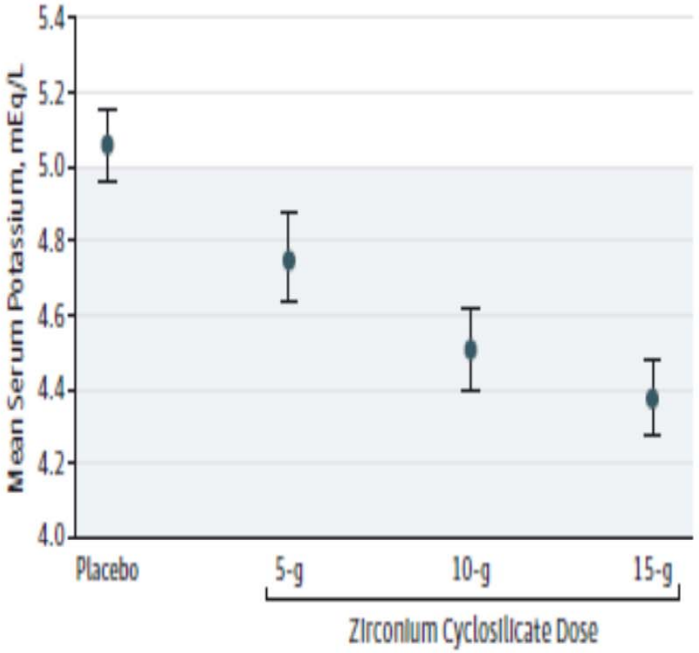
- Statistically significant and meaningful decrease from baseline at 1 hour after first dose of SZC
- Median time to normalisation (potassium 3.5 to 5.0 mmol/L) 2.17 hours after first SZC dose

ZS-004:mean serum potassium during maintenance phase study days 8-29

Primary outcome in ZS-004

Mean serum potassium levels in randomised phase (days 8–29) by dose

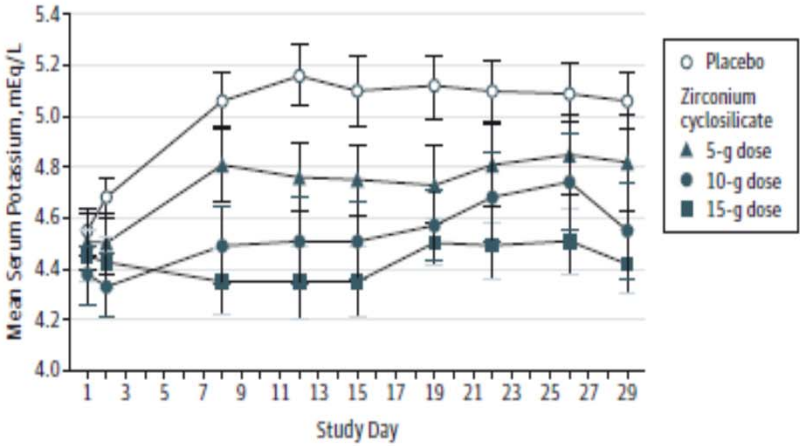
A



No. of patients	82	45	50	54
Mean baseline potassium, mEq/L	5.55	5.53	5.58	5.55

Serum potassium levels during the randomised phase by study day

B



No. of patients									
Placebo	82	81	81	80	80	78	77	74	73
5-g dose	45	45	45	44	44	43	43	42	39
10-g dose	50	49	50	47	47	47	45	45	38
15-g dose	54	54	54	53	52	51	51	51	43

- SZC enabled maintenance of potassium levels between 3.5 and 5.0mmol/L from days 8-29
- Mean serum potassium statistically significantly lower than placebo ($p \leq 0.0001$) for each dose

NICE

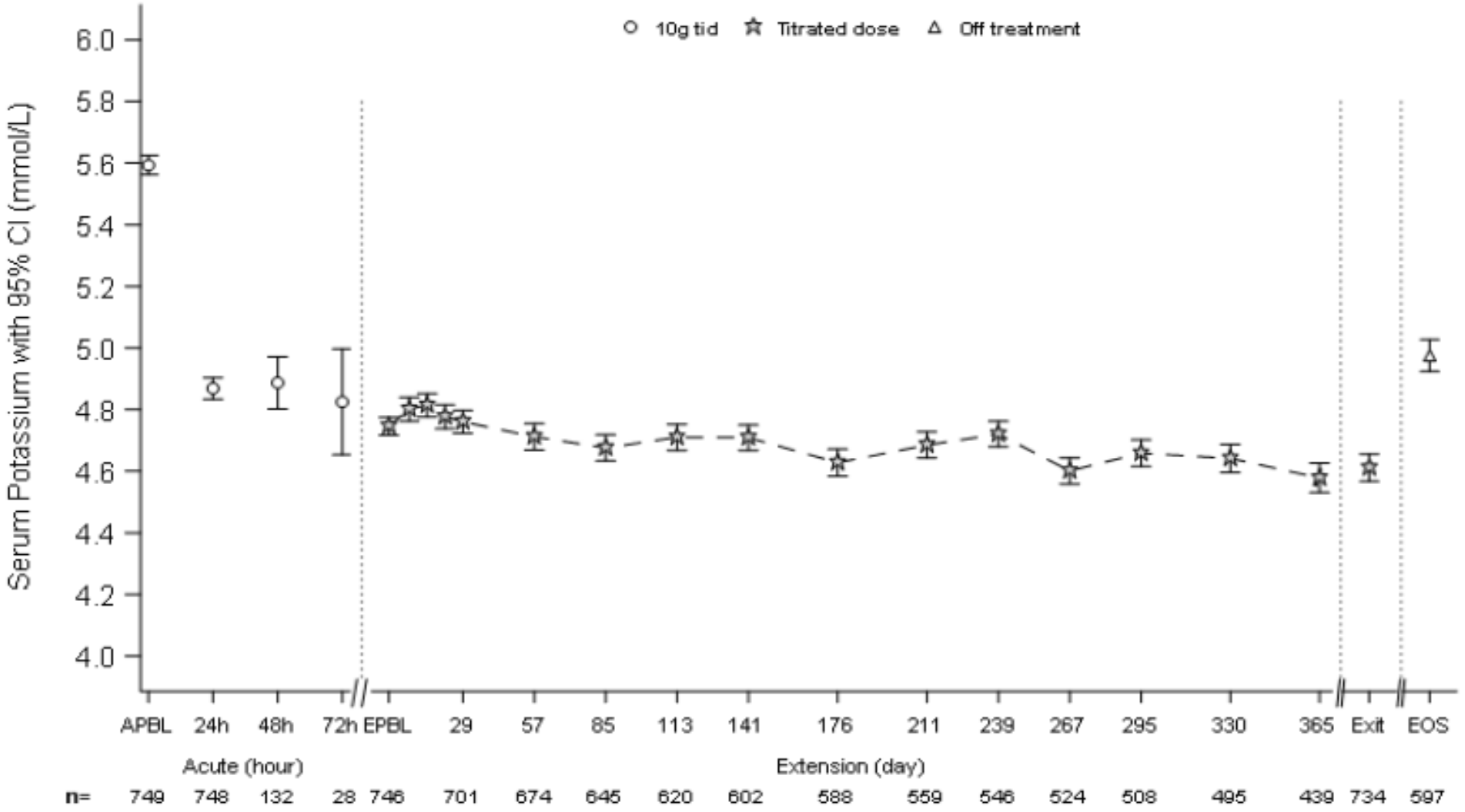
ZS-005: mean serum potassium in extended dosing phase

Proportion of patients with mean serum potassium values ≤ 5.1 (primary outcome in ZS-005) or ≤ 5.5 mmol/L across extended dosing phase (days 85–365)

– intention to treat population

	SZC daily (N=734)		
	n/N	Proportion	95% CI
Proportion with mean serum potassium ≤ 5.1 mmol/L	571/646	0.88	0.86 to 0.91
Proportion with mean serum potassium ≤ 5.5 mmol/L	638/646	0.99	0.98 to 1.00

ZS-005 extended dosing phase: mean serum potassium over time



ZS-005 extended dosing phase: RAASi use

Start of acute phase (n, %)		Extended dosing phase (n, %)	
On RAASi	****	Continued same dose	****
		Increased dose	****
		Decreased dose	****
		Stopped	****
Not on RAASi	****	Started RAASi	****

- Among the patients who were on RAASi during the extended dosing phase, the mean serum potassium at acute phase baseline was **********
- Following acute phase dosing, the mean serum potassium among these patients at the extended dosing phase baseline was within the normal range **********

Adverse events

Adverse events (AEs), n (%)	ZS-004				ZS-005	
	Acute phase – SZC 10 g (n=258)	Extended dosing phase – 28 days			Acute phase – SZC 10 g (n=751)	Extended dosing phase – 52 weeks (n=746)
		Placebo (n=85)	SZC 5 g (n=45)	SZC 10 g (n=51)		
Any AE	20 (7.8)	27 (31.8)	24 (53.3)	15 (29.4)	31 (4.1)	489 (65.5)
Any treatment-related AE	6 (2.3)	7 (8.2)	3 (6.7)	3 (5.9)	7 (0.9)	90 (12.1)
Any severe AE	0	1 (1.2)	4 (8.9)	1 (2.0)	2 (0.3)	125 (16.8)
Death*	0	0	0	1 (2.0)	0	8 (1.1)
Serious AE	0	0	5 (11.1)	2 (3.9)	1 (0.1)	161 (21.6)
AE leading to discontinuation	1 (0.4)	0	4 (8.9)	0	2 (0.3)	102 (13.7)

- *No deaths were considered to be related to the study drug
- Most common adverse events in ZS-005 extended dosing phase were hypertension (11%), peripheral oedema (9.7%) and urinary tract infection (7.9%)

Stopping sodium zirconium cyclosilicate (SZC) early and dose modifications

Early stopping of study drug:

- 35.8% (n=44) in extended maintenance phase of ZS-004 trial (ZS-004 E, 11 months)
- 37.5% (n=280) in ZS-005 (12 months)
- **Clinical advice to ERG:**
  - people may be more likely to stop SZC because it is a powder/drink rather than a tablet
  - "Discontinuation of SZC could lead to potentially dangerous clinical scenarios if clinicians use SZC in order to use extra RAASi and the goal of SZC treatment is to protect patients from the risks associated with potassium-increasing drugs"

Dose modifications:

- Summary of product characteristics states:
  - Serum potassium levels should be monitored periodically during treatment. Monitoring frequency will depend upon a variety of factors including other medications, progression of chronic kidney disease and dietary potassium intake
  - If severe hypokalaemia should occur Lokelma (SZC) should be discontinued and the patient re-evaluated.
  - "In clinical trials 2.3% of patients developed hypokalaemia with a serum potassium value less than 3.5 mmol/L, which was resolved with dose adjustment or discontinuation of Lokelma"
- **Clinical advice to the ERG:** hyperkalaemia would be closely monitored and it is unlikely that SZC would need additional monitoring in the acute setting

ERG overall conclusions on clinical effectiveness evidence

- The clinical effectiveness evidence shows that sodium zirconium cyclosilicate (SZC) lowers serum potassium levels in the study population of chronic, stable patients versus placebo
- It does not provide direct evidence for:
  - SZC as plausible alternative for dietary modification or versus any active comparator (no narrative or formal data synthesis in the systematic review to compare SZC versus anything)
  - SZC efficacy or safety in acutely unwell patients

Cost effectiveness

Please note some of the company base case model assumptions were updated in response to the Evidence Review Group's clarification questions.
Only the company's final base case is presented here.

Company's modelling approach - overview

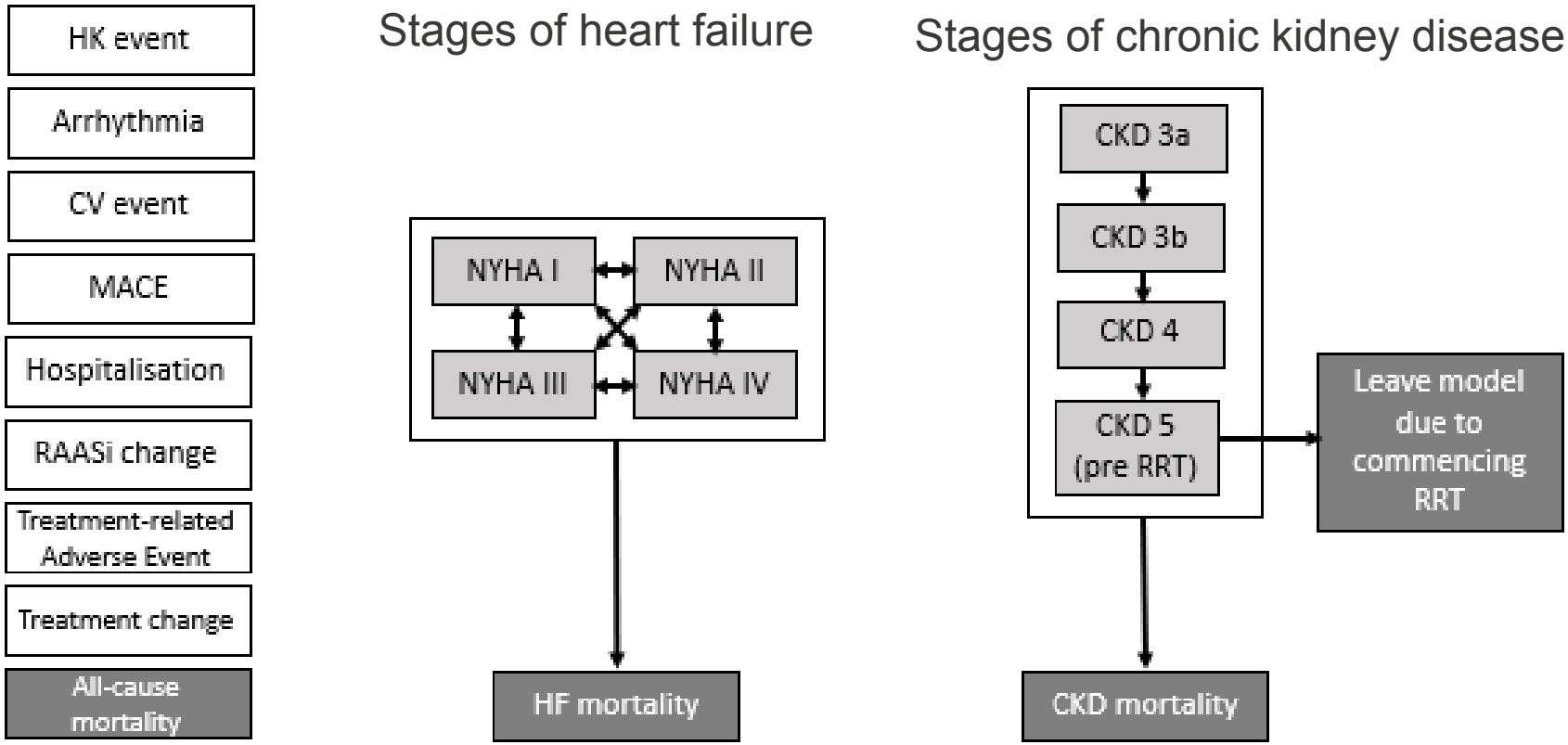
- Patient level simulation model. Rationale for this type of model:
  - clinical outcomes depend significantly on individual patient serum potassium levels
  - multiple co-existing and competing conditional risks of having an acute clinical event with hyperkalaemia
  - Markov approach would need unduly large number of health states
- Modelled population has either chronic kidney disease (pre-renal replacement therapy) or heart failure
- Acute setting hyperkalaemia (serum potassium ≥ 6.0 presenting in A&E) and chronic setting hyperkalaemia (serum potassium ≥ 5.5 presenting during routine follow up) modelled separately
  - treatment pathway and comparator (standard of care) differed in these scenarios
- Lifetime horizon used (80 years- maximum age in model 100 years). Max treatment duration (SZC or standard care) after initial correction of hyperkalaemia 28 days in acute setting, up to 1 year in chronic setting
- Cycle length in acute scenario (first 4 weeks) varies 1 day to 2 weeks, chronic management 28 days based on ZS-004 and ZS-005

Modelled population

	Chronic kidney disease	Heart failure	Source
% modelled population	64%	36%	ZS005
(alternative estimated of CKD/HF split suggested by company for scenario analysis)	89%	11%	Horne et al. 2017
Average age (years)	64	65	ZS004/5
Sex, % female	37%	37%	
eGFR mL/min/1.73m^2	31.63	68.14	
Taking RAASi	36%	70%	ZS005
Starting Serum potassium acute setting	≥ 6.0 mmol/L		Data from people meeting these criteria in ZS004/5
Starting Serum potassium chronic setting	≥ 5.5 mmol/L		

NICE CKD, chronic kidney disease; HF, heart failure; RAASi, Renin-angiotensin-aldosterone system inhibitor; eGFR, estimated glomerular filtration rate

Company's model structure



Absorbing state	Health state	Non-fatal event

- Assumed that patients have heart failure or chronic kidney disease
- Takes into account disease progression of heart failure and chronic kidney disease
- Patients can experience non-fatal events (listed in white boxes)
- Patients exit model if die or are due to start renal replacement therapy (RRT)

HK, hyperkalaemia; RAASi, Renin-angiotensin-aldosterone system inhibitor; RRT, renal replacement therapy, NHYA, New York Health Association; CKD, chronic kidney disease; HF, heart failure

Definitions of stage of chronic kidney disease and heart failure

Criteria for chronic kidney disease stages:

CKD stages	eGFR lower bound	eGFR upper bound
3a	≥45 mL/min/1.73 m^2	**<60 mL/min/1.73 m^2**
3b	≥30 mL/min/1.73 m^2	**<45 mL/min/1.73 m^2**
4	≥15 mL/min/1.73 m^2	**<30 mL/min/1.73 m^2**
5	**≥0 mL/min/1.73 m^2**	**<15 mL/min/1.73 m^2**

Criteria for heart failure stages:

NYHA classification	Patient symptoms
I	**No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea (shortness of breath)**
II	**Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea (shortness of breath)**
III	**Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnoea**
IV	**Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases**

Clinical trial evidence used in the model

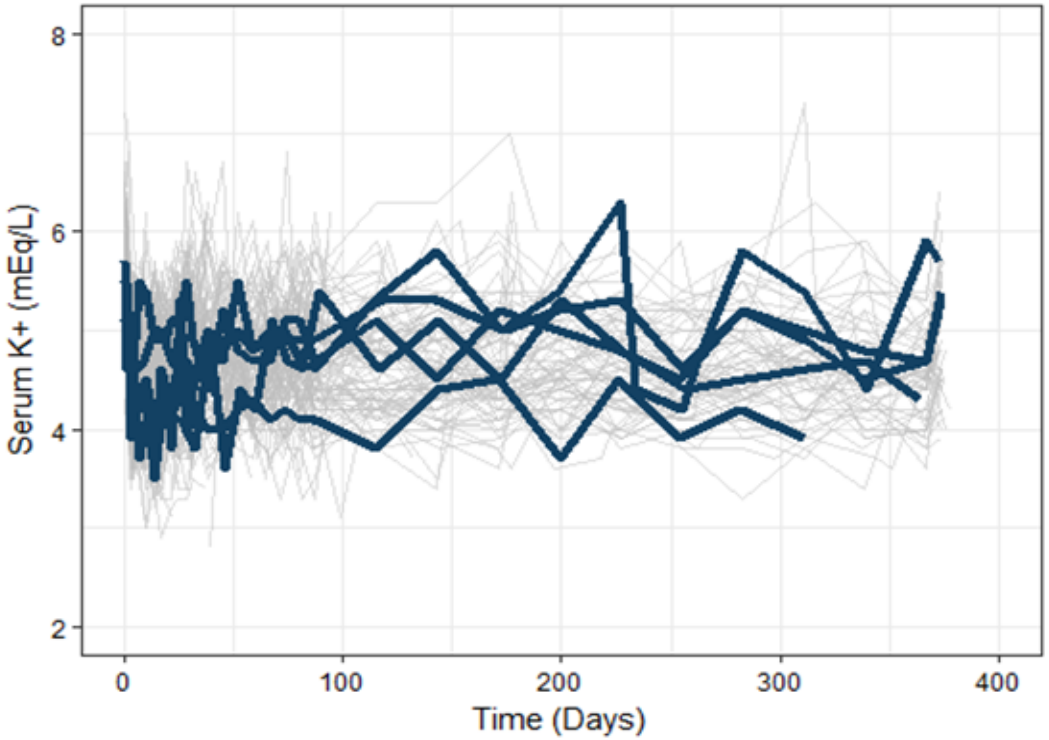
- Clinical effectiveness of sodium zirconium cyclosilicate (SZC) and standard of care:
  - 1st 28 days (ZS-004, for SZC and standard of care)
  - Days 29- 52 (SZC only ZS-005, longest follow up in this trial)
  - Costs and clinical outcomes not extrapolated beyond trial period, but multiple retreatments allowed (if person has another hyperkalaemia event).
    - Company: no evidence from the trials that a previous hyperkalaemia event affects response to SZC
- Used to simulate individual serum-potassium trajectories based on:
  - 1) a fixed trajectory of the mean serum potassium levels for the average patient on SZC and standard care
  - 2) the underlying serum potassium of each individual person being modelled (random patient component) i.e. if high/low serum potassium at baseline, more likely to have higher/lower than average serum potassium
  - 3) the underlying variability of serum potassium over time in each patient (measurement component)

Clinical inputs: serum potassium levels

Figure 7 ERG report: mean serum potassium levels with sodium zirconium cyclosilicate (SZC) and standard care

[redacted]

Figure 18 company submission illustrating how serum potassium varies between patients and over time in a particular patient



ERG queried whether the mean decrease in serum potassium after 29 days in the SZC arm was a modelling artefact. The company thought its modelled outcome was plausible but tested a scenario in which there was no decrease in serum potassium levels between day 28 and subsequent time points in the SZC arm (this had a minor effect on the cost effectiveness results).

Renin-angiotensin- aldosteronesystem inhibitor (RAASi) use

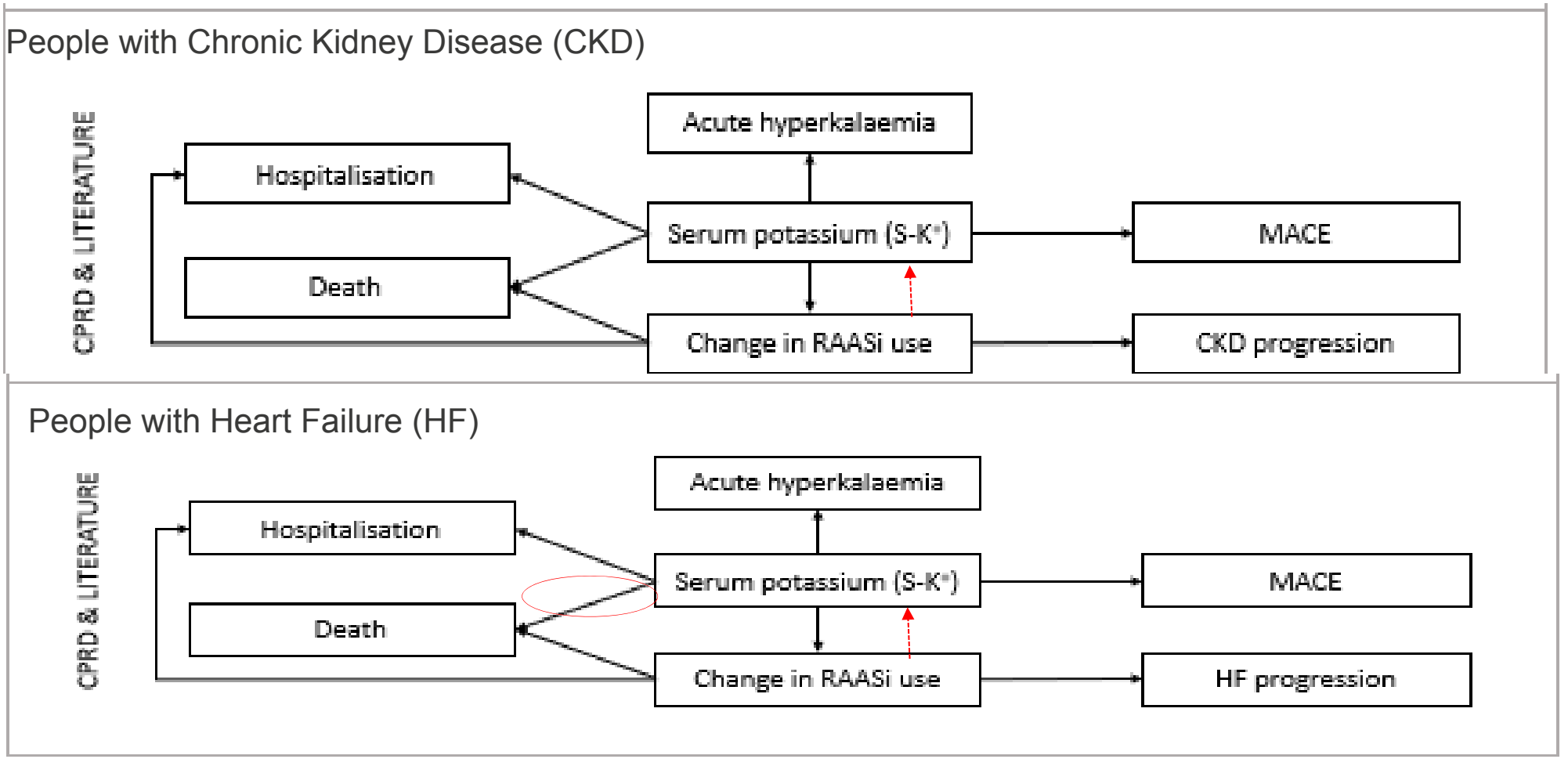
- 3 RAASi states:
  - RAASi “max” – RAASi use in line with European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure
  - RAASi “sub-max”- RAASi use in line with the mean dose at baseline observed in the Clinical Practice Research Database cohort intended to represent imperfect RAASi use
  - No RAASi use
- The 70.2% of patients in the modelled cohort using RAASi at baseline are all assumed to be on the maximum dose at this point
- At any stage in the model, patients can:
  - discontinue RAASi
  - down-titrate from “max” to “sub-max” and up-titrate from “none” or “sub-max” to “max”. See next slide for stopping and down-titration rules used by the company

Decision rules for discontinuing RAASi in the model (people receiving standard care)

Serum potassium	RAASi use	Action	Rationale
≥ 6.0	On RAASi	Discontinue RAASi	Recommended in NICE clinical guideline (CG) 182
≥ 5.5 -6.0	On RAASi	20% patients discontinue RAASi 80% down-titrate	Clinical expert advice
any	Sub-max RAASi	Continue down titration	Assumption: more conservative than CG182, thought to better reflect clinical practice

- People taking SZC in the maintenance phase of model who have hyperkalaemia do not discontinue RAASi (n.b. company tested scenario in which people taking SZC who had serum potassium >6.0 mmol/L stopped treatment with RAASi for 12 weeks)
- People can return to max RAASi use in chronic setting; returns occur in 49.7% of eligible cycles based on a study of uptitration after stopping RAASi in people with CKD (Luo et al). Assumed to be same for people with HF

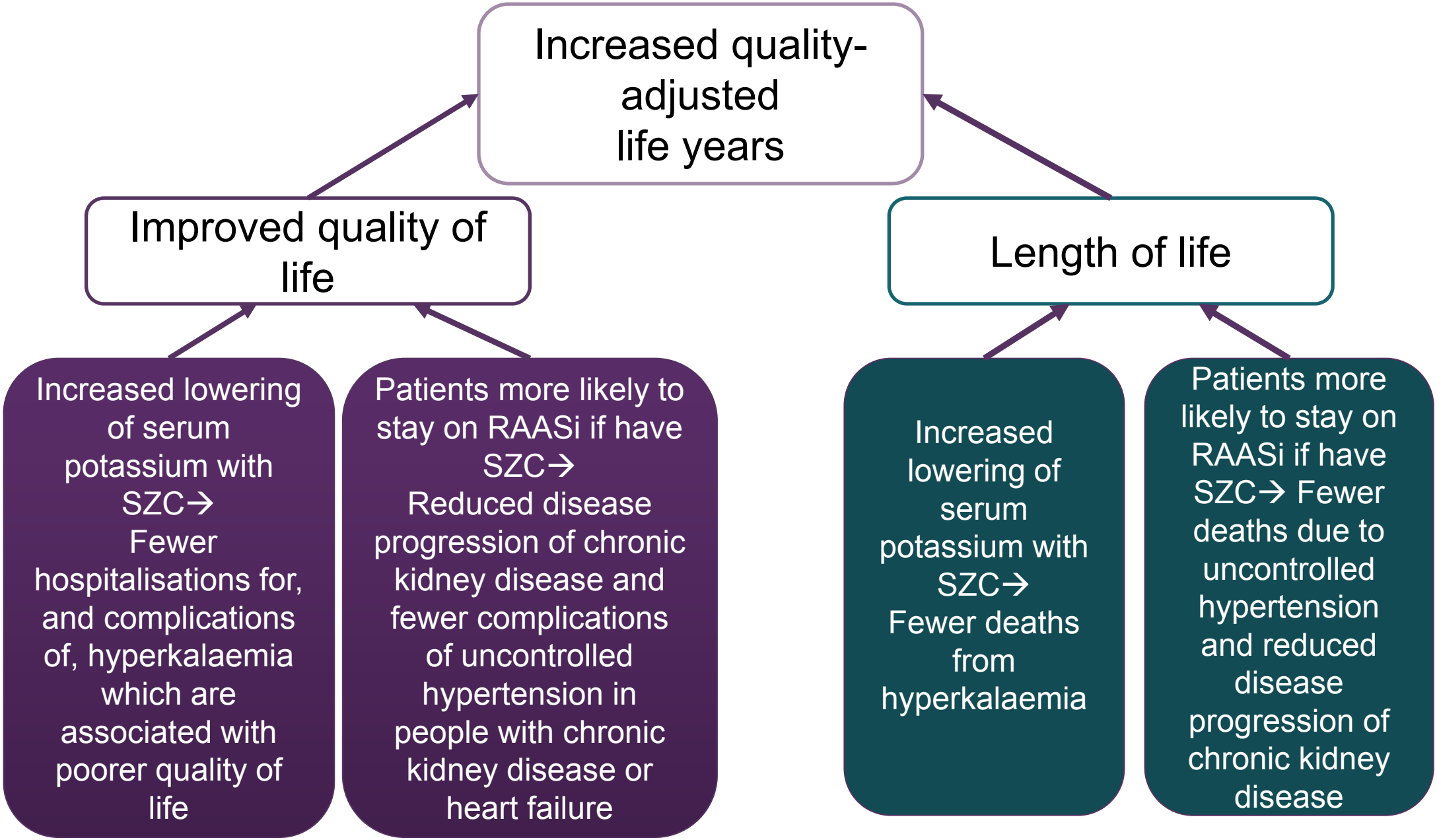
Serum potassium + changes in RAASi use are used to estimate clinical outcomes in model



ERG noted that the effect of change in RAASi use on serum potassium is not included in the model

ERG used different literature source for risk of death associated with serum potassium in people with heart failure

Overview: how QALYs accrue when SZC clinically effective



Risks of disease progression

Health state	Dependent on	Source of risk estimates
People with chronic kidney disease (CKD)		
eGFR (estimated glomerular filtration rate) decline (disease progression to higher stage CKD)	RAASi use (people taking RAASi have a slower rate of eGFR decline) • on RAASi: annual mean eGFR decline 2.34 mL/min/1.73 m^2 • no RAASi: annual mean eGFR decline 3.52 mL/min/1.73 m^2	Evans et al (2012)
People with heart failure		
Disease progression to higher stage New York Health Association (NYHA) classification	• assumed not dependent on RAASi use because no evidence was found for the impact of RAASi on the probability of disease progression • also assumed to be independent of serum potassium	Yao et al (2007)

Risks of events

Event/ health state	Dependent on	Source of risk estimates
People with chronic kidney disease (CKD)		
Cardiovascular event, hospitalisation, mortality, MACE	RAASi use¤ Odds ratio on-RAASi treatment vs no-RAASi • Mortality: 0.870 for max RAASi (sub-max RAASi benefit halved i.e. OR 0.935) • Hospitalisation: no data, assumed odds ratio= 1 Serum potassium* eGFR (CKD disease severity)†	¤Xie et al. (2016) * Luo et al. (2016) †Go et al. (2004)
People with heart failure (HF)		
Hospitalisation	RAASi use¥ Disease progression health state‡	¥Flather et al. (2000), assumption ‡Ford et al. (2012
MACE	CRPD risk equation (risk factors based on age, sex, history of MACE, cancer peripheral vascular disease, medication use) + serum potassium	CRPD, Luo et al. (2016)
Mortality	Seattle heart failure model + serum potassium	SHFM, Krogager et al. (2016)

ERG exploratory analyses: modelling relationship between RAASi use and serum potassium

- ERG identified that in the model serum potassium levels were assumed independent of RAASi use, which neither agreed with clinical opinion or published literature and considered this a major limitation of the model
- Company response to clarification: '*We agree that the relationship between RAASi down-titration or discontinuation with [serum potassium] reductions is not currently explicitly modelled. However, due to the methods and data used to model the S-K trajectory in the model, [we] believe any [serum potassium] related benefits from RAASi down-titration or discontinuation to be more than accounted for'*
- ERG provide 2 estimates of the relationship between maximum RAASi use and serum potassium
  - increase of 0.23 mmol/L based on increase associated with mineralocorticoid receptor antagonist (spironolactone) identified in a systematic review and meta analysis of RCTs in people with CKD n= 1581 (Ng et al., 2015). **This was the ERG's preferred estimate**
  - increase of 0.1 mmol/L based on reported increases in serum potassium in clinical trials n=39 (Weir et al., 2010). These values were typically below 0.3 mmol/L for patients with CKD and between 0.1 and 0.3 mmol/L for patients with HF
- For both ERG scenarios, the increase in serum potassium associated with sub-optimal RAASi use was 50% of with maximum RAASi use

Company's response to ERG's modelling of relationship between RAASi use and serum potassium

- Acknowledged that increase in serum potassium associated with RAASi had not been explicitly modelled by company
- Suggested that serum potassium in the standard of care arm had been underestimated and the clinical effectiveness of standard care overestimated in company base case because people in the placebo arm of ZS-004 had received SZC before placebo, which would have lowered serum potassium in the standard care arm to a lower level than seen on standard care in clinical practice (see figure 7 on slide 42)
  - [in chronic setting]: no treatment effect of standard care. No pharmacological interventions are given in 1st 3 days. A low potassium diet may be tried but this is associated with low compliance and a systematic literature search found no evidence of effect on serum potassium levels of diet.
- Company suggest that this potential overestimation of the clinical effectiveness of standard care in the company model [chronic setting base case] "more than accounts for the clinical effectiveness estimated by reducing or discontinuing RAASi" and the ERG modelling of serum potassium levels on stopping RAASi in standard care further over estimates clinical effectiveness of standard care and is pessimistic to SZC

ERG alternative estimates for relationship between serum potassium and heart failure mortality

- The values for the risk of heart failure mortality were based on people with hypertension Clinical advice to the ERG was that this was not appropriate
- ERG alternative estimate of the relationship between serum potassium and heart failure mortality is based on 19,549 patients with chronic heart failure (Aldahl et al., 2017)
- In general the risk of mortality at serum potassium >5.1 mmol/L was **lower** in the ERG estimates compared with the company estimates

S-K level	Company base case	ERG base case
<3.5	2.19	3.16
3.5 – 3.9	1.91	1.62
3.9 – 4.2	1.00	1.29
4.2 – 4.6	1.10	1.00
4.6 – 5.1	1.47	1.34
5.1 – 5.5	2.28	1.60
>5.5	6.60	3.31

Utility values: disease health states

- No HRQoL data collected in ZS-004 and ZS-005 so utility values

Health state	Utility	Source	Type of data
NYHA I	0.855	Göhler et al (2009)	EQ-5D from eplerone post-acute MI heart failure efficacy and survival study trial
NYHA II	0.771		
NYHA III	0.673		
NYHA IV	0.532		
CKD 3 a	0.870	Gorodetskaya et al (2005)	Time trade off survey of 205 people with CKD
CKD 3b	0.870		
CKD 4	0.850		
CKD 5 (pre-RRT)	0.850*		
ERG alternative estimates for chronic kidney disease (CKD) disease states			
CKD 3a	0.848	Gorodetskaya et al (2005)	HUI-3
CKD 3b	0.848		
CKD 4	0.696		
CKD 5 (pre-RRT)	0.684		
N.B. in response to its factual accuracy check of the ERG report the company introduced new data for CKD states , based on EQ-5D (source: abstract only and unclear how identified ERG unable to validate). Values were 0.85, 0.85,0.81 and 0.74 for CKD 3a/b to 5 respectively			

NICE *(value updated in clarification response)

Disutility values for adverse events

Health state	No. cycles applied for	Utility	Source
Oedema	13 (1 year)	−0.0029	Sullivan et al.
Constipation	13 (1 year)	−0.0056	
Diarrhoea	13 (1 year)	−0.0008	
Nausea	13 (1 year)	−0.0037	Kristiansen et al.
Hypomagnesaemia	13 (1 year)	−0.0028	Nafees et al.
Anorexia	13 (1 year)	−0.0029	Sullivan et al.
Hypokalaemia	13 (1 year)	0.0000	Assumption – no study identified
Anaemia	13 (1 year)	−0.0015	Sullivan et al.
Urinary tract infection	13 (1 year)	−0.0004	Sullivan et al.
MACE event	1	−0.050	Palmer et al.
Hospitalisation	1	−0.024	Göhler et al.

The ERG did not comment on these values
Abbreviation MACE, major adverse cardiac event

Costs and resource use: summary of costs included

Health state/event	cost	source
Annual cost by disease health state		
Chronic kidney disease	£3,511 (stages 3a, 3b and 4) £5,478 stage 5	NICE Clinical guideline182
Heart failure	£90.99 (NYHA Class I); £104.82 (NYHA Class II); £135.95 (NYHA Class III); and £145.10 (NYHA Class IV). (values from clarification response)	Ford et al. (2012) converted from Australian dollars and inflated to 2017 prices
Clinical events		
Acute hyperkalaemia	£2,297 people treated with SZC and £3,093 for people treated with standard care*	NHS reference costs 2014 to 2015
Hospitalisation	£2,444.80	Colquitt et al.
MACE	£4,952	Kent et al.

NICE

Abbreviations: MACE, major adverse cardiac event; NYHA., New York Health Association

Costs and resource use: summary of drug costs included

	Company assumption	ERG alternative assumption
SZC	***** for a 5g sachet and ***** for a 10g sachet. company estimate a cost of £***** over the initial 28 days of treatment and a cost of ***** for 52 weeks of treatment. SZC comes in packs of 3 sachets. Assumed wastage for first 28 days of treatment*	Company assumption + ERG costed 30 sachets for every 28 sachets prescribed throughout model
RAASi	Max dose: £46 (CKD); £50 HF Suboptimal £25 (CKD); £29 (HF) Cost of discontinuing RAASi: £481.48 Cost of up-titrating RAASi (£129.72) Cost of down-titration (£722.22)	Assumed that visit to change dosage of RAASi treatment done as outpatient rather than 25% visits as inpatient (company) Cost of discontinuing: £186.48 Cost of downtitration: £279.72
Drug costs of insulin and glucose were based on BNF costs (annual costs of both in combination for severe hyperkalaemia event ~£70. Calcium gluconate and salbutamol costs from NHS eMIT (annual costs of calcium gluconate £1 and salbutamol 13p for severe hyperkalaemia event)		

NICE

* Company assumed that wastage varied by cycle. Please see table 29 in company response to clarification for breakdown of wastage by cycle

Company revised deterministic base case results

- In response to clarification, company provided its base case results for the chronic kidney disease (CKD) and heart failure (HF) populations separately, alongside the results for the combined CKD and HF populations. It also included changes to some of its assumptions from its original submission
- The revised base case also fixed coding errors identified by the ERG

Population	Incremental cost of SZC treatment	Incremental QALYs of SZC treatment	ICER (£/QALY)
Chronic Setting			
CKD or HF	£16,803	0.769	£21,849
CKD only	£14,623	0.577	£25,363
HF only	£9,722	0.726	£13,458
Acute setting			
CKD or HF	-£853	0.052	SZC dominates standard care
CKD only	-£1,027	0.037	
HF only	£393	0.053	£7,380

NICE ERG noted probabilistic results were similar but there were key parameters excluded from the probabilistic sensitivity results

Company's additional sensitivity analyses

- The company also did an 'all relevant scenarios' analysis which added the following changes to the base case in response to the ERG's clarification questions:
  - withholding RAASi treatment for 12 weeks for patients in the SZC arm who have an S-K level of > 6.0 mmol/L (see slide 44 for discussion)
  - assuming that there was no decrease in serum potassium levels between day 28 and subsequent time points for people receiving SZC (see slide 42 for discussion)
  - assuming that the eGFR level was not equal for all patients but were distributed between Stages 3b and 5 (pre-RRT) (see slide 39 for discussion)

Population	Incremental cost of SZC treatment	Incremental QALYs of SZC treatment	Cost per QALY
Chronic Setting			
CKD or HF	£15,867	0.646	£24,575
CKD only	£20,111	0.706	£28,487
HF only	£9,370	0.615	£15,244
Acute Setting			
CKD or HF	-£641	0.047	SZC dominates standard care
CKD only	-£1,105	0.051	
HF only	£291	0.048	£6,022

ERG exploratory base case summary

	see slide
stop RAASi treatment for 12 weeks for patients in the SZC arm who have a serum potassium level of > 6.0 mmol/L (*company assumption was that RAASi treatment would not stop if taking SZC*)	44
Assuming RAASi treatment is related to serum potassium serum potassium levels. Increase in serum potassium levels associated with RAASi treatment was: i) 0.23 (ERG base case 1) (**ERG preferred**) ii) 0.1 mmol/L (ERG base case 2) (*company did not explicitly model this relationship*)	49
Using different utility values for chronic kidney disease than that assumed by the company (*company used utility values based on time trade off survey, ERG's based on HUI-3*)	52
Using an alternative relationship between serum potassium levels and heart failure mortality(*company's estimated risk was based on people with hypertension, ERG's based on people with heart failure*)	51
Assuming a higher level of drug wastage associated with SZC treatment	55
Assuming that the costs associated with RAASi dose changes are lower than assumed by the company (*company had assumed that some of the consultations to change RAASi dose would be done in an inpatient setting which raises the cost)*	55

ERG proposed a shorter time horizon **(52 weeks) for acute setting base cases**

- Company acute setting base case has a lifetime horizon, but does not model follow up in the chronic setting following multiple hyperkalaemia episodes
- ERG suggests people identified with hyperkalaemia in the acute setting would be followed up in the chronic setting following multiple episodes
- Suggest that using a short time horizon in acute setting (52 weeks), then assuming that the chronic setting cost effectiveness results apply to these people is valid
- Trial data is for people presenting in chronic setting only and modelling of acute setting patients based on a sample of people serum potassium >6.0 mmol/L at the start, but these concentrations decrease over time in the acute setting model and may reflect the characteristics of the chronic setting modelled population at the end of the time horizon

ERG exploratory deterministic base case results: **CKD in acute setting**

Scenario	Incremental life years	Incremental costs	Incremental QALYs	ICER
Company base case	**0.061**	**£1,027**	**0.037**	SZC dominates
Company base case 52 weeks*	**0.002**	**-£256**	**0.002**	
1) Stop RAASi if serum potassium ≥ 6.0 both treatment arms	0.002	-£256	0.002	
2a) serum potassium decrease with stopping RAASi (0.23)	0.001	£195	0.001	£289,171
2b) As above but value (0.1)	0.001	£10	0.001	£2,627
3) HUI-3 utility values for CKD	0.002	-£256	0.001	SZC dominates
5) ERG assumptions on wastage	0.002	-£234	0.002	
6) Lower costs for RAASi changes	0.002	-£255	0.002	
ERG base case 1 (1, 2a, 3, 5 and 6)	**0.001**	**£204**	**0.001**	**£346,485**
ERG base case 2 (1, 2b, 3, 5 and 6)	**0.001**	**£824**	**0.001**	**£28,760**

ERG exploratory deterministic base case results: **heart failure in acute setting**

Scenario	Incremental life years	Incremental costs	Incremental QALYs	ICER
Company base case lifetime	**0.103**	**£404**	**0.053**	**£7,380**
Company base case 52 weeks*	**0.016**	**£91**	**0.009**	**£10,263**
1) Stop RAASi if serum potassium ≥ 6.0 both treatment arms	0.016	£91	0.009	£10,263
2a) Increase in serum potassium with RAASi (0.23)	0.010	£289	0.005	£51,652
2b) As above but value (0.1)	0.013	£208	0.007	£28,223
4) Alternative risk between serum potassium and heart failure mortality	0.008	-£69	0.004	SZC dominates
5) ERG assumptions on wastage	0.016	£107	0.009	£12,098
6) Lower costs for RAASi changes	0.016	£91	0.009	£10,263
ERG base case 1 (1, 2a, 4, 5 and 6)	**0.004**	**£255**	**0.002**	**£100,093**
ERG base case 2 (1, 2b, 4, 5 and 6)	**0.007**	**£130**	**0.003**	**£37,097**

ERG interpretation of acute setting results

- For patients in the acute clinical setting it is highly plausible that the ICERs are below £30,000 per quality adjusted life year (QALY) gained when the reduced mortality within the 52-week period is extrapolated to longer time horizons
- 52 week time horizon analyses conservative because sodium zirconium cyclosilicate has a life years advantage which would expect to result in QALY gains over a longer time horizon
- There remains uncertainty in the ICERs within the acute clinical setting as there are no data on these specific patients

ERG exploratory deterministic base case results: **CKD in chronic setting**

Scenario	Incremental life years	Incremental costs	Incremental QALYs	ICER
Company base case	**1.080**	**£14,624**	**0.576**	**£25,363**
1) Stop RAASi if serum potassium ≥ 6.0 both treatment arms	1.010	£14,614	0.540	£27,056
2a) Increase in serum potassium with RAASi (0.23)	0.863	£15,045	0.453	£33,200
2b) As above but value (0.1)	0.978	£14,946	0.518	£28,851
3) HUI-3 utility values for CKD	1.080	£12,624	0.479	£30,537
5) ERG assumptions on wastage	1.080	£15,499	0.576	£26,882
6) Lower costs for RAASi changes	1.080	£15,289	0.576	£26,683
ERG base case 1 (1, 2a, 3, 5 and 6)	**0.798**	**£16,299**	**0.347**	**£46,936**
ERG base case 2 (1, 2b, 3, 5 and 6)	**0.911**	**£16,266**	**0.400**	**£40,731**

ERG exploratory deterministic base case results: **heart failure in chronic setting**

Scenario	Incremental life years	Incremental costs	Incremental QALYs	ICER
Company base case	**1.609**	**£9,772**	**0.726**	**£13,458**
1) Stop RAASi if serum potassium ≥ 6.0 both treatment arms	1.567	£9,943	0.707	£14,063
2a) Increase in serum potassium with RAASi (0.23)	1.096	£9,282	0.488	£19,012
2b) As above but value (0.1)	1.400	£9,626	0.628	£15,333
4) Alternative risk between serum potassium and heart failure mortality	1.666	£11,684	0.689	£16,952
5) ERG assumptions on wastage	1.609	£10,405	0.726	£14,329
6) Lower costs for RAASi changes	1.609	£10,384	0.726	£14,301
ERG base case 1 (1, 2a, 4, 5 and 6)	**1.101**	**£13,112**	**0.449**	**£29,239**
ERG base case 2 (1, 2b, 4, 5 and 6)	**1.387**	**£13,284**	**0.570**	**£23,296**

ERG exploratory deterministic base case results: summary of all analyses

Scenario	Heart failure acute*	CKD acute*	Heart failure chronic	CKD chronic
Company base case (lifetime)	**£7,380**	SZC dominates	£13,458	£25,363
1) Stop RAASi if serum potassium ≥ 6.0 both treatment arms	£10,263		£14,063	£27,056
2a) Increase in serum potassium with RAASi (0.23)	£51,652	£289,171	£19,012	£33,200
2b) As above but value (0.1)	£28,223	£2,627	£15,333	£28,851
3) HUI-3 utility values for CKD	-	SZC dominates	-	£30,537
4) Alternative risk between serum potassium and heart failure mortality	SZC dominates	-	£16,952	-
5) ERG assumptions on wastage	£12,098	SZC dominates	£14,329	£26,882
6) Lower costs for RAASi changes	£10,263		£14,301	£26,683
ERG base case 1 (assumption 2a)	**£100,093**	**£346,485**	£29,239	£46,936
ERG base case 2 (assumption 2b)	**£37,097**	**£28,760**	£23,296	£40,731
ERG combined population base case 1	£159,616		£37,983	

ERG additional scenarios around ERG exploratory base case

Setting	Scenario	Base case 1		Base case 2	
		HF	CKD	HF	CKD
Acute	**ERG Base case**	£100,093	£346,485	£37,097	£28,760
	Restarting on RAASi treatment allowed at 12 weeks (*company assume never restarted. Clinical advice to ERG if hyperkalaemia not life threatening RAASi could be restarted*)	£196,049	£140,264	£72,109	£44,566
Chronic	**ERG Base case**	£29,239	£46,936	£23,296	£40,731
	Lifetime SZC (*not max 12 months which was based on length of follow in trials. ERG clinical experts: life time SZC plausible if SZC efficacious)*	£30,668	£53,685	£25,056	£46,135
	Hospital stay independent of treatment (*not longer with standard care as assumed by company*)	£29,257	£46,965	£23,313	£40,761

ERG additional scenarios in response to company's factual accuracy check

Setting	Scenario	ICER around company base case		ICER around ERG base case 1	
Chronic		**Heart failure**	**Chronic kidney disease**	**Heart failure**	**Chronic kidney disease**
	Base case	£13,458	£25,363	£29,239	£46,936
	Company's assumption that standard of care has no treatment effect (n.b. ERG consider this optimistic and note does not appear to be based on data)	£5,641	£4,532	£8817	£15,877
	EQ-5D values for CKD identified by the company n.b. ERG do not consider applying these to be valid (see slide 52)	Not applicable	£26,928	Not applied	Not applied

Equality

- No equality issues were raised

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Sodium Zirconium Cyclosilicate for Hyperkalaemia [ID 1293]

Document B

Company evidence submission

July 2018

File name	Version	Contains confidential information	Date
ID1293_SZC_Document B_V2.0_[ACIC]	V2.0	Yes	24-Sep-18

Contents

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Abbreviations

ACE	Angiotensin-converting-enzyme
AE	Adverse event
A&E	Accident and Emergency
AKI	Acute kidney injury
AMU	Acute Medical Unit
ARB	Angiotensin II receptor blocker
BICD	Biventricular implantable cardioverter defibrillator
BMI	Body mass index
BNF	British National Formulary
BP	Blood pressure
CC	Complications and comorbidities
CHF	Congestive heart failure
CI	Confidence interval
CKD	Chronic kidney disease
CPD	Chronic pulmonary disease
CPRD	Clinical Practice Research Datalink
CSR	Clinical study report
eGFR	Estimated glomerular filtration rate
eMIT	Electronic Market Information Tool
ECG	Electrocardiogram
ESC	European Society of Cardiology
ESRD	End-stage renal disease
Hb	Haemoglobin
HF	Heart failure
HK	Hyperkalaemia
HRQoL	Health-related quality of life
ICD	Implantable cardioverter defibrillator
ICER	Incremental cost-effectivness ratio
ITT	Intent-to-treat
K+	Potassium
LoS	Length of study
LS	Least-squares
MACE	Major adverse cardiac event
MedDRA	Medical Dictionary of Regulatory Activities
MRA	Mineralocorticoid-receptor antagonists
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
NYHA	New York Heart Association
OD	Once daily (dosing)
PSS	Personal Social Services
PVD	Peripheral vascular disease
QALY	Quality-adujusted life-year
QoL	Quality of life
RAASi	Renin-angiotensin-aldosterone system inhibitor
RRT	Renal replacement therapy
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SHFM	Seattle Heart Failure Model
S-K	Serum potassium
SZC	Sodium zirconium cyclosilicate
TEAE	Treatment-emergent adverse event
TID	Three times daily (dosing)
TRAE	Treatment-related adverse event
VAS	Visual Analogue Scale
WBC	White blood cell

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1 *Decision problem*

The submission covers the technology's full marketing authorisation for this indication.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with hyperkalaemia (HK)	Adults with HK in a comorbid patient population comprising chronic kidney disease (CKD) (stage 3–5) or heart failure (HF) The patient population in which HK is reported is complex and comorbid. HK occurs predominantly in patients with an underlying degree of CKD or HF due to disease pathophysiology and the wide use of cardio-renal protective medicines, such as RAASi, which significantly increase the risk of developing HK due to their mechanism of action. Therefore, the patient population presented in the SZC clinical trial programme (68.3% with CKD and 37.9% with HF in ZS-005 trial) represents the most relevant patient population in UK clinical practice.	N/A
Intervention	Sodium zirconium cyclosilicate (SZC)	As per scope	
Comparator(s)	Standard care. This includes a low potassium (K^+) diet with or without agents that reduce levels of potassium in the body	Standard of care: Acute setting: Intermittent use of calcium resonium (with some patients receiving a repeat dose of insulin-glucose) Chronic setting: no therapy administered. All patients are managed with lifestyle interventions for the background maintenance of serum potassium (S-K) (e.g. dietary intervention and modification of concomitant medications, such as RAASi)	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	The outcome measures to be considered include: Serum potassium level Use of RAASi therapy Mortality Time to normalisation Adverse effects (AE) of treatment Health-related quality of life (HRQoL)	Outcomes included in the submission, include: • S-K level • Time to normalisation • AEs of treatment • Use of RAASi therapy (exploratory endpoint)	Mortality was not an outcome in the clinical trial programme for SZC as this would be confounded by underlying comorbidities. HRQoL was not collected in the clinical trial programme for SZC as HK symptoms often go unnoticed and outcomes such as cardiovascular events and mortality were not captured in the trials.
Economic analysis	The reference case stipulates that cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life-year (QALY). The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from a National Health Service (NHS) and Personal Social Services perspective	As per scope	N/A
Subgroups to be considered	If the evidence allows, the following subgroups will be considered People with acidosis People with acute HK People with CKD People with HF	The base-case analysis includes adults with HK and comorbidity for CKD or HF. This population is consistent with those that more commonly experience HK in clinical practice. Patients can present in the acute (S-K ≥6.0 mmol/L) and chronic (S-K ≥5.5 mmol/L) settings. Those	The clinical trial programme for SZC did not evaluate people with acidosis.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator	presenting in the acute setting are those with acute HK.	
Special considerations including issues related to equity or equality	None	N/A	N/A

Abbreviations: AE, adverse event; CKD, chronic heart disease; HK, hyperkalaemia; HF, heart failure; HRQoL, health-related quality of life; MRA, mineralocorticoid-receptor antagonist; NHS, National Health Service; QALY, quality-adjusted life-year; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate.

B.1.2 *Description of the technology being appraised*

The summary of product characteristics and European public assessment report can be found in Appendix C.

Table 2. Technology being appraised

UK approved name and brand name	Sodium zirconium cyclosilicate (Lokelma)
Mechanism of action	SZC is a non-absorbed, non-polymer inorganic powder with a uniform micropore structure that preferentially captures potassium in exchange for hydrogen and sodium cations. SZC is highly selective for potassium ions, even in the presence of other cations such as calcium and magnesium, in vitro. SZC captures potassium throughout the entire gastrointestinal (GI) tract and reduces the concentration of free potassium in the GI lumen, thereby lowering serum potassium levels and increasing faecal potassium excretion to resolve hyperkalaemia.[1-3] (Appendix C)
Marketing authorisation/CE mark status	SZC received marketing authorisation from the European Commission on 22 March 2018.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	SZC is indicated for the treatment of HK in adult patients.
Method of administration and dosage	SZC is a 5 g or 10 g powder for oral suspension. The entire contents of the sachet should be emptied into a drinking glass containing approximately 45 mL of water and stirred well. It should be drunk while still cloudy. **Correction phase** The recommended starting dose of SZC is 10 g, administered three times a day orally (TID). Typically, normokalaemia is achieved within 24-48 hours. If patients are still hyperkalaemic after 48 hours, the same regimen can be continued for an additional 24 hours. If normokalaemia is not achieved after 72 hours of treatment, other treatment approaches should be considered. **Maintenance phase** When normokalaemia is achieved, the maintenance regimen should be followed. A starting dose of 5 g once-daily (OD) is recommended with possible titration up to 10 g OD or down to 5 g once every other day, as needed, to maintain a normal potassium level. The suspension can be taken with or without food and does not require separation from other medications.
Additional tests or investigations	S-K levels should be monitored when clinically indicated, including after changes are made to medicinal products that affect the S-K concentration, e.g. RAASi or diuretics, and after the SZC dose is titrated.
List price and average cost of a course of treatment	List price: SZC 5 g = £[redacted]; SZC 10 g = £[redacted] <u>Treatment cost in the acute setting:</u> Costing for a first HK event (over 28 days of treatment) =£[redacted] Cost for a subsequent HK event (over 28 days of treatment) = £[redacted]

UK approved name and brand name	Sodium zirconium cyclosilicate (Lokelma)
	Treatment cost in the chronic setting: Cost for a first HK event (over 28 days of treatment) = £[redacted] Cost for a subsequent HK event: Chronic (over 52 weeks of treatment) = £[redacted]
Patient access scheme (if applicable)	Not applicable

Abbreviations: GI, gastrointestinal; GIT, gastrointestinal tract; HK, hyperkalaemia; OD, once-daily; RAASi, renin-angiotensin-aldosterone system inhibitors; S-K, serum potassium; SZC, sodium zirconium cyclosilicate; TID, three times a day.

B.1.3 *Health condition and position of the technology in the treatment pathway*

B.1.3.1 *Disease overview*

In UK clinical practice, patients with HK are generally managed in the acute (i.e. accident and emergency [A&E]/acute medical unit [AMU]) or chronic (i.e. outpatient) settings in the hospital.

B.1.3.1.1 Definition of hyperkalaemia

HK is a debilitating and potentially life-threatening condition that occurs when the serum potassium (S-K) concentrations increases above 5.0 mmol/L. It is generally accepted that normokalaemia (i.e. normal levels of S-K) is achieved when S-K levels range between 3.5 and 5.0 mmol/L. There is some variation in the cut-off S-K levels used to define HK based on the guidelines and clinical practice. For the purposes of this submission, the cut-off levels routinely used in clinical practice in England are applied; the diagnosis and treatment of HK is based on S-K levels of ≥6.0 mmol/L in the acute setting and ≥5.5 mmol/L in the chronic setting based on expert opinion and local clinical guidelines. This is consistent with UK guidelines, including the UK Renal Associations Clinical Practice Guidelines and the British Society of Heart Failure position statement for HK.[4-8]

B.1.3.1.2 Symptoms, causes and risk factors for hyperkalaemia overview

The symptoms of hyperkalaemia often go unnoticed and are detected in blood test results as part of the patient's routine appointments in clinics. Reported symptoms can range from diarrhoea, nausea and vomiting, difficulty breathing, abdominal pains, muscle pain, weakness and paralysis, to life-threatening symptoms and consequences, including respiratory failure, cardiac arrhythmia, cardiac arrest, and sudden death.[9-12]

Risk factors: Chronic kidney disease or heart failure

The concentration of potassium is regulated by a number of mechanisms, including the transport of potassium between extracellular and intracellular spaces and the excretion of potassium via the kidneys. The increase in S-K associated with HK can be the result of increased potassium intake, disrupted intracellular redistribution of potassium, impaired potassium excretion, or a combination of these, and can therefore have many underlying causes. Renal failure or failure to augment distal tubular potassium secretion is largely responsible for the maintenance of HK.[13]

Therefore, people with CKD or HF, as well as people of advancing age, are at an increased risk of developing HK, typically due to decreasing renal function and capacity for renal excretion. Of these, reduced renal function is the strongest independent predictor for HK.[14-18]

Risk factors: Renin-angiotension aldosterone system inhibitors

Drug-induced HK arises in patients as a result of medications used in the management of CKD or HF. The most commonly used medications for these conditions are collectively known as renin-angiotensin-aldosterone system (RAAS) therapies, which can include angiotensin-converting-enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARBs) and mineralocorticoid-receptor antagonists (MRAs).[7,8] Despite, the cardiorenal protective effects of RASSi therapies, these medicines increase S-K levels by reducing renal excretion of potassium. This is supported by a strong clinical evidence base. A meta-analysis of 21 trials showed that the use of MRAs was associated with increased S-K levels (mean difference in S-K MRA vs control = 0.23; 95% confidence interval [CI], 0.13 to 0.33, p<0.001) and an increased risk of HK of 1.76 (relative risk [RR]; 95% CI, 1.20 to 2.57, p=0.004).[19] This has been further supported by the UK studies published by Horne et al. (2017) and Michel et al.[16,20]

Despite the increased risk of developing HK, RAASi therapies (i.e. ACEi, ARBs and MRAs) offer cardiorenal protective effects. As such, RASSi therapies are the mainstay treatment option for patients with HF or CKD, and are widely used in the UK, as recommended by various guidelines and consensus statements, including NICE, European Society of Cardiology – Heart Failure (ESC-HF) and British Society for Heart Failure.[7,8] The available randomised data on dosing such as from the ATLAS and HEAAL, suggests that higher doses are more effective and clinicians should strive for target doses as recommended and specified in guidelines.[21-23]

However, despite guideline recommendations, patients frequently down-titrate their RAASi medication or discontinue treatment due to drug-induced HK – and therefore have suboptimal outcomes, including the potentially life-saving effects of these treatments.[24] The BIOSTAT-CHF European study, for example, showed that only 22% (470 of 2100) of HF patients achieved the recommended dose of ACEi or ARB over a median follow-up period of 21 months.[25] More importantly, patients who received 0–49% of the recommended ACEi/ARB dose had a higher risk of mortality and hospitalisation compared to those reaching ≥100% of the recommended dose. In the UK, Qin et al (2017) analysed 23,541 patients with heart failure from Clinical Practice Research Datalink (CPRD) data, and found that 44.62% patients on ACEi and 65.99% on ARBs achieved <50% of the recommended target dose of these therapies.[26]

Due to the drug-induced risk of HK, patients with CKD or HF are at increased risk of hospitalisation. Juurlink et al. undertook a population-based time series analysis, examining trends in the rate of spironolactone prescription and the rate of hospitalisation for HK before and after the publication of RALES, and found the rate of prescription rose from 34 in 1000 to 149 in 1000 patients, and the rate of hospitalisation for HK rose from 2.4 per 1000 patients to 11 per 1000 patients, and the associated mortality rose from 0.3 per 1000 to 2.0 per 1000.[27]

In the UK, Qin et al (2017) analysed 23,541 patients with HF from CPRD data, and found that three-quarters of the HF cohort experienced ≥1 HK event, and a J-shaped association between S-K and incident rate ratios (IRRs) was observed with the rate of RAASi discontinuation for patients with a S-K ≥6.0 mmol/L estimated to be around 2.5 times greater than in patients with S-K in the reference range (p<0.001). These data demonstrated that a substantial proportion of HF patients in the UK received <50% of the guideline recommended dose of therapies and that physicians were more likely to discontinue therapy in patients with HF and HK.[26]

This was also shown by the same authors in 144,388 UK patients with stage ≥3 CKD: 37.5% and 60% of patients on ACEis and ARBs received <50% of target dose respectively. Over 80% of patients experienced ≥ 1 hyperkalaemic event, and there was a J-shaped association between S-K

and adjusted IRRs, with the rate of discontinuation for patients with S-K ≥6.0 mmol/L estimated to be 3.4 times greater than in patients with S-K in the reference range (p<0.001).[28] Furthermore, UK clinical expert opinion confirms that in patients with acute HK (i.e. those with S-K ≥6.0 mmol/L), ACEi, ARB and MRAs will be stopped and often not re-started in the community, and that in patients with chronic HK (i.e. those with S-K ≥5.5 mmol/L), these medications will often be down-titrated or ceased with a reluctance to optimise, despite best practice recommendations.[29] The impact of HK on down-titration of RAASi therapy has also been demonstrated in studies conducted in Europe and the US. [30,31]

In summary, these studies together demonstrate the life-saving effects of optimal RAASi therapy; however, despite the beneficial effects RAASi therapy in treating renal and cardiovascular disease, the presence of drug-induced HK can complicate and compromise the management of chronic conditions by leading to discontinuation or suboptimal use of RAASi therapy. This leads to patients receiving suboptimal treatment or treatment cessation, which puts patients at a higher risk of hospitalisation, morbidity and mortality due to their underlying health condition.

B.1.3.1.3 Incidence and prevalence

Given the varying definitions of HK, estimating the number of people suffering from HK is complex. Furthermore, as the current treatment options for HK are limited and the causes of HK are broad ranging from acute kidney injury to drug-induced, the majority of patients with HK are not coded appropriately in secondary care due to the nature of medical record keeping in the UK, and therefore hospital episode statistics data are likely to be unreliable and present a conservative estimate. However, the Renal Association estimates that between 1 and 10% of hospital inpatients have HK,[4] and The National Kidney Foundation has reported estimates from the literature for the prevalence of HK in the general population of between 2 and 3%, with a higher prevalence of up to 40–50% estimated for patients with CKD.[32,33]

Although the incidence and prevalence of HK are difficult to estimate, multiple studies examining incidence rates have been reported worldwide, including the UK, Europe, and the USA. The incident rates of HK in the UK in the general population are presented in Table 3. In this study by Horne et al, the strongest predictor of an incident HK event was the presence of an eGFR test, the concomitant use of MRAs, ACEi and ARBs.[16]

Recent studies in Europe have revealed a marked increase in the incidence of HK in patients with CKD or HF, with a further increase observed as CKD severity increases.[17,18] A study conducted by Thomsen et al. (2017) in Northern Denmark studied the incidence rate of HK in a population-based cohort of all newly diagnosed CKD patients (eGFR <60 mL/min/1.73 m^2 or hospital diagnosis). Of 157,766 patients with CKD, 28% experienced HK with an overall incidence rate of 7.0 per 100 person-years. Among patients with stage 3A, 3B, 4 or 5 CKD, 9, 18, 31 and 42%, respectively experienced HK within the first year of diagnosis.[17] Furthermore, Nilsson et al. (2017) conducted a study in patients with CKD stage 1–4 in Sweden and demonstrated an increased incidence of HK with disease severity, with an incidence rate of 1.08 per 100 person-years in patients with CKD stage 1–2 increasing to 13.3 per 100 person-years in those with CKD stage 4.[18] In patients with HF, Thomsen et al. (2017) found that 39% of the patients experienced HK over a mean follow-up of 2.2 years, and when compared to the general population, have an incidence rate of 17.8 per 100 person-years in patients with HF.[15] Together these studies demonstrate that patients with CKD and HF are at increased risk of HK and there is a higher incidence in these populations.

Overall, it is clear there are large numbers of patients suffering from HK globally, with a greater incidence reported among those with underlying comorbidities.

Table 3: Summary of hyperkalaemia incidence rates from studies in England

Publication and data source	Country	Patient group	Definition of hyperkalaemia	Incidence rate (per 100 person-years)
Horne 2017[26] *(Poster)*; CRPD-HES	England		S-K ≥5.0 mmol/L	2.86
			S-K 5.0–5.4 mmol/L	2.61
			S-K 5.4–5.9 mmol/L	0.21
			S-K ≥6.0 mmol/L	0.05

Abbreviations: CRPD-HES, Clinical Practice Research Database and Hospital Episodes Statistic; S-K, serum potassium.

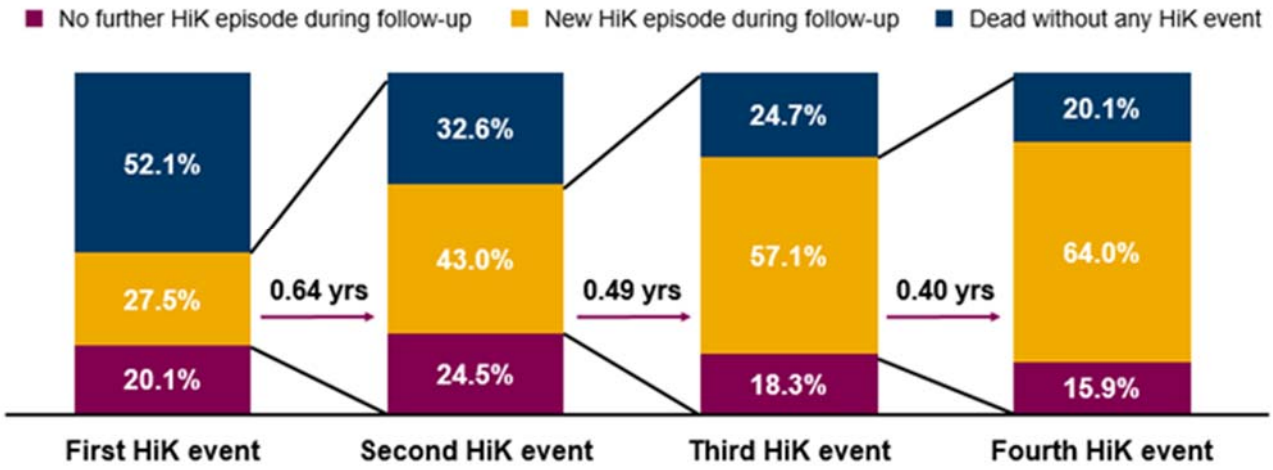
As with incidence, HK prevalence rates vary considerably based on the population of interest, with a number of these studies reporting a higher prevalence of HK among patients with comorbidities, such as CKD, HF, and diabetes/insulin resistance, compared to those without these conditions.[34-38] Kyriakou et al. (2017) conducted a prospective cohort study in Greek patients in the nephrology outpatient setting and found a prevalence of HK (S-K >5.0 mmol/L) of 30.5% in patients with CKD stage 3–4.[39] A review carried out by Kovesdy et al. (2014) reported that HK can be prevalent in 40–50% of patients, particularly those with advanced CKD and diabetes, kidney transplant recipients and patients treated with RAASi.[33] In the UK, Sarafidis et al. (2012) found in 238 patients under regular follow-up in the low clearance clinic, 54.2% had a S-K of >5.0 mmol/L, whilst 31.5% and 8.4% had potassium levels ≥5.5 and ≥6.0, respectively. Hence, this demonstrates that even when HK is defined at a level relevant to UK clinical practice at ≥5.5 mmol/L, there is a high prevalence of HK in UK practice.[40]

B.1.3.1.4 Recurrence of hyperkalaemia

Recurrence of HK is common, and patients with CKD or HF taking RAASi therapy are at a greater risk when compared with the general population.

Recurrence of HK has been reported in a number of real-world, observational studies conducted in the UK, Northern Denmark and Sweden. In the UK, Horne et al. (2017) found that of 195,178 patients with a first event of HK, the overall incidence of recurrence was 8.07 per 100 patient-years, with a higher rate reported for patients with incident S-K > 6.0 mmol/L. In the SCREAM and LABKA studies, the recurrence of a second event of HK occurred in 35.0% and 27.5% of patients who had a first event of HK, respectively, during the study follow-up periods.[18,41] In addition, the LABKA study revealed that the proportion of patients who experienced a HK event increased with each subsequent event and the duration between successive events decreased. For example, between the first and fourth HK event, the proportion of patients who experienced a recurrent event increased from 27% to 64%, and the duration between events decreased from 0.64 years to 0.4 years (see Figure 1).

Figure 1: LABKA study: Proportion of CKD patients experiencing a new hyperkalaemia event



Abbreviations: CKD, chronic kidney disease; HiK, hyperkalaemia.
Source: Thomsen and colleagues (2017) (Oral presentation)[41]

Recurrence of HK has also been reported by Rossignol et al. (2017) as part of a prospective, French registry study of patients receiving haemodialysis.[42] In patients with an initial event of HK of either >5.1 mmol/L (n=389), >5.5 mmol/L (n=305) or >6 mmol/L (n=182) at any time during a 2-year study follow-up period, the proportion of patients experiencing a recurring event of HK within 3 months were 73.2%, 59.7% and 35.6%, respectively. The high rate of recurrence described from each of the above studies, indicates the importance of monitoring S-K levels following the initial HK event and the need for longer-term control of S-K levels.

In summary, recurrence of HK is high in patients, particularly in those with CKD, multiple comorbidities and taking RAASi therapy. Typically, down-titration or discontinuation of RAASi and MRA therapy is common in response to a hyperkalaemic event, which is expanded upon in Section B.1.3.5. Therefore, there is a need to ensure appropriate monitoring and an unmet need to allow for longer-term control of S-K levels and maintenance of disease-modifying therapy.

B.1.3.2 *Burden to patients, carers and society*

Overview

There is significant burden of disease associated with HK both in terms of increased patient morbidity and mortality. Across different patient groups, such as those patients with CKD and HF, the risk of adverse clinical outcomes, such as major cardiovascular events (MACE) or mortality, has been shown to follow a 'U-shaped' association in which the risk of an event increases at the more extreme S-K levels (see Figure 2 and Figure 3).[43,44-46] These studies will be discussed, in the following Sections B.1.3.2.1 and B.1.3.2.2 – first, looking at patients with CKD followed by HF.

Morbidity burden

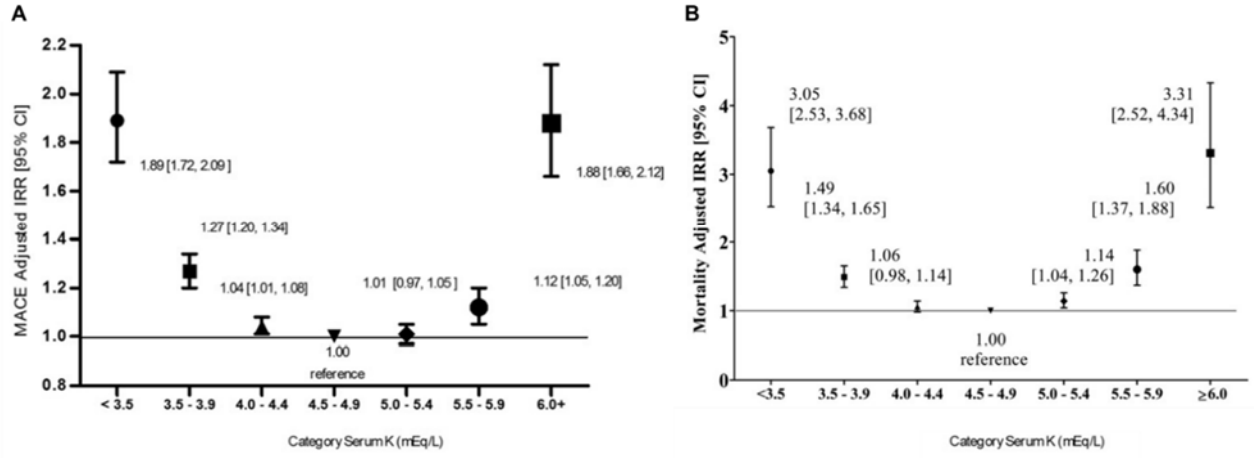
HK is a major cause of patient morbidity, with an increased risk of cardiovascular events reported in studies of patients with CKD and HF.[15,17,43-48] The associated risk of adverse clinical outcomes to S-K levels has been shown, with more severe events of HK being associated with higher risk of morbidity. Horne et al. (2017) conducted a retrospective cohort analysis of 195,178 UK patients, and found that patients in the UK with more severe cases of HK have a higher incidence of adverse

clinical outcomes, including MACE outcomes (e.g. cardiac arrhythmia) and all-cause hospitalisation.[49]

Mortality burden

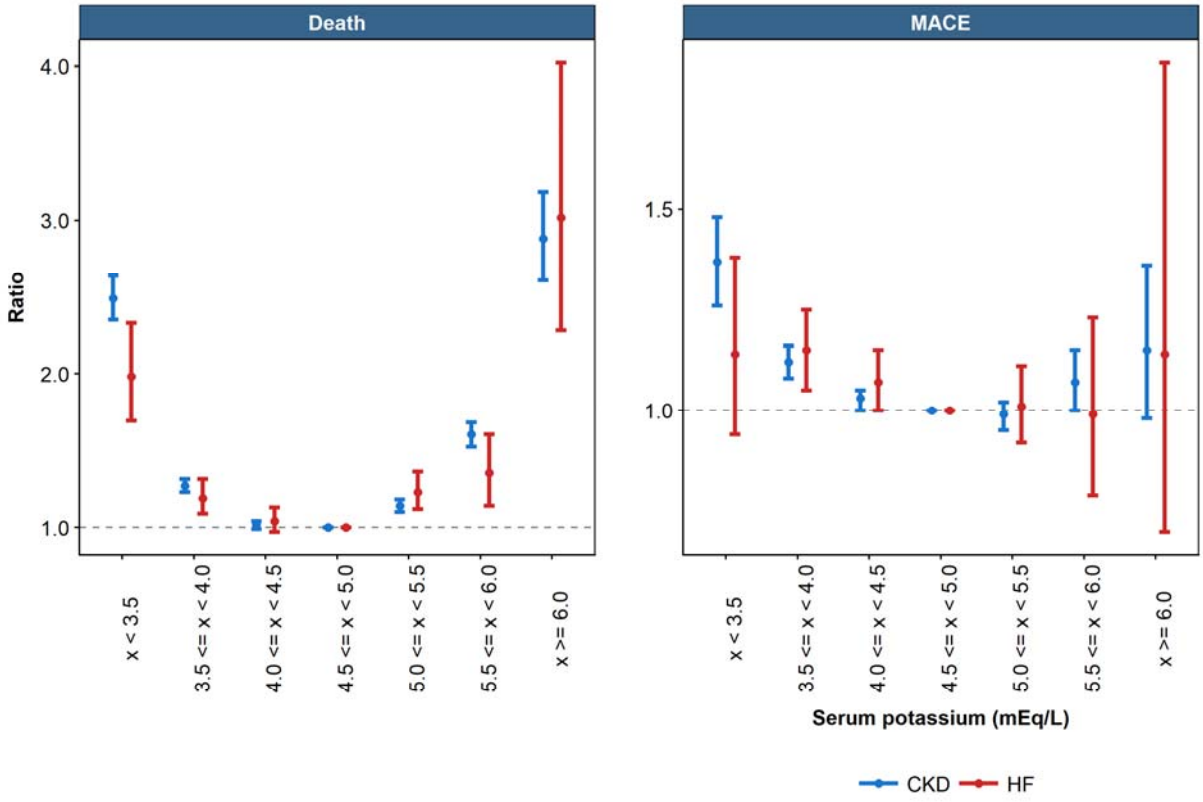
HK is associated with an increased risk of death if untreated.[15,41,43,44,50-54] A number of studies, including the large retrospective cohort study by Luo et al (2015)[43] and the UK CPRD risk equation study[44-46], have shown a 'U-shaped' association between levels of S-K and the risk of death for CKD or HF patients, as shown in Figure 2 and Figure 3.[43-46,53-55] Such an association has also been observed in studies of hospitalised patients, and patients with other comorbidities, such as hypertension and diabetes.[50,51,54,56,57]

Figure 2: Adjusted IRRs for A) MACE and B) mortality in CKD patients according to S-K – pooled across eGFR data



Abbreviations: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IRR, incidence rate ratio; MACE, major adverse cardiovascular event; S-K, serum potassium.
Source: Luo et al.[43]

Figure 3: UK CPRD risk equation study: adjusted IRRs for mortality and MACE by levels of S-K in CKD and HF patients



Abbreviations: CKD, chronic kidney disease; CPRD, Clinical Practice Research Datalink; HF, heart failure; IRR, incidence rate ratio; MACE, major adverse cardiovascular events; S-K, serum potassium.
Source: Qin et al. 2017, Qin et al. 2017, McEwan et al. 2017.[44-46]

B.1.3.2.1 Hyperkalaemia in CKD

Morbidity

Luo et al. (2015) conducted a retrospective analysis of the association between S-K levels and MACE, which comprised arrhythmia, myocardial infarction (MI), stroke and HF exacerbation, in 55,266 patients with CKD in the USA. Overall, they found a 'U-shaped' association between S-K levels at the IRR for MACE (pooled across all eGFR strata see Figure 2); indicating that patients with an abnormally low and high level of potassium had a significantly higher incidence of events. This study showed that the IRR for MACE and mortality was 1.88 (95% CI, 1.66 to 2.12) and 3.13 (95% CI, 2.52 to 4.34) respectively, for CKD patients with S-K ≥6.0 mmol/L compared to those with S-K 4.5–4.9 mmol/L.[43] This association between S-K levels and MACE outcomes is supported by further published data from a pooled analysis of CKD and HF patients in Qin et al. (see Figure 3) and the LABKA study in patients with CKD.[41,44,46,47]

Mortality

Several studies have identified a 'U-shaped' association between S-K levels and mortality in CKD patients, specifically.[41,43,44,51,54,58,59] Kovesdy et al. (2018) analysed 1,217,986 patients, in the CKD Prognosis Consortium (CKD-PC); a global collaboration, incorporating cohorts with at least 1000 participants, and includes patients from the UK. The risk relationship between potassium levels and adverse outcome was U-shaped, with the lowest risk at serum potassium of 4–4.5 mmol/L. Compared with a reference of 4.2 mmol/L, the adjusted hazard ratio (HR) for all-cause mortality was

1.22 (95% CI, 1.15 to 1.29) at 5.5 mmol/L and 1.49 (95% CI, 1.26 to 1.76) at 6.0 mmol/L. Risks were similar by eGFR, albuminuria, RAASi use and across all cohorts.[59]

In their analysis of electronic health records of CKD patients in the US (n=55,266), Luo et al. (2015) found that compared with S-K levels between 4.5 and 4.9 mmol/L, the risk of mortality was higher in each of the other S-K bands (both lower and higher), as was seen for the association of S-K and the risk of MACE.[43] The rate of mortality was 14% higher for those patients with S-K between 5.0 and 5.4 mmol/L (IRR 1.14; 95% CI, 1.04 to 1.26), 60% higher for the 5.5–5.9 mmol/L group (IRR 1.60; 95% CI, 1.37 to 1.88), and three times higher for patients with S-K levels ≥6.0 mmol/L (IRR 3.31; 95% CI, 2.52 to 4.34).

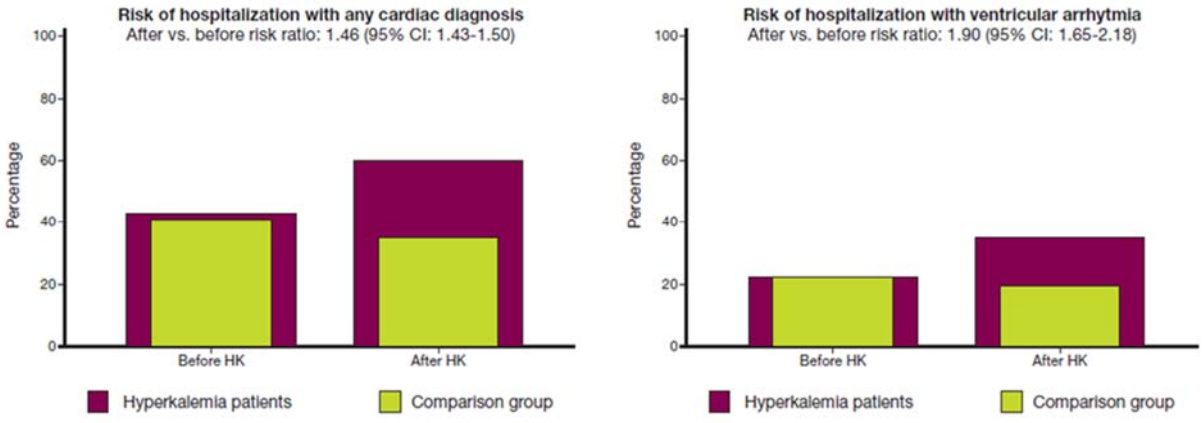
The relationship between HK and mortality has also been investigated as part of the UK CPRD Risk Equation study in the UK, and also the LABKA study in Northern Denmark.[41,44,60]

B.1.3.2.2 Hyperkalaemia in heart failure

Morbidity

Data is available from the UK CPRD risk equation study and the LABKA study on the cardiovascular outcomes of HK patients with HF.[15,53] In the LABKA study of HF patients with HK (n=12,340), the risk of hospitalisation due to ventricular arrhythmia or any cardiac hospital diagnosis was found to increase in the time intervals of 6 months before and 6 months after the defining HK event, whereas the risk remained relatively unchanged for matched patients without HK (see Figure 4).[15] In the UK CPRD risk equation study, the analysis of clinical outcomes of HF patients (n=23,541) showed a U-shaped association between MACE and S-K, with higher IRRs observed for cases of both hyper- and hypokalaemia when compared with S-K ≥4.5 to <5.0 mmol/L (see Figure 3). [44-46]

Figure 4 LABKA study: Risk of hospitalisation due to ventricular arrhythmia or any cardiac diagnosis



Purple bars show outcomes 6 months before and after the date of the HK event in HF patients with HK. Green bars show outcomes in matched HF patients without HK. Corresponding after vs before risk ratios are estimated, adjusted for competing risk of death after HK.
Abbreviations: CI, confidence interval; HK, hyperkalaemia.
Source: Thomsen and colleagues (2017) *(Poster)*[15]

Mortality

Several studies have shown a significant association between HK and risk of mortality in patients with HF.[15,52-54,61-64]

Nunez et al. (2018) conducted a prospective study to determine the association between S-K values collected at follow-up and all-cause mortality in patients discharged from an acute heart failure

admission. A U-shaped association between potassium levels and mortality was reported in a total of 2,164 patients. Furthermore, dynamic changes in potassium were independently associated with substantial differences in mortality risk. Potassium normalisation was independently associated with lower mortality risk (p=0.001).[63]

Furthermore, Qin and colleagues (2017) observed a 'U-shaped' association between mortality and S-K in the analysis of HF patients included in the UK CPRD risk equation study (see Figure 3).[53,60] Compared with HF patients with S-K ≥4.5–<5.0 mmol/L, the risk of mortality was higher among HF patients with S-K ≥5.0–<5.5 mmol/L (adjusted IRR 1.23; 95% CI, 1.14 to 1.31), S-K ≥5.5 to <6.0 mmol/L (adjusted IRR 1.55; 95% CI, 1.38 to 1.75), and S-K ≥6.0 mmol/L (adjusted IRR 3.54; 95% CI, 2.93 to 4.28).[53] In the LABKA study, the 6-month mortality rate following the defining HK event was 36% for HF patients with HK versus 14% for matched HF controls without HK and the hazard of death at 6 months was greater for those HF patients with HK (HR 3.16; 95% CI, 2.99 to 3.35).[15]

B.1.3.2.3 Summary of morbidity and mortality burden

As highlighted by the evidence presented in section B.1.3.2, HK is associated with an increased burden to patients, carers and society as a consequence of the increased risk of MACE events and mortality at more extreme S-K levels. The risk of adverse clinical outcomes associated with HK, such as MACE or mortality, has been shown to follow a 'U-shaped' association in which the risk of an event increases at the more extreme S-K levels. When S-K levels are normalised, the risk of complications such as MACE events and mortality is reduced.

B.1.3.3 *Quality of life*

The quality of life (QoL) of patients with HK is affected by the day to day management of the condition and the adverse clinical outcomes, such as MACE events, hospitalisation or premature mortality.

Current treatment options for the management of HK are limited, with the mainstay options including down-titration/discontinuation of RAASi therapy, and the implementation of a low potassium diet where there can be a focus on restriction of fruits and vegetables due to concerns of higher potassium and phosphate levels. Healthy dietary patterns with adequate intake of fruits and vegetables and limited alcohol consumption are associated with a delay in CKD progression and improved survival in patients with stage 3 or 4 CKD.[64]

Dietary and fluid restrictions impact upon many key areas of life, in patients with end-stage renal disease (ESRD). This includes time and practicalities in organising specific diets, sensory pleasure taken from food/drink, loss of control/freedom, effect on social situations with family and friends, effect on close family members/carers and being a constant reminder of the condition.[65] As such, patients find adherence to low potassium diets a challenge (and sometimes impossible), with compliance rates reported to be low from expert clinical feedback. While a low potassium diet is one of the mainstay treatment options for managing HK, it is not viewed as particularly healthy and places the patient under a significant degree of burden/limitations as to what they can enjoy eating.[29,66]

A systematic review of 46 qualitative studies, including 816 patients with CKD, conducted by Palmer et al, in 2013 aimed to summarise patients' perspectives of dietary and fluid management and concluded that dietary and fluid restrictions are disorientating and an intense burden for patients with CKD.[67] For example, patients reported that dietary and fluid restrictions had significant

challenges for them socially, left them feeling deprived and experienced difficulties navigating change, frequently fighting the temptation to enjoy food. Some of the comments raised by patients included:

- '*It means that … sometimes you go to some place to eat and there's all this food lying around and you realise that if you don't eat … you know, offend somebody*' and '*I don't have any social life now, although I could do but I don't trust myself to go to dinners or cocktail parties because of drinking and eating*'
- *'Lots of changes … Well, my diet. It took away all my goodies.' 'I found my diet has been quite difficult … of all the healthy food I've been cooking it has had to stop'*
- '*Just name anything and you'd find out that I shouldn't eat it'.*

A UK study carried out by Hollingdale et al. (2008) explored how the role of diet in renal disease is conceptualised by patients in terms of its relevance, importance and ease of adoption. Three key themes were apparent from six interview transcripts, including: 1) personal attitudes/emotions; 2) impact on life; and, 3) information and knowledge. Theme 1 highlighted the negative emotions displayed by patients including confusion, depression, uncertainty and frustration about what diet they should be following at different stages of their renal disease. One main issue was the perception that they were giving up a 'healthy diet', an issue that most patients found difficult to comprehend. Theme 2 included the impact of dialysis, diet, renal disease and symptoms on patients' lives (it was commonly discussed that the nature of the renal diet was restrictive) and adherence issues. Theme 3 highlighted that patients wanted more information, given in a timely and simple manner.[66]

HK may also lead to an emergency hospital admission with some patients being hospitalised with an extended duration of stay, thus further reducing QoL.[68-70] The impact of hospitalisation on QoL was studied in a prospective, observational study of 933 patients in the US and Canada with new onset atrial fibrillation.[71] The study showed that being hospitalised was associated with decrements in QoL for patients. Furthermore, due to the need of discontinuation/ down-titration of RAASi therapy, HK creates an additional burden on QoL by complicating and compromising the management of patients' underlying conditions, such as CKD and HF.[11,72,73]

There is limited QoL data on the direct impact of HK as there are no disease-specific QoL instruments. However, dietary restrictions that are routinely used as part of clinical practice have been shown in qualitative analyses, to impact on the QoL of patients and their carers. Furthermore, it can lead to hospitalisations and alternations in life-saving medications. Together, these demonstrate that there is an unmet need around HK, dietary restrictions and QoL for patients and their carers. Hence managing HK by liberating patient dietary restrictions may offer hope to patients who have struggled to maintain an appropriate diet, and ultimately improve QoL for patients and carers.

B.1.3.4 *Economic burden*

Overview

In addition to the substantial impact of HK on mortality and morbidity, there is also a significant economic burden associated with HK in terms of increased healthcare utilisation (from increased MACE events, the number of hospitalisations and the overall management of HK), and the costs associated with this resource use. An analysis of patients with CKD who a hyperkalaemic event in Northern and Central Denmark reported a significant increase in healthcare resource (HCR) use in

the first 6 months after their first hyperkalaemic event when compared to matched CKD patients. When comparing the HCR costs in the 6 months prior to and after the event there was an increase of €8,391 in those patients with an HK event versus those without.[74]

While there is limited UK data evaluating the economic burden, numerous studies across the EU and US have reported a consistent association between HK, severity of the event, and increase in healthcare resource use as described below.

Healthcare utilisation

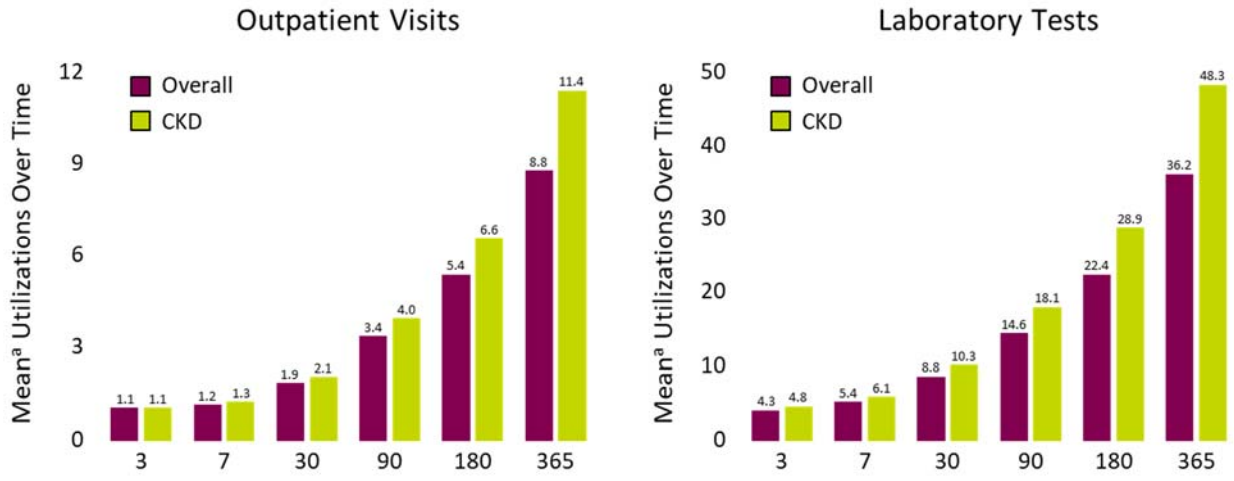
The healthcare resource utilised by patients with HK has been assessed in a number of US-based studies, with a higher level of resource use reported for those patients with HK than for those without the condition.[75-77] For example, the study conducted by Xie and colleagues (2014) (N=90,528 Medicare patients) found that patients with high potassium levels (International Classification of Diseases [ICD]-9-CM diagnosis code 276.7) were more likely to utilise healthcare resources, such as inpatient visits (37.4% versus 3.4%) and outpatient visits (75.5% versus 47.7%), compared to those matched controls without HK.[75]

Higher levels of resource use for patients with HK compared to those without HK have also been reported for specific comorbidities, such as CKD and HF, as described below.

Hyperkalaemia in CKD patients and healthcare resource utilisation

In the UK, healthcare resource use associated with CKD patients who had a first event of HK up to 365 days after the incident event were analysed as part of the UK CPRD analysis.[78] The proportion of patients using healthcare resources, such as outpatient visits, hospitalisations and laboratory tests, increased by >70% between days 3 and 7 and continued to rise over time for all healthcare resource outcomes, including outpatient visits and tests, for both the overall study population and the CKD subgroup (see Figure 5). Compared to the overall population, the mean number of healthcare resource utilisations was greater for patients with CKD.

Figure 5: UK CPRD analysis: mean number of healthcare resource utilisations over time in the overall population and CKD subgroup (n=34,912)



Mean calculated among patients who had experienced ≥1 healthcare resource utilisation
Abbreviations: CKD, chronic kidney disease; CPRD, Clinical Practice Research Datalink.
Source: Qin and colleagues (2017) *(Poster)*[78]

Further data has shown a consistent impact on resource use.[41,43,47]

B.1.3.4.1 Hyperkalaemia in HF and healthcare resource utilisation

Resource use associated with HF patients with a first event of HK was reported as part of the LABKA study.[15,79] Of the 12,340 incident HF patients with HK in this study, the proportion of patients with any acute hospitalisation increased in the 6-month period after the first HK event (73.7%), when compared with the 6-month period before the first HK event (53.3%) (RR, 1.41; 95% CI, 1.38 to 1.44), as did the proportion of patients admitted to intensive care (increased from 3.3% to 14.9%; RR, 5.29; 95% CI, 4.77 to 5.86).[15,79] When compared with matched CKD patients without HK, the hazard ratios for acute hospitalisations (HR 2.57; 95% CI, 2.48 to 2.66) and intensive care unit (ICU) admission (HR 4.92; 95% CI, 4.44 to 5.45) 6 months after the HK event were higher for those patients with HK.[15] Increased hospitalisation rates and healthcare resource use have been observed in additional studies in patients with HK and HF/CKD.[27,43,80-82]

Hospital length of stay

HK is also associated with increased hospital length of stay (LoS), which raises costs for both healthcare systems and patients.[74,79,83, 13, 76, 83, 90, 96, 98] LoS for patients with HK and concomitant CKD or HF was analysed as part of the LABKA study.[47,79] This analysis found that, on average, the number of hospital bed days (acute and non-acute) approximately doubled in the 6 months after the first event of HK compared with the 6-month interval before the event for both CKD and HF patients (significant increase in non-acute hospital bed days for CKD patients; $p<0.05$), whereas for matched patients without a HK event during follow-up, the number of acute and non-acute hospital bed days remained relatively stable across the same time period.[47,79] A UK study using CPRD data to identify patients with CKD reported a statistically significant increase in the LoS in patients with HK, defined as ≥5.0, ≥5.5 and ≥6.0 mmol/L. [84]

Summary

Due to the increased use of healthcare resources and LoS, HK is associated with considerable direct medical costs via the development of complications, such as MACE events, additional disease management and premature mortality. For example, research from Germany has investigated the cost of preventable HK, and, based on published data on hospitalisations and mortality reported in MRA trials, the authors concluded that HK may be responsible for an unnecessary expenditure of €21.8 million (2007 value).[85]

B.1.3.5 *Clinical pathway of care*

Patients with HK can be managed via two discrete treatment pathways depending on their S-K levels and where they present to hospital. In general, patients may present with HK in the acute or chronic setting as part of the patient's ongoing care of CKD or HF.

The acute management of patients is usually reserved for those that require emergency treatment in A&E or an acute medical unit (AMU) to stabilise the myocardium and shift potassium into the cells as quickly as possible. Due to serious AEs associated with severe HK (usually defined as ≥6 mmol/L), temporising agents are commonly used to lower S-K levels. Following the initial reduction, there is need to treat the underlying condition that led to the patient becoming hyperkalaemic, and to ensure that potassium levels remain within the normal range.

In contrast, the chronic management of patients is usually the responsibility of nephrologists, cardiologists and HF nurses who routinely manage patients with CKD and/or HF (in addition to other comorbidities) as an outpatient. In this setting, the majority of patients (approx. 80%) will be on cardiorenal protective medicines, such as RAASi therapies, and therefore patients' S-K levels will be

regularly monitored. UK clinical expert input from seven cardiologists and nephrologists indicated that treatment of HK would typically begin at a threshold of ≥5.5 mmol/L.[29] In contrast to acute care physicians, cardiologists/nephrologists have a greater experience at managing patients with comorbid conditions and HK, and therefore would not typically consider emergency treatment with temporising agents until a higher S-K threshold of ≥6.5 mmol/L.

Based on feedback from a clinical advisory board and expert clinical opinion (2x A&E consultants, 3x nephrologists, and 2x cardiologists),[29,86] SZC is expected to be positioned within the acute care pathway following treatment with temporising agents such as insulin-glucose, and an alternative to calcium resonium, and in the chronic setting as an alternative to current standard of care, which is down-titration and discontinuation of RAASi therapy and low potassium diet. Current standard of care is aligned to national guidelines (e.g. NICE and Kidney Disease: Improving Global Outcomes [KDIGO]), and has been validated with UK clinicians.

A summary of the current recommendations from UK clinical experts and anticipated positioning of SZC is present below and in Figure 6 [29]

B.1.3.5.1 Acute HK management

The UK Renal Association guidelines recommend following a logical five-step-approach to the treatment of acute HK: Step 1. Protect the heart; Step 2. Shift potassium into cells; Step 3. Remove potassium from body; Step 4. Monitor potassium and glucose; Step 5. Prevent recurrence.[4]

These steps are summarised as followed:

- Step 1: Protect the heart: Intravenous (IV) calcium salts – It is recommended that IV calcium chloride or calcium gluconate is given to patients with HK, in the presence of electrocardiogram (ECG) evidence of HK
- Step 2: Shift potassium into cells: insulin-glucose infusion, salbutamol nebuliser: It is recommended that insulin-glucose by IV infusion is used to treat moderate and severe HK (K ≥6.0 mmol/L). It is recommended that salbutamol is used as an adjuvant therapy for moderate and severe HK (K ≥6.0 mmol/L)
- Step 3: Remove potassium from the body: cation-exchange resins: It is recommended that cation-exchange resins are not used in the emergency management of severe HK, but may be considered in patients with mild-to-moderate HK (S-K=5.5–6.4mmol/L). This recommendation is based on evidence that shows sodium or calcium cations have a slow onset of action that limits their use in emergencies. Calcium resonium is more commonly prescribed
- Step 4: It is recommended that S-K is closely monitored to assess efficacy of treatment and to look for rebound HK after the initial response to treatment wanes, and that blood glucose concentrations are monitored at regular intervals
- Step 5: Prevent recurrence of HK with the use of calcium resonium

Many local guidelines reflect the national guidelines, with acute IV treatments recommended with S-K ≥6.0 mmol/L.[87-94] Some guidelines recommend concurrent administration of calcium resonium, with the caveat that the onset of action is slow,[88,92] as well as ceasing all potassium retaining medications such as ACEi/ARBs and MRAs and dietary advice.[88,89,91-93]

In clinical practice, UK clinicians confirmed that local guidelines broadly replicate the recommendations presented by the UK Renal Association and these are adhered to in the acute setting, such as A&E and AMU. In general, clinicians confirmed that all patients with S-K levels

≥6.0 mmol/L would be treated with temporising agents followed by calcium resonium in some cases. Due to the temporising nature of insulin-glucose, feedback indicated that it was not uncommon for patients to require at least one additional IV infusion of insulin-glucose to maintain normokalaemia. In addition, acute care physicians would generally discontinue all medications which contribute to HK, such as RAASi therapy, with approximately 70-80% of patients likely to be receiving treatment with these medications.[29]

However, there are a number of issues arising from this approach:

- Hypoglycaemia is a common complication of insulin-glucose treatment
- Insulin-glucose/salbutamol are only temporising agents and last no more than 4–6 hours, with the majority of patients requiring re-treatment as total body S-K is not reduced
- Calcium resonium has a long onset of action, so it is inappropriate for the emergency setting and is often described by patients as unpalatable
- If patients are on ACEi/ARB/MRAs, these medications are ceased and often primary care are reluctant to re-start these medications as the discontinuation is typically recorded as an allergy on the patient's summary of care record[29]

Therefore, given the fast onset of action and favourable tolerability profile vs insulin-glucose, clinicians would recommend that SZC should be positioned as a treatment option following initial treatment with insulin-glucose and as alternative to repeat treatment with IV insulin-glucose and calcium resonium. [29]

B.1.3.5.2 Chronic HK management

There are limited treatment pathways for the management of patients in the chronic setting, however, NICE guidelines for 'Chronic Kidney Disease in Adults: Assessment and Management state (CG182)' recommends the following:

- 1.6.8: Do not routinely offer a RAASi to people with CKD if their pre-treatment serum potassium concentration in greater than 5.0 mmol/L, and
- 1.6.11: Stop RAASi if the serum potassium concentration increases to 6.0 mmol/L or more and other drugs known to promote HK have been discontinued[7]

The cut-off S-K levels routinely used in clinical practice in England to initiate treatment HK are most relevant to this submission; the diagnosis of HK and treatment initiation is based on S-K level ≥6.0 mmol/L in the acute setting and ≥5.5 mmol/L in the chronic setting based on UK expert opinion and local clinical guidelines. This is consistent with UK guidelines, including the UK Renal Associations Clinical Practice Guidelines and the British Society of Heart Failure position statement for HK.[4-8]

The issues in the chronic setting, are as described in the literature and referenced in the section 'Risk factors: RAASi induced' and hence revolve around

- Patients not receiving treatment with RAASi treatment due to HK, in particular in those with HF and CKD where these treatments reduce morbidity and mortality
- Patients not being optimised to maximal dose of these medications, due to HK, which is also a cause of increased morbidity and mortality
- Non-compliance with reduced potassium diets and an effect of QoL in these patients, due to these restrictive diets

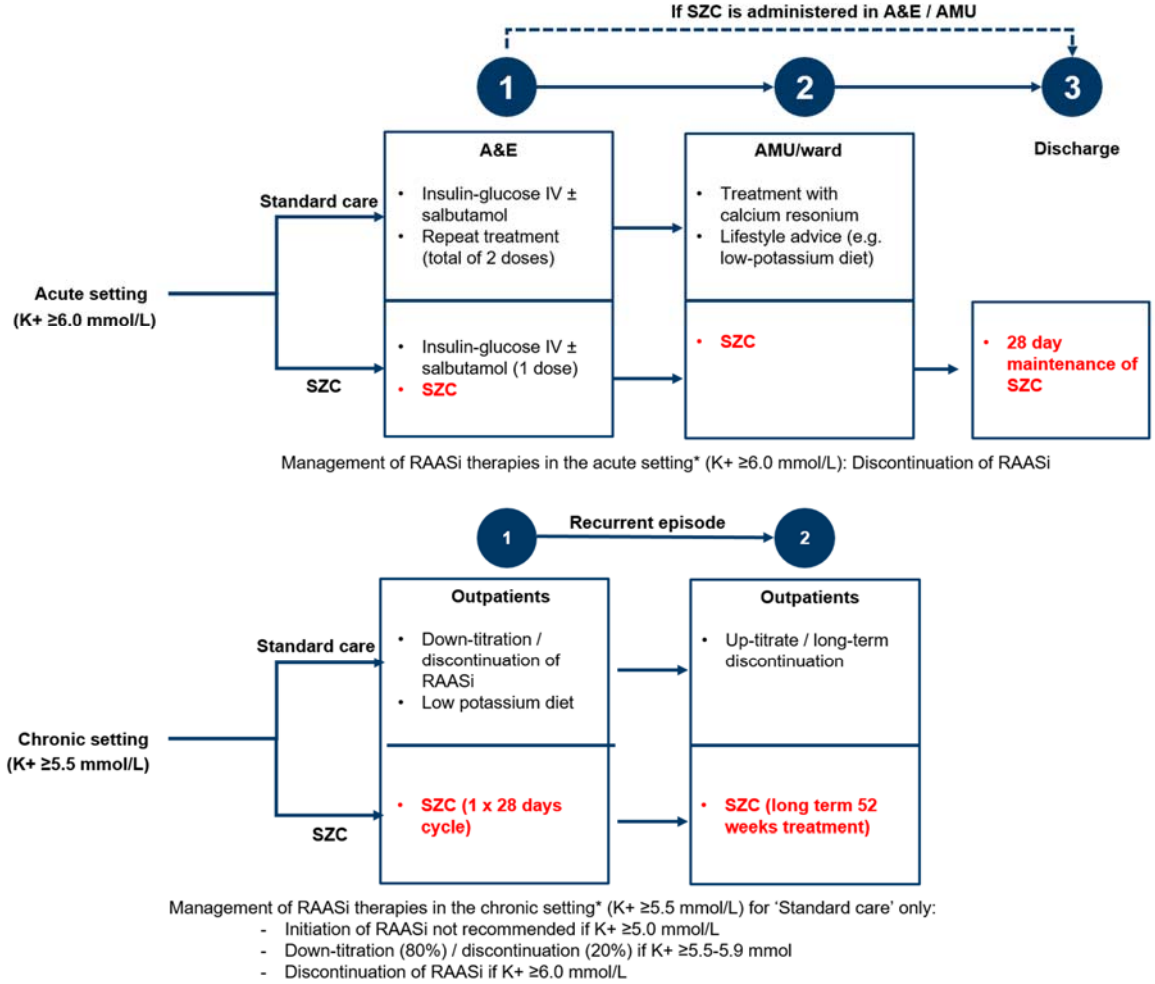
Furthermore, clinical experts indicated that HK is a significant challenge in clinical practice, and that initiating/optimising RAASi therapy is typically limited by the increased risk of HK; particularly those patients with HF and more advanced stages of CKD. In addition, clinicians also confirmed that there are currently no pharmacological interventions used in clinical practice to remove excess potassium, and the mainstay treatment options comprised down-titration/discontinuation of RAASi therapy, as per clinical guidance. In general, clinicians would begin down-titrating patients with S-K ≥5.5 mmol/L, and discontinue if levels increased ≥6.0 mmol/L. Furthermore, in those clinicians who would typically wait until higher thresholds prior to down-titration/discontinuing RAASi therapy, a threshold of ≥5.5 mmol/L was deemed clinically appropriate if an effective and well tolerated pharmacological intervention was to be available[29].

In line with clinical recommendations, in the chronic pathway, SZC is anticipated to be used as an alternative treatment option to down-titration and discontinuation to RAASi therapy at potassium thresholds of ≥5.5 mmol/L.

B.1.3.5.3 Clinical pathway of care and anticipated positioning of SZC in UK clinical practice

The anticipated positioning of SZC in the UK is summarised in Figure 6 below.

Figure 6: Anticipated positioning of SZC in UK clinical practice



* As per clinical experts opinion [29]: Abbreviations: A&E, accident and emergency, AMU, acute medical unit, RAASi, renin-angiotensin-aldosterone system inhibitor; SZC, sodium zirconium cyclosilicate; IV, intravenous.

B.1.3.6 *Equality considerations*

We do not expect assessment of this technology to raise any equality issues.

B.2. Clinical effectiveness

B.2.1 *Identification and selection of relevant studies*

Please see Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 *List of relevant clinical effectiveness evidence*

Table 4. Clinical effectiveness evidence for study ZS-002

Study	**ZS-002, NCT01493024, Ash et al, 2015 [3]**				
Study design	Multicentre, prospective, randomised, double-blind, placebo-controlled, Phase 2 study with three dose cohorts				
Population	Patients aged >18 years with stable Stage 3 CKD, an estimated glomerular filtration rate of 30–60 ml/min per 1.73 m^2 estimated by CKD Epidemiology Collaboration (CKD-EPI) equation, serum potassium levels between 5.0 and 6.0 mEq/L and with the ability to have repeated blood draws or effective venous catheterisation				
Intervention(s)	Sodium zirconium cyclosilicate				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes	X	**Indicate if trial used in the economic model**	Yes	
	No			No	X
Rationale if trial not used in model	Dose-escalating study with only 24 patients receiving a licensed dose of SZC (10g).				
Reported outcomes specified in the decision problem	• S-K levels • Time to normalisation • AE of treatment				
All other reported outcomes	• Changes from baseline for sodium, magnesium, calcium, bicarbonate and blood urea nitrogen • Serum calcium, magnesium, sodium, blood urea nitrogen, creatinine, bicarbonate • Urinary sodium, potassium, creatinine excretion, • Urinary sediment and urea nitrogen excretion				

Table 5: Clinical effectiveness evidence for Study ZS-003

Study	**ZS-003, NCT01737697, Packham et al., 2015 (ZS-003) [1,95-98]**
Study design	Multicentre, two-stage, double-blind, placebo-controlled, Phase 3 study
Population	Patients aged >18 years of age with an i-STAT potassium value between 5.0 and 6.5 mmol/L at screening and the ability to have repeated blood draws or effective venous catheterisation
Intervention(s)	Sodium zirconium cyclosilicate

Study	ZS-003, NCT01737697, Packham et al., 2015 (ZS-003) [1,95-98]				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	**Yes**	X	**Indicate if trial used in the economic model**	**Yes**	
	No			**No**	X
Rationale if trial not used in model	The ZS-003 trial population is not consistent and generalisable to UK clinical management of patients with HK and CKD or HF due to approximately three-quarters of patients having a baseline S-K level below 5.5% mmol/L (threshold at which treatment begins in UK clinical practice)				
Reported outcomes specified in the decision problem	• S-K levels • Time to normalisation • AE of treatment				
All other reported outcomes	• Changes from baseline for sodium, magnesium, calcium, bicarbonate and blood urea nitrogen • The proportion of patients receiving RAASi is reported within the patient baseline characteristics				

Abbreviations: AE, adverse event; CKD, chronic kidney disease; HK, hyperkalaemia; RAASi, renin-angiotensin-aldosterone system inhibitors; S-K, serum potassium.

Table 6: Clinical effectiveness evidence for Study ZS-004

Study	ZS-004, NCT02088073, Kosiborod et al., 2014 (004) [1,98-101]				
Study design	Multicentre, multi-phase, multi-dose, prospective, randomised, double-blind, placebo-controlled maintenance Phase 3 study				
Population	Adult patients aged >18 years of age with an i-STAT potassium value ≥5.1 mmol/L				
Intervention(s)	Sodium zirconium cyclosilicate				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	**Yes**	X	**Indicate if trial used in the economic model**	**Yes**	X
	No			**No**	
Rationale if trial not used in model	N/A				
Reported outcomes specified in the decision problem	• **S-K levels** • **Use of RAASi therapy** • **Time to normalisation** • **AE of treatment**				
All other reported outcomes	• Changes from baseline for sodium, magnesium, calcium, bicarbonate and blood urea nitrogen				

Abbreviations: AE, adverse event; RAASi, renin-angiotensin-aldosterone system inhibitors; S-K, serum potassium.

Table 7: Clinical effectiveness evidence for Study ZS-004E

Study	**ZS-004E** [1,102]				
Study design	An open-label extension Phase 3 study on HARMONIZE, study ZS-004				
Population	All patients who completed Study ZS-004 and had an i-STAT potassium value between 3.5 and 6.2 mmol/L, inclusive, or who prematurely discontinued the Extended Dosing Phase of Study ZS-004 due to hypokalaemia or hyperkalaemia and had a mean i-STAT potassium value between 3.5 and 6.2 mmol/L were eligible to participate in Study ZS-004E				
Intervention(s)	Sodium zirconium cyclosilicate. No mandated dietary restrictions or changes in RAASi therapy were required				
Comparator(s)	None				
Indicate if trial supports application for marketing authorisation	**Yes**	X	**Indicate if trial used in the economic model**	**Yes**	
	No			**No**	X
Rationale if trial not used in model	The ZS-005 study provides more robust long-term data due to the limitations in the study design of this extension study. A meta-analysis is not feasible (see Section B.2.8)				
Reported outcomes specified in the decision problem	• S-K levels • Time to normalisation • AE of treatment				
All other reported outcomes	• Changes from baseline for sodium, magnesium, calcium, bicarbonate, blood urea nitrogen, creatinine, phosphorus, and serum aldosterone				

Abbreviations: AE, adverse event; RAASi, renin-angiotensin-aldosterone system inhibitors; S-K, serum potassium.

Table 8: Clinical effectiveness evidence for Study ZS-005

Study	**ZS-005 (005)** [103-105]				
Study design	Prospective, international, open-label, single-arm Phase 3 study				
Population	Adult outpatients (aged ≥18 years) with HK (defined as a S-K ≥5.1 mmol/L)				
Intervention(s)	Sodium zirconium cyclosilicate. No mandated dietary restrictions or changes in RAASi therapy were required				
Comparator(s)	None				
Indicate if trial supports application for marketing authorisation	**Yes**	X	**Indicate if trial used in the economic model**	**Yes**	X
	No			**No**	

Study	ZS-005 (005) [103-105]
Rationale if trial not used in model	N/A
Reported outcomes specified in the decision problem	• S-K levels • Use of RAASi therapy • Time to normalisation • AE of treatment
All other reported outcomes	• Changes from baseline for sodium, magnesium, calcium, bicarbonate and blood urea nitrogen

Abbreviations: AE, adverse event; RAASi, renin-angiotensin-aldosterone system inhibitors; S-K, serum potassium.

B.2.2.1 *Studies not included in the economic model*

Studies ZS-002, ZS-003, and ZS-004E were not used to populate the economic model; however, the results of these studies support the efficacy and safety profile in patients with HK and are presented in Appendix L.

The studies ZS-002, ZS-003 and ZS-004E were not included in the economic model because:

- Study ZS-002 was a double-blind placebo-controlled dose-escalating phase 2 study in patients with CKD and HK. Patients were randomised to receive escalating doses of SZC (0.3 g, 3 g, and 10 g) or placebo, TID for 2-4 days. Only 24 patients receiving a licensed dose of SZC (10 g).
- Study ZS-003 was a dosing phase 3 study randomising patients in a 1:1:1:1:1 ratio to receive treatment with placebo, or SZC at 1.25 g, 2.5 g, 5 g, or 10 g TID, followed by further randomisation of the four active treatment arms in a 1:1 ratio to continue treatment with SZC or placebo. As such, patient numbers in the licensed doses (5 g and 10 g) are small, the duration of therapy is limited, and a meta-analysis was deemed to be infeasible.
- Study ZS-004E was an 11-month extension phase 3 study to study ZS-004, where patients could be enrolled to receive treatment with 5 g or 10 g OD or 5 g once every other day, depending on serum potassium levels. However, enrolment was at the investigators' decision and did not form part of the original statistical analysis plan for Study ZS-004. In addition, 77 patients who completed Study ZS-004 and qualified for entry into this extension study were unable to participate as investigational product was not available.

Due to methodological limitations, studies ZS-004 and ZS-005 were deemed to be the most appropriate studies/data to include in the economic model.

B.2.3 *Summary of methodology of the relevant clinical evidence base*

B.2.3.1 *Comparative summary of RCT methodology*

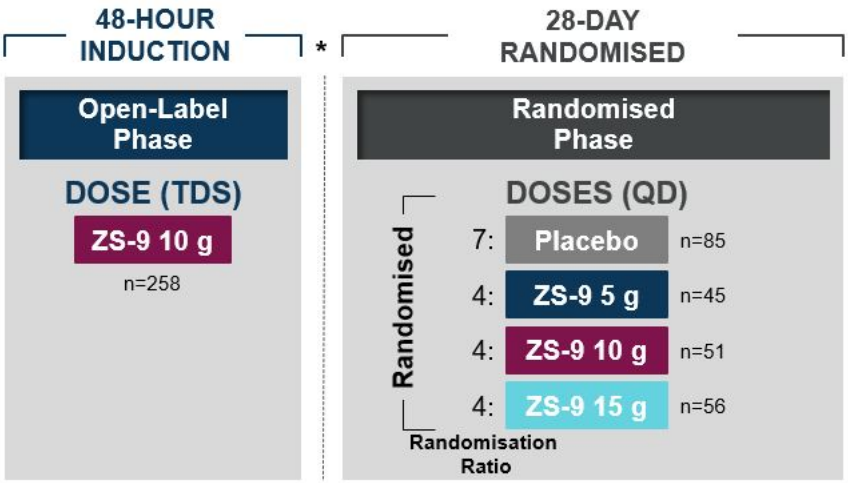
The key clinical trials used to inform the clinical efficacy, safety, and tolerability of SZC in this submission are two Phase 3 trials (ZS-004 and ZS-005) given that the populations are consistent and generalisable to UK clinical practice and management. All data from studies ZS-004 and ZS-005 are presented below. Similar data for studies ZS-002, ZS-003 and ZS-004E are presented in Appendix L. A summary of the methodologies used in the studies are summarised in Table 9. A summary of the key inclusion and exclusion criteria are shown in Table 10.

B.2.3.2 *Trial design*

The licensed dose for SZC is 5 g and 10 g and while the clinical trial programme included the 15 g dose, this is not relevant and the results for this dose are not reported. The trial designs for the relevant studies are summarised below:

- **Study ZS-004** was a Phase 3, multicentre, prospective, randomised, placebo-controlled, double-blind, dose-ranging maintenance study. A summary of the study design is shown in Figure 7. All patients were to be treated with SZC 10 g TID for the initial 48 hours (6 doses). Patients who achieved normokalaemia during the acute phase were to be randomised in a double-blind manner in a 4:4:4:7 ratio to 1 of 3 doses of SZC (5 g, 10 g, or 15 g) or placebo administered OD for a further 28 days (maintenance phase).

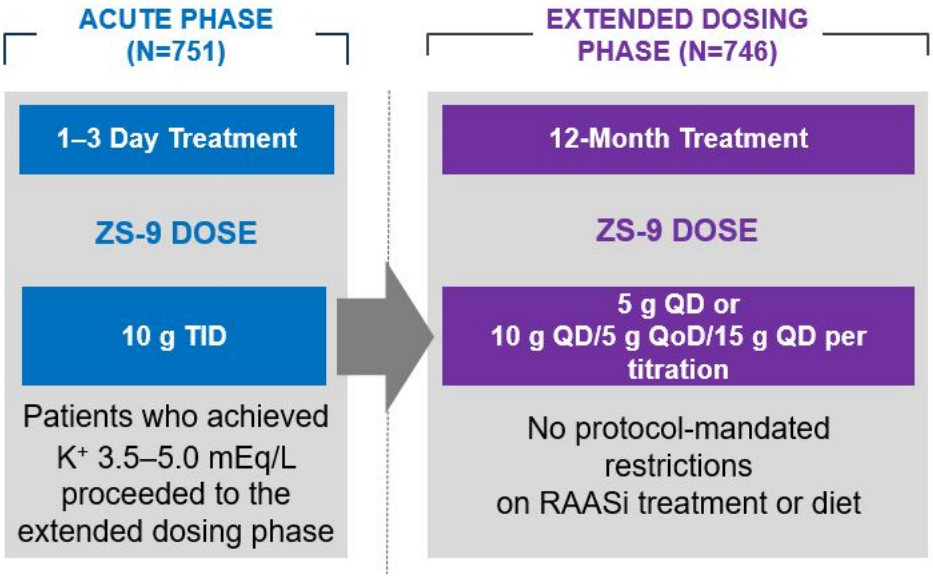
Figure 7: Study design for Study ZS-004



Abbreviations: QD, once a day; TDS, three times a day

- **Study ZS-005** was an open-label, Phase 3, multicentre, multi-dose, prospective, maintenance study to investigate the long-term (up to 12 months) safety and efficacy of SZC. A summary of the study design is shown in Figure 8. Patients in the acute phase received treatment with SZC 10 g TID for between 24 and 72 hours until normokalaemia was achieved. All patients enrolled in the open-label Extended dosing phase were dosed with SZC at a starting dose of 5 g OD and were titrated to 10 g or 15 g OD or 5 g once every other day, depending on their serum potassium levels (see Table 9).

Figure 8: Study design for Study ZS-005



Abbreviations: QD, once a day; QoD, one dose every other day; RAASi, renin-angiotensin-aldosterone system inhibitors; TID, three times a day.

Table 9: Summary of methodology of studies ZS-004 and ZS-005

Trial no. (acronym)	ZS-004	ZS-005
Trial design	Phase 3, multicentre, prospective, randomised, placebo-controlled, double-blind, dose-ranging study	Open-label, Phase 3, multicentre, multi-dose, prospective, maintenance study to investigate the long-term (up to 12 months) safety and efficacy of SZC
Study location	44 sites across the United States, Australia and South Africa	56 sites across the United States, Australia, Germany, United Kingdom, The Netherlands, and South Africa
Duration of study	• Open-label phase: 48–72 hours • Maintenance phase: 28 days	• Acute phase: 48–72 hours • Maintenance phase: 12 months
Method of randomisation	• Randomisation was deployed using a telephone-based IVRS or a web-based IWRS system which assigned each patient with a unique number • During the maintenance phase, patients were randomly allocated to 1 of 3 doses of SZC (5 g,10 g, and 15 g) or placebo in a 4:4:4:7 ratio. All randomisations were assigned in a double-blind fashion using the kit number based on the randomisation	• As the study was an open-label study, there was no blinding or randomisation. All patients were assigned a unique identification number and drug kits were assigned by a telephone-based IVRS or web-based IWRS system
Method of blinding	Study was double-blind (patient and care provider)	N/A
Eligibility criteria for participants	Adults aged ≥18 years with i-STAT K values ≥5.1 mmol/L within day 1 of the acute phase study	Adults aged ≥18 years) with i-STAT K values ≥5.1 mmol/L within day 1 of the acute phase study
Trial drugs	In total, 258 patients received 10 g SZC TID for 48 hours, followed by randomisation to receive the following OD (n=251): • SZC 5 g (n=45) • SZC 10 g (n=51) • SZC 15 g (n=56) • Placebo (n=85)	In total, 751 patients received 10 g SZC TID for 24–72 hours depending on the i-STAT potassium values followed by 5 g SZC OD for up to 12 months (n=746). Thereafter, the dose was adjusted based on i-STAT potassium values

Trial no. (acronym)	ZS-004	ZS-005
Dose titration		During the Extended dosing phase, the starting dose was SZC 5 g OD. Thereafter, the dose was increased or decreased in increments/decrements of 5 g OD for up to a maximum of 15 g OD or a minimum of 5 g once every other day if i-STAT potassium increased to >5.5 mmol/L or decreased to between 3.0 and 3.4 mmol/L, respectively. All i-STAT measurements triggering a dose adjustment were to be confirmed by taking a second measurement after a 10 (± 2)-minute interval. Dose adjustments required that both i-STAT potassium values met the escalation/de-escalation criterion. Any time the SZC dose was adjusted, the patient returned to the site 7 (± 1) days later for a potassium measurement and recording of AEs and concomitant medications
Permitted and disallowed concomitant medications	All patients were to continue the treatments they were on upon admission into the study There were no dietary restrictions	
Efficacy assessments performed	• The primary efficacy variable was effect on S-K. All potassium values were analysed by i-STAT as well as by the central laboratory • In Study ZS-005 aldosterone and renin samples were also obtained from sites in North America to assess the possible impact of SZC on the RAAS	
Safety assessments performed	• Safety assessments and procedures performed included physical examination with vital signs and body weight, 12-lead ECG, clinical laboratory testing, recording of concomitant medications, and the occurrence of any AEs • In Study ZS-004, healthcare utilisation data were also collected and included non-protocol-specified physician, hospital, and emergency room visits	

Trial no. (acronym)	ZS-004	ZS-005
Primary outcomes	**Maintenance phase** • Mean S-K value during study days 8–29 of the maintenance phase	**Acute phase** • **Restoration of normal serum potassium levels during the Acute Phase (S-K 3.5 to 5.0 mmol/L)** **Extended dosing phase** • **Maintenance of normokalemia (proportion of patientpatients with mean S-K+ < 5.1 mmol/L between months 3-12 (i.e. say 85-365) during the Extended Phase**
Secondary outcomes	Secondary outcomes included: **Acute phase** • Exponential rate of change in S-K values during the initial 48 hours of study drug treatment • Change and percent change from baseline in S-K values at 24 and 48 hours after start of dosing • Proportion of patientpatients who achieved normalisation in S-K values at 24 and 48 hours after start of dosing • Time to normalisation of S-K+ values (S-K 3.5 mmol/L to 5.0 mmol/L) **Maintenance phase** • Time to hyperkalaemia • Number of normokalaemic days during the maintenance phase inclusive of days 8–29 and change • Mean change and mean percent change in S-K+ values from acute phase baseline • Mean change and mean percent change in S-K+ values from maintenance phase baseline • Proportion of normokalemic patients in the Maintenance Phase	Secondary outcomes included: • Proportion of patients with mean S-K between 3.5 and 5.5 mmol/L, inclusive, months 3–12 • Mean S-K values months 3–12, months 6–9, and months 9–12 • Change (absolute and percent) from acute phase baseline in S-K values at each Extended dosing phase day 8–365/end of study for patients in the Extended Dosing Phase ITT population

Trial no. (acronym)	ZS-004	ZS-005
Pre-specified exploratory outcomes (ZS-005 only)	• Proportion of patients using RAASi at Extended Dosing Phase baseline and at quarterly intervals thereafter • Proportion of patients who had an increase in RAASi dose or start on RAASi overall and by quarterly interval using the Extended Dosing Phase Safety Population presented for all patients, all diabetic patients, all HF patients, and all patients with eGFR <60 mL/min • Among those in the Extended Dosing Phase Safety Population initially on RAASi at baseline: proportion of patients who had a decrease in RAASi dose or discontinuation of RAASi overall and by quarterly intervals and Kaplan-Meier life table of the time to RAASi decrease or discontinuation overall and by quarterly intervals	
Pre-planned subgroups	• CKD • DM • HF • RAASi • Baseline eGFR • Baseline S-K • Age was also considered as a subgroup in ZS-005	

Abbreviations: AE, adverse event; CKD, chronic kidney disease; DM, diabetes mellitus; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HF, heart failure; ITT, intent-to-treat; IVRS, interactive voice response system; IWRS, interactive web response system; OD, once a day; RAASi, renin-angiotensin-aldosterone system inhibitors; S-K, serum potassium; SZC, sodium zirconium cyclosilicate; TID, three times a day.

B.2.3.3 *Eligibility criteria*

Table 10: Key inclusion/exclusion criteria for studies ZS-004 and ZS-005

Inclusion	Exclusion
Studies ZS-004 and ZS-005 • Provision of written informed consent • Male or female patients over 18 years of age • Ability to have repeated blood draws or effective venous catheterisation • Women of childbearing potential were to be using two forms of medically acceptable contraception (at least one barrier method) and have a negative pregnancy test at screening. Women who were surgically sterile or those who were post-menopausal for at least 2 years were not considered to be of childbearing potential **Study ZS-004 only** • Two consecutive i-STAT potassium values, measured 60 minutes apart, both ≥5.1 mmol/L and measured within 1 day of the first SZC dose on acute phase study day 1: there was no limitation on the upper limit of S-K measurements **Study ZS-005 only** • For patients outside Germany: Two consecutive i-STAT potassium values, measured 60 (±15) minutes apart, both ≥5.1 mmol/L and measured within 1 day before the first dose of SZC on acute phase day 1 • For patients in Germany: Two consecutive i-STAT potassium values, measured 60 (±15) minutes apart, both ≥5.1 mmol/L and ≤6.5 mmol/L and measured within 1 day before the first dose of SZC on acute phase day 1 • Outside the EU: Women of childbearing potential must have had a negative pregnancy test within 1 day prior to the first dose of SZC on acute phase day 1 and sexually active women of childbearing potential must have been using two forms of medically acceptable contraception, with at least one being a barrier method • For patients in the European Union: Women of childbearing potential must have had a negative pregnancy test within 1 day prior to the first dose of SZC on acute	**Studies ZS-004 and ZS-005** • Pseudohyperkalaemia signs and symptoms, such as haemolysed blood specimen due to excessive fist clenching to make veins prominent, difficult or traumatic venipuncture, or history of severe leukocytosis or thrombocytosis • Treatment with lactulose, rifaximin, or other non-absorbed antibiotics for hyperammonaemia within the last 7 days • Treatment with resins (such as sevelamer acetate, SPS [e.g. Kayexalate®]), calcium acetate, calcium carbonate, or lanthanum carbonate, within the last 7 days • Life-expectancy of less than 3 months • Severely physically or mentally incapacitated and, in the opinion of the investigator, was unable to perform the tasks associated with the protocol • Women who were pregnant, lactating, or planning to become pregnant • Diabetic ketoacidosis • Presence of any condition which, in the opinion of the investigator, placed the patient at undue risk or potentially jeopardised the quality of the data to be generated • Known hypersensitivity or previous anaphylaxis to SZC or to components thereof • Previous treatment with SZC • Treatment with a drug or device within the last 30 days that had not received regulatory approval at the time of study entry • Cardiac arrhythmias that required immediate treatment • Receiving dialysis **Study ZS-005 only** • Documented GFR <15 mL/min within 90 days prior to study entry • For patients in Germany: Patients presenting with a heart-rate QTc interval of 450 msec and additional risk factors for Torsade de pointes (e.g. heart failure or family history of long QT-syndrome) and taking concomitant medications causing QT prolongation • For patients in Germany: Patients who were committed to an institution by an order issued

Inclusion	Exclusion
phase day 1 and sexually active women of childbearing potential must have been using a highly effective medically acceptable contraception • Women who were surgically sterile or those who were post-menopausal for at least 2 years were not considered to be of childbearing potential	either by the judicial or the administrative authorities • For patients in Germany: Patients who were dependents of the Sponsor, investigator, or institution

Abbreviations: GFR, glomerular filtration rate; QTc, correct QT; S-K, serum potassium; SZC, sodium zirconium cyclosilicate.

B.2.3.4 *Study objectives*

B.2.3.4.1 Study ZS-004

The primary objective was to evaluate the safety and efficacy of three different doses of SZC administered daily for 28 days in maintaining normokalaemia (defined as S-K between 3.5 and 5.0 mmol/L, inclusive) in patients achieving normokalaemia following 2 days of acute therapy for patients with HK at baseline.

The secondary objectives were:

- Evaluating the safety and efficacy of the SZC 10 g TID dose administered for 48 hours in the acute phase in patients with HK
- Assessing the robustness of efficacy with SZC treatment for:
  - Normalising S-K (acute phase)
  - Maintaining normalised S-K (maintenance phase)
- Evaluating the effect of SZC on other electrolytes

B.2.3.4.2 Study ZS-005

The primary objective was to generate open-label, long-term (up to 12 months) safety and tolerability data for SZC in patients with HK (S-K ≥ 5.1 mmol/L).

The secondary objectives were to evaluate:

- The proportion of SZC-treated patients in whom normokalaemia was maintained over prolonged periods of time, using a dose range from 5 g once every other day to 15 g OD
- The effect of SZC on various renal and bone biomarkers over prolonged periods of time, using a dose range from 5 g once every other day to 15 g OD.

B.2.3.5 *Baseline characteristics and demographics*

Baseline demographics and disease characteristics are summarised in Table 11 and Table 12 for Studies ZS-004 and ZS-005, respectively. Across trials the patient demographics were generally similar between treatment groups. The mean age of patients ranged from 63.6 and 64.0 years, and the majority of patients were male (57.8–59.7%) and were white (83.1–83.3%). Baseline S-K values (per central laboratory) were <5.5 mmol/L for46.1% of patients,

5.5 to <6.0 mmol/L for 38.8% of patients, and ≥6.0 mmol/L for 15.1% of patients in Study ZS-004 and 38.2%, 45.0%, and 16.8% patients, respectively in Study ZS-005. Therefore, the majority of patients had a S-K value above the threshold deemed to be clinically significant and requires treatment in the UK. Consistent with the UK clinical feedback[29], most patients were receiving treatment with RAASi therapy at enrolment (69.8–80.2%) and during entry into the maintenance/extending dosing phases of the studies (58.9–73.3%). Across the trials, approximately two-thirds had CKD and one-third HF.

Table 11: Patient baseline characteristics for Study ZS-004

Characteristic	Open-label phase SZC 10 g (n=258)	Randomised maintenance phase			
		Placebo group (n=85)	SZC dose group		
			5 g (n=45)	10 g (n=51)	15 g* (n=56)
Age	64.0 (12.7)	64.3 (12.1)	61.5 (16.9)	63.8 (10.0)	64.9 (12.9)
Male – no (%)	149 (57.8)	44 (51.8)	27 (60.0)	27 (52.9)	40 (71.4)
Race – no (%)					
White	215 (83.3)	73 (85.9)	36 (80.0)	44 (86.3)	46 (82.1)
Black	37 (14.3)	10 (11.8)	8 (17.8)	5 (9.8)	9 (16.1)
Asian	5 (1.9)	3 (3.5)	0	1 (2.0)	1 (1.8)
Other	3 (1.2)	1 (1.2)	1 (2.2)	1 (2.0)	0
Weight, mean (SD), kg	87.9 (22.9)	85.1 (18.6)	89.6 (23.9)	87.4 (25.6)	87.2 (18.6)
Baseline S-K – mean (SD)	5.6 (0.4)	4.6 (0.4)	4.5 (0.4)	4.4 (0.4)	4.5 (0.4)
Acute phase S-K baseline, n (%)					
<5.5	119 (46.1)	43 (50.6)	23 (51.1)	19 (37.3)	24 (42.9)
5.5 to <6.0	100 (38.8)	30 (35.3)	17 (37.8)	23 (45.1)	26 (46.4)
≥6.0	39 (15.1)	12 (14.1)	5 (11.1)	9 (17.6)	6 (10.7)
eGFR, mean (SD)	46.3 (30.5)	48.0 (28.8)	48.0 (30.7)	44.7 (30.7)	44.9 (29.5)
Acute phase eGFR at baseline, n (%)					
<60 mL/min	179 (69.4)	52 (61.2)	31 (68.9)	38 (74.5)	41 (73.2)
≥ 60 mL/min	72 (27.9)	28 (32.9)	12 (26.7)	13 (25.5)	15 (26.8)
Comorbidities, n (%)					
CKD	169 (65.5)	50 (58.8)	29 (64.4)	36 (70.6)	37 (66.1)
HF	94 (36.4)	26 (30.6)	18 (40.0)	18 (35.3)	25 (44.6)
DM	170 (65.9)	54 (63.5)	26 (57.8)	38 (74.5)	39 (69.6)
Use of RAASi medication, n (%)	180 (69.8)	61 (71.8)	33 (73.3)	36 (70.6)	33 (58.9)

*15 g dose not licensed.

Abbreviations: CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HF, heart failure; RAASi, renin-angiotensin-aldosterone system inhibitor; SD, standard deviation; S-K, serum potassium.

Table 12: Patient baseline characteristics for Study ZS-005

Characteristic	Overall SZC group (n=751)
Age, mean (SD)	63.6 (13.03)
Male, n (%)	448 (59.7)
Race, n (%)	
White	624 (83.1)
Black	89 (11.9)
Asian	25 (3.3)
Other	13 (1.7)
Acute phase S-K baseline, n (%)	
<5.5	287 (38.2)
5.5 to <6.0	338 (45.0)
≥6.0	126 (16.8)
Acute phase eGFR at baseline, n (%)	
<60 mL/min	552 (73.5)
≥60 mL/min	190 (25.3)
Comorbidities, n (%)	
CKD	513 (58.3)
HF	285 (37.9)
DM	471 (62.7)
History of HT	622 (82.8)
Use of RAASi medication – no (%)	527 (70.2)
Diuretic use n (%)	383 (51.0)

Abbreviations: CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HF, heart failure; HT, heart transplant; RAASi, renin-angiotensin-aldosterone system inhibitor; SD, standard deviation; S-K, serum potassium.

The participant flow in the relevant RCTs is shown in Appendix D.

B.2.4 [redacted] *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

B.2.4.1 *Study ZS-004*

B.2.4.1.1 Determination of sample size

The sample size was based on the mean S-K during maintenance phase study day 8 through to 29. To optimise the comparison of three active doses versus placebo control, the placebo group had 1.73 x the number of patients per active dose. A 4:4:4:7 allocation best approximated the optimum Dunnett's allocation.

A sample size of 232 maintenance phase patients (49 per active dose and 85 placebo controls) had 90% power and 5% type 1 error for a 2-sided hypothesis to detect a mean

0.3 mmol/L advantage for maintenance phase study days 9 through 20 for any active dose versus placebo control, using a pre-specified closed testing order (highest to lowest dose); a mean 0.3 mmol/L decrease represents a meaningful advantage between any dose and placebo for a pooled 0.5 standard deviation. The sample size also had 90% power and 5% Type 1 error to detect a mean 4-day increase in days normokalaemic between any dose and placebo over the 28-day maintenance phase for a pooled 6-day standard deviation.

B.2.4.1.2 Interim analyses and stopping guidelines

No interim analyses to stop the study early for positive efficacy results were planned or performed.

If a patient developed i-STAT potassium values >7.0 or <3.0 mmol/L, or a significant cardiac arrhythmia (serious cardiac arrhythmia such as ventricular tachycardia, ventricular fibrillation, new atrial fibrillation or flutter or new paroxysmal supraventricular tachycardia, new 2nd or 3rd degree atrioventricular block, or significant bradycardia, acute heart failure or significant increase in PR interval, widening of the QRS complex or peaked T wave), the patient was to receive appropriate medical treatment and be discontinued from study drug.

B.2.4.1.3 Analysis population

The statistical analysis plan prospectively defined four study populations based on separate evaluability rules for the acute phase and maintenance phase.

Acute phase safety population

The acute phase safety population was defined as all patients who received at least one acute phase dose administration. This population was used for analyses of acute phase safety. Patients were analysed for safety as treated.

Acute phase intent-to-treat population

The acute phase intent-to-treat (ITT) population included all patients who were included in the acute phase safety population and had any post-baseline S-K values after receiving the investigational product during the first 48 hours. This population was used for analyses of acute phase efficacy. Patients were analysed for efficacy as treated.

Maintenance phase safety population

The maintenance phase safety population was defined as all randomised patients who received at least one maintenance phase dose administration. This population was used for analyses of maintenance phase safety. Patients were analysed for safety as treated.

Maintenance phase intent-to-treat population

The maintenance phase ITT population included all patients who were included in the maintenance phase safety population and had at least one observed S-K value on or after maintenance phase day 8. This population was used for the primary analyses of maintenance phase efficacy. Patients were analysed for efficacy as randomised.

B.2.4.1.4 Methods used to take account of missing data, censoring methods

Aberrant S-K data, defined as either a S-K change ≥1.5 mmol/L for central laboratory data between consecutive maintenance phase visits or ≥1.0 mmol/L difference between the paired i-STAT and central laboratory data at the same maintenance phase visit, were reviewed by data management, medical, and statistical personnel to determine if the data should be considered invalid and thus considered missing for the data analysis. All such changes were made before the database was unblinded and were documented by the ZS-004 Project Manager and approved by the Chief Scientific Officer and Chief Biostatistician.

In the event of missing S-K data from the central laboratory, the i-STAT data were used to replace missing data by adjusting for the average paired difference between the central and i-STAT values collected at the same visit. Less than 1% of central laboratory S-K values were missing. As illustration of the change methodology, if the mean difference between central laboratory and i-STAT assessments for patients/visits with both was 0.12 mmol/L higher for the central laboratory assessment, then 0.12 mmol/L was added to the i-STAT value to impute the missing central laboratory assessment.

If both the central laboratory and i-STAT values were missing, the end of study value was used if it was within 1 day of a target study day and the last dose date.

If a patient's maintenance phase study day 29 S-K assessment was made more than 1 day after the last dose, it was treated as missing in data analysis and handled as defined above.

If a patient discontinued the maintenance phase before study day 8, a maintenance phase study day 8 S-K was interpolated based on an expectation/maximization algorithm in which the maintenance phase study day 8 average from patients with maintenance phase study day 8 data in the same treatment group was used. These data were only used in a confirmatory analysis of the primary efficacy assessment.

B.2.4.1.5 Statistical methods used to compare groups for primary and secondary outcomes

Efficacy analysis

Separate analyses were performed for the acute and maintenance phases. All potassium analyses were based on the S-K values from the central laboratory. All efficacy data were analysed for the ITT population for both study phases.

Acute phase analyses

Secondary efficacy endpoints included the exponential rate of change in S-K values during the initial 48 hours of study drug treatment; change and percent change from baseline in S-K values at 24 and 48 hours after start of dosing; proportion of patients who achieved normalisation in S-K values at 24 and 48 hours after start of dosing; and time to normalisation of S-K (as defined by S-K values of 3.5 to 5.0 mmol/L, inclusive).

The exponential rate of change in S-K values (as of the 48-hour time point) was derived from a mixed effect model of serial S-K values during the acute phase (log-transformed) on time, baseline eGFR, CKD status, HF status, RAASi use, diabetes status, and age. The mean

change and mean percent change from baseline in S-K values were assessed using the 2-sided, paired t-test. Additionally, 95% CIs for mean change and mean percent change from baseline in S-K values were estimated.

The proportions of patients who achieved normokalaemia at 24 hours and 48 hours and corresponding 95% 2-sided CIs were calculated and a 2-sided Fisher Exact test assessed the null hypotheses of no difference. The time to normalisation of S-K was summarised using Kaplan-Meier life table curves. All acute phase assessments (e.g. not just those at 24 and 48 hours) were used.

Maintenance phase analyses

The primary efficacy endpoint was the model-based least-squares mean (LS mean) of all available S-K values inclusive of maintenance phase study days 8 to 29.

The primary efficacy endpoint was analysed with a longitudinal model (SAS PROC MIXED) that simultaneously compared each active dose (highest to lowest dose) versus placebo control as follows:

- Dependent variable: S-K data at scheduled visits inclusive of maintenance phase study days 8–29
- Unstructured variance-covariance matrix
- Random effect: patient
- Fixed effects: Maintenance phase treatment group; acute phase baseline eGFR; acute phase and maintenance phase baseline S-K; age (<55, 55–64, >65 years); binary indicators for RAASi use, CKD, HF, and DM.
- LS means of the treatment effect with the observed margins were used to estimate the primary efficacy parameter

Secondary efficacy endpoints included:

- Number of normokalaemic days during the maintenance phase inclusive of days 8–29. This parameter was calculated assuming that the time interval between assessments was normokalaemic only if both the beginning and end assessments for that time interval displayed normal S-K values. If an intermediate assessment time point was missing, the time interval was extended until the next non-missing time point.
- Change and percent change from acute phase baseline to each maintenance phase follow-up time point.

Additional efficacy endpoints for maintenance phase study days 8–29 included:

- Change and percent change from acute phase baseline to the last visit that was within 1 day of the last dose (maintenance phase study day 29/exit) for aldosterone and renin

The number of normokalaemic days was analysed using a linear regression model with the same covariates delineated above for the primary efficacy endpoint.

The change and percent change in S-K from acute phase and maintenance phase baselines to maintenance phase follow-up time points were summarised by time point and analysed using a mixed effect regression model with the same covariates delineated above for the

primary efficacy endpoint. Additionally, within-treatment group changes were assessed using 2-sided, paired t-tests, and comparisons between treatment groups were assessed using 2-sided, 2-sample t-tests.

The intra-patient standard deviation was calculated as the square root of the back-transformed mean square error from a 1-way analysis of variance (PROC GLM) by treatment group of the natural log-transformed S-K values for maintenance phase study days 8–29, inclusive, with a factor for patient.

The proportion of patients who remained normokalaemic at each maintenance phase follow-up time point was compared for each active dose (highest to lowest) versus placebo control using a 2-sided Fisher Exact test. Additionally, for the maintenance phase study day 29/exit time point, the percentage of normokalaemic patients at maintenance phase study day 29/exit was compared using a logistic regression model containing the same baseline covariates as for the primary efficacy endpoint.

All continuous-scaled parameters were summarised by time point and for their change and percent change from acute phase baseline, for acute phase follow-up time points, for both the acute phase and maintenance phase baseline, and for maintenance phase follow-up time points. For continuous parameters, within-treatment group changes from baseline were assessed using 2-sided, paired t-tests and, for the maintenance phase, comparisons between treatment groups for the change from baseline were assessed using 2-sided, 2-sample t-tests.

Nominal-scaled endpoints were assessed for within-treatment group statistical significance using 2-sided, paired t-tests or a binomial test, as appropriate. For the maintenance phase, comparisons between treatment groups were assessed using 2-sided, 2-sample t-tests or a 2-sided Fisher Exact test, as appropriate.

If outcomes adjusted for covariates, provide the rationale

The mixed effect model of serial S-K observations between maintenance phase study days 8 and 29 included a patient random effect and the following fixed effects: maintenance phase treatment group; acute phase baseline eGFR; acute phase and maintenance phase baseline serum potassium; age (<55, 55–64, ≥65 years); and binary indicators for RAASi use, CKD, HF, and diabetes mellitus.

B.2.4.2 *Study ZS-005*

B.2.4.2.1 Determination of sample size

Approximately 750 patients will be enrolled in the study and be treated with SZC. With 700 enrolled patients, there is 90% power and two-sided 5% type I error to rule out 80% success percent for the primary efficacy endpoint relative to an 85% alternative hypothesis. There is also 90% power and two-sided 5% type I error to detect a 0.123 effect size for the change from baseline for continuous endpoints. Two-sided 95% CIs will be able to establish normokalaemia success percentages of at least 80% (or 90%) if higher than 83.1% (or 92.2%) success percentages were observed according to a two-sided 95% lower confidence bound. In addition, the mean improvement from baseline to averaged day 8/end of study (EOS) and day 29/EOS will also be evaluated. There is 80% power to detect a 0.1 effect

size. Thus, if there is >99% power to detect a conservative 0.5 mmol/L improvement with a two-sided test with 5% type I error relative to a null hypothesis of no mean S-K change. Moreover, if the real mean S-K difference was 0.7 mmol/L, then the two-sided 95% lower bound would exceed 0.5 mmol/L, which would confirm sustained efficacy. Safety-related endpoints can be similarly assessed using two-sided 95% CIs to rule out safety-related event rates with percentages higher than 5% (or 2.5%) if lower than 3.4% (or 1.3%) percentages were observed according to a two-sided 95% upper confidence bound. Two-sided 95% CIs will also be computed for the intra-patient S-K variance. This allows inference of the intra-patient S-K range. With 700 patients, the two-sided 95% CI for the variance estimate will be +10% relative to the true variance. Thus, the study is adequately powered to assess all efficacy and safety.

B.2.4.2.2 Interim analyses and stopping guidelines

The sponsor performed four interim analyses of the data from this study while it was ongoing in order to provide relevant efficacy and safety data in regulatory submissions filed in the US and in Europe. The protocol, including the statistical methods section, was not amended based on any of these interim results; however, additional analyses were detailed in the statistical analysis plan based on interim results. No alpha adjustment was made since the study was not to be stopped for efficacy.

Stopping guidelines as per the Study ZS-004.

B.2.4.2.3 Analysis population

Study populations were prospectively defined based on separate evaluability rules for the acute phase and extended dosing phase. Patients excluded from each analysis population were tabulated.

Acute phase safety population

Patients who received at least one dose of SZC in the acute phase were included in the acute phase safety population. The acute phase safety population was used for the description of acute phase safety.

Acute phase intent-to-treat population

Patients who were in the acute phase safety population and had at least one S-K assessment after administration of acute phase SZC were included in the acute phase ITT population. The acute phase ITT population was used for description of acute phase efficacy.

Extended dosing phase safety population

Patients who received at least one dose of SZC in the extended dosing phase were included in the extended dosing phase safety population. The extended dosing phase safety population was used for the description of extended dosing phase safety.

Extended dosing phase intent-to-treat population

Patients who were in the extended dosing phase safety population and had at least one S-K assessment after administration of extended dosing phase SZC were included in the

extended dosing phase ITT population. The extended dosing phase ITT population was used for description of extended dosing phase efficacy.

B.2.4.2.4 Methods used to take account of missing data, censoring methods

As per Study ZS-004 (please see B.2.4.1.4).

B.2.4.2.5 Statistical methods used to compare groups for primary and secondary outcomes:

Efficacy analysis[106]

Separate analyses were performed for the acute and extended phases. All potassium analyses were based on the S-K values from the central laboratory. All efficacy data were analysed for the ITT population for both study phases. Laboratory-based results are limited to extended phase results. No adjustments were conducted for multiple comparisons since this was an open-label, non-randomised study.

When means, proportions, nominal changes or percent changes were presented, 95% CIs and t-tests (paired from baseline or independent 2-group) with 2-sided p-values were presented where appropriate.

Acute phase analyses

The primary efficacy endpoint for the acute phase was the restoration of normal S-K values (3.5–5.0 mmol/L, inclusive).

S-K values, proportion of normokalaemic patients and proportion of patients with S-K between 3.5 and 5.5 mmol/L at 24, 48, and 72 hours, and last (qualifying) were assessed using 95% CIs and the 2-sided paired t-test. The time to normalisation of S-K was summarised using Kaplan-Meier life table curves. All acute phase assessments (e.g. not just those at 24 and 48 hours) were used.

Extended phase analyses

The primary efficacy endpoint for the extended phase was the maintenance of normokalaemia (proportion of patients with mean S-K <5.1 mmol/L from months 3 to 12).

Secondary efficacy endpoints included the proportion of patients with mean S-K 3.5–5.5 mmol/L from months 3 to 12, the mean S-K levels in months 3–12, months 6–9, and months 9–12, and the change and percent change from baseline in S-K values at each visit. In addition, exploratory analyses included Kaplan-Meier lifetables of the time to first recurrent HK ≥5.6 mmol/L, and proportions using RAASi at the extended phase baseline and at quarterly intervals.

The primary efficacy endpoint was analysed by tabulating measurements by visit and averaging over intervals. For the proportion of patients who are normokalaemic over time during the extended phase, data were tabulated using 95% CIs for the proportion normokalaemic at day 8 through 365/EOS and averaged over the interval. The number and percentage of patients hyperkalaemic at each time point were tabulated.

The nominal and percentage changes in S-K values from the acute phase to extended phase baseline and to extended phase follow-up time points were assessed using one-

sample, two-sided t-tests of the null hypothesis of no change. The number of normokalaemic days was assessed using two-sided 95% CIs with the number of days computed using linear interpolation.

S-K endpoints and present normokalaemic were assessed by logistic regression and longitudinal models using the following covariates:

- Acute phase baseline S-K and eGFR
- Extended phase baseline S-K and eGFR
- Age (<55, 55–64, >65 years)
- Binary indicators for RAASi use, CKD, HF, and DM

Log-transformed S-K during the extended phase was analysed using a repeated-measures mixed model to obtain model-based LS means using the same covariates delineated above for the S-K endpoints. The between-patient and intra-patient standard deviations after natural log transformation of S-K assessments were presented with 95% CIs.

Adverse events were classified by Medical Dictionary for Regulatory Activities (MedDRA) (version 17.0). The number and percentage of patients who experienced an adverse event was tabulated.

Exploratory endpoints included:

Proportion of patients using RAASi at extended dosing phase baseline and at quarterly intervals thereafter, with an additional 2 × 3 display to show the RAASi decrease, same, or increase as columns and baseline RAASi use (no, yes) as rows using the extended dosing phase safety population.

Proportion of patients who had an increase in RAASi dose or start on RAASi overall and by quarterly interval using the extended dosing phase safety population presented for all patients, all diabetic patients, all HF patients, and all patients with eGFR <60 mL/min.

Among those in the extended dosing phase safety population initially on RAASi at baseline: proportion of patients who had a decrease in RAASi dose or discontinuation of RAASi overall and by quarterly intervals and Kaplan-Meier life table of the time to RAASi decrease or discontinuation overall and by quarterly intervals.

Safety analysis

Safety analyses were conducted for the acute phase safety population and extended dosing phase safety population. No missing laboratory or adverse-event data were imputed for the safety analyses. Safety endpoints included adverse events, vital signs, ECGs, and standard haematology, chemistry, and urinalysis parameters. Laboratory safety analyses were performed using central laboratory values.

B.2.4.2.6 If outcomes adjusted for covariates, provide the rationale

The mixed effect model of S-K endpoints included a random effect for patient and the following fixed effects: acute phase baseline eGFR; acute phase and extended dosing phase

baseline S-K; age; and binary indicators for RAASi use, CKD, heart failure, and diabetes mellitus. The logistic regression model also included the same fixed effects.

B.2.5 *Quality assessment of the relevant clinical effectiveness evidence*

See Appendix D for a full quality assessment of each trial.

B.2.6 *Clinical effectiveness results of the relevant clinical trials*

Summary of key efficacy data

- SZC has been demonstrated to be highly effective in reducing S-K levels over the first 48 hours as an acute treatment. Furthermore, sustained benefits with SZC have been demonstrated through a maintenance phase up to 12 months.
- The key trials (ZS-004 and ZS-005) included SZC arms for the licensed doses (5 g and 10 g) and 15 g (not licensed). Only data regarding the licensed doses are relevant to this appraisal. Both the 5 g and 10 g are equally effective.
- Participants in ZS-004 and ZS-005 studies have similar baseline characteristics to patients with CKD or HF and the results are therefore generalisable to UK clinical practice.
- SZC has demonstrated a rapid onset of action during the acute phases. The median time to normalisation of S-K values during the acute phase was 2.17 hours after the first dose of SZC (ZS-004), with a significant proportion reaching normokalaemia (i.e. normal levels of S-K) within the initial 48 hours.

Primary endpoints

- ZS-004 study: The mean S-K value between maintenance phase study days 8–29 was significantly smaller for all of the SZC treatment groups vs the placebo group ($p<0.001$), demonstrating sustained reductions during days 8–29 in the active SZC treatment arms.
- ZS-005: Rapid reduction of S-K into the normokalaemic range within 24–72 hours after initiating SZC 10 g TID (acute phase), with 92.5% (95% CI: 90.4– 94.3) and 97.9% (95% CI: 96.5–98.8) of patients reaching S-K levels of 3.5–5.5 mmol/L compared to baseline at 24 and 48 hours, respectively; normokalaemia maintained over 12 months (extended dosing phase), 88.4% (95% CI: 85.7– 90.8) and 98.8% (95% CI: 97.6–99.5) of patients had a mean S-K value ≤5.1 mmol/L and ≤5.5 mmol/L respectively from month 3 to month 12.

Secondary endpoints

- In Study ZS-004, patients treated with SZC 10 g TID in the acute phase patients, showed that 84.3% and rising to 97.6% of patients' S-K levels normalised at 24 hours and 48 hours respectively, based on the Kaplan-Meier estimates.
- In comparison to patients receiving placebo, those receiving SZC achieved normokalemia faster and maintained it for longer. A large majority of patients were able to achieve normokalaemia.

Subgroups

- Consistent results across subgroups defined by age, baseline eGFR, RAASi use, and presence of HF and CKD.

B.2.6.1 *Study ZS-004*

The study methodology for Study ZS-004 is summarised in B.2.3. The study involved an acute phase with a 48-hour induction with SZC 10 g TID (n=258), with those patients who achieved normokalaemia subsequently randomised into placebo or SZC treatment arms during a maintenance phase for 28 days.

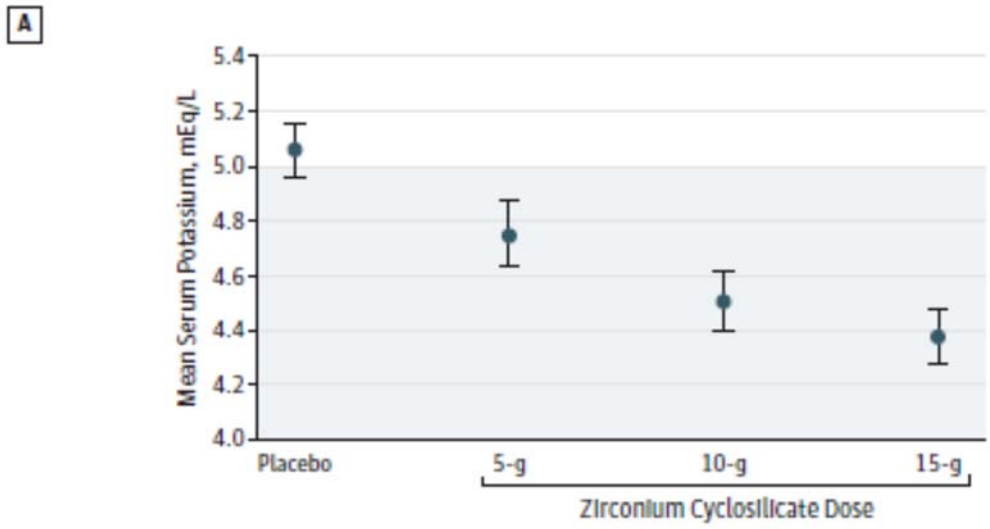
B.2.6.1.1 Primary efficacy outcome

The primary outcome for Study ZS-004 was the comparison of mean S-K value between placebo and each SZC treatment arm from study day 8 to 29 of the maintenance phase.

Within the maintenance phase 237 patients were randomised and treated. The results for the ITT population are reported below, where 4 patients (3 placebo, 1 SZC 10 g OD) that did not have any S-K measurements between study days 8 and 29 due to early termination from the study were excluded. As no significant protocol deviations were identified for any patient in the maintenance phase ITT population, analysis of a modified ITT population was not required.

The mean S-K value between maintenance phase study days 8–29 was statistically significantly smaller mean S-K value than the placebo group, for all the SZC treatment groups ($p<0.001$). Among the SZC groups, the mean S-K value decreased with increasing doses of SZC (4.8 mmol/L, and 4.5 mmol/L for the 5 and 10 g daily doses respectively) compared with placebo (5.1 mmol/L). See Figure 9 below.

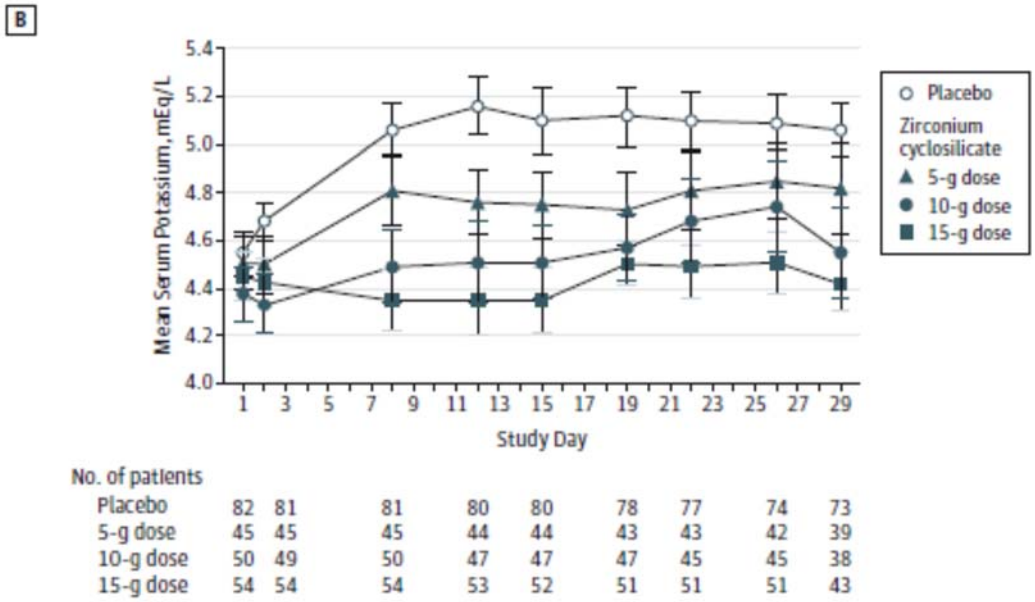
Figure 9: Serum potassium levels during the randomised phase (days 8–29) according to SZC dose



Abbreviations: SZC, sodium zirconium cyclosilicate.

Mean S-K values during the maintenance phase are summarised graphically over time, by treatment group in Figure 10 below, demonstrating sustained reductions during days 8–29 in the active treatment arms.

Figure 10: Serum potassium levels during the randomised phase



B.2.6.1.2 Secondary efficacy outcomes

B.2.6.1.3 Acute phase

Secondary efficacy endpoints included in the acute phase were:

- The exponential rate of change in S-K values during the initial 48 hours of study drug treatment
- Change and percent change from baseline in S-K values at 24 and 48 hours after start of dosing
- Proportion of patients who achieved normalisation in S-K values at 24 and 48 hours after start of dosing
- And time to normalisation of S-K (as defined by S-K values of 3.5 to 5.0 mmol/L, inclusive).

Mean exponential change at 24 and 48 hours

There was a statistically significant improvement from baseline with S-K with SZC 10 g TID, with Kaplan-Meier estimates showing that 84.3% and rising to 97.6% of patients' S-K levels normalised at 24 hours and 48 hours respectively, as summarised in Table 13.

Table 13: Secondary outcome results for mean exponential change at 24 and 48 hours

Time point	Parameter	Estimate for SZC 10 g TID (n=258)	P value for H_0: parameter = 0
24 hours after start of SZC dosing	Mean exponential rate of change	-0.00373	<0.0001
	Mean (median) S-K change	-0.68 (-0.70)	<0.0001
	Mean (median) S-K percent change	-12.03 (-12.50)	<0.0001
	Percent normalised (KM estimate)	84.28	Not applicable

Time point	Parameter	Estimate for SZC 10 g TID (n=258)	P value for H_0: parameter = 0
	Percent normalised at 24 hours	66.1 (168/254)	Not applicable
48 hours after start of SZC dosing	Mean exponential rate of change	-0.00324	<0.0001
	Mean (median) S-K change	-1.05 (-1.10)	<0.0001
	Mean (median) S-K percent change	-18.56 (-19.23)	<0.0001
	Median time to normalisation	2.17	Not applicable
	Percent normalised (KM estimate)	97.62	Not applicable
	Percent normalised at 48 hours	88.0 (221/251)	Not applicable

Abbreviations: KM, Kaplan-Meier; S-K, serum potassium; TID, three times a day.

Mean change and mean percent change from baseline in serum potassium values

Statistically significant mean decreases and mean percent decreases from baseline in S-K were observed from 1 hour to 28 hours after the start of SZC 10 g TID dosing, with a change of -0.23 mmol/L CI -0.28, -0.17 at 1 hour, and -0.41 95% CI -.046, -0.35 at 2 hours, p<0.0001 for both. The changes at 24 and 48 hours are summarised in Table 13.

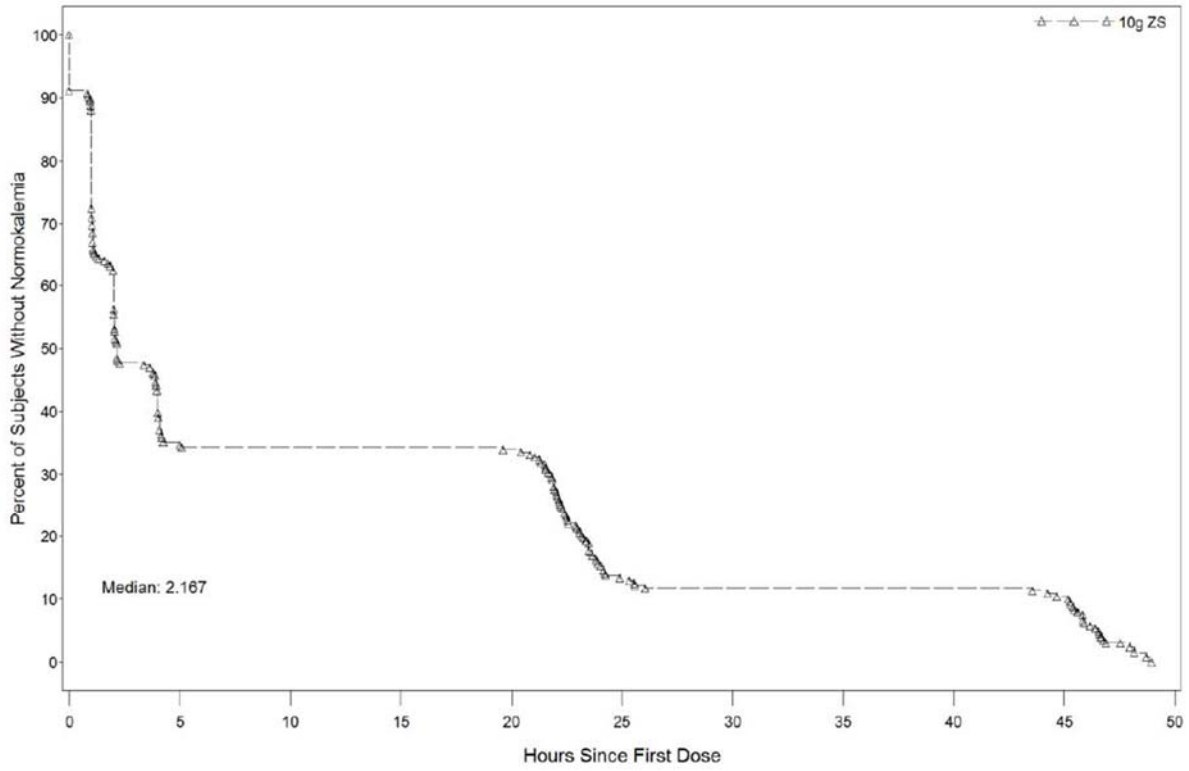
Proportion of normokalaemic patients at 24 and 48 hours after first dose of SZC

A significant proportion of patients reached normalised S-K levels with 24 and 48 hours. An estimated 66.1% of patients had normalised S-K values 24 hours after the first dose of SZC and 88.0% of patients at 48 hours. The Kaplan-Meier estimate of the percentage of normokalaemic patients was 84.28% at 24 hours and 97.62% at 48 hours after the first dose of SZC.

Time to normalisation of S-K values

A rapid onset of action was observed, with the median time to normalisation of S-K values during the acute phase achieved approximately 2.2 hours after the first dose of SZC (Figure 11).

Figure 11: Time to normalisation in S-K values – ITT population



Abbreviations: ITT, intent-to-treat; S-K, serum potassium.

B.2.6.1.4 Maintenance phase

The secondary efficacy endpoints for the maintenance phase included:

- Number of normokalaemic days during maintenance phase study days 8–29, inclusive
- Mean change and mean percent change from acute phase baseline in S-K

Time to hyperkalaemia

Median time to hyperkalaemia from the Maintenance Phase baseline was longer with SZC than with placebo: 7 days with placebo versus 14 days in the 5g SZC once-daily group ($p = 0.0012$). The median time to hyperkalaemia was not reached in the 10g SZC once-daily group. Fewer than 50% of patients in the 10 g and SZC once-daily group experienced a hyperkalaemic event during the Maintenance Phase. Time to hyperkalaemia was statistically significantly later with continued SZC treatment than with placebo ($p < 0.0001$), indicating that SZC is more effective at maintaining normalisation for longer than placebo.

Number of normokalaemic days during study days 8–29 inclusive

The mean number of normokalaemic days – a key outcome associated with improved outcomes – was consistent across the licensed doses of SZC (13.4 over 22 days for SZC 5 g OD and 13.9 over 22 days for SZC 10 g OD) and higher than placebo (7.4 over 22 days).

Mean change and mean percent change from acute phase baseline in S-K values

At the end of the maintenance phase in Study ZS-004 (day 29), the decrease in S-K levels was significantly greater for SZC 5 g and 10 g than placebo. The mean decrease in S-K

levels (standard deviation) for placebo, SZC, 5 g and SZC 10 g is 0.44 (0.515) mmol/L, -0.77 (0.559) mmol/L and -1.10 (0.813) mmol/L, respectively. The mean percent decrease in S-K levels (standard deviation) for placebo, SZC, 5 g and SZC 10 g -7.68 (8.940)%, -13.85 (9.568)% and -19.28 (11.086)%.

Proportion of normokalemic patients in the Maintenance Phase

A higher proportion of patients remained normokalemic at Day 29 in the SZC groups versus placebo: 47.6% of placebo patients, 71.1% of 5g SZC once-daily patients ($p \leq 0.05$), and 76.0% of 10g SZC once-daily patients ($p \leq 0.01$).

B.2.6.1.5 Conclusion

SZC was highly effective in reducing S-K in patients with HK, demonstrating statistically significant improvement from baseline in S-K with SZC 10 g TID over the first 48 hours of dosing. Based on Kaplan-Meier estimates, 84.3% of patients had normalised S-K values at 24 hours after the first dose of SZC, and 97.6% of patients had normalised S-K values at 48 hours after the first dose of SZC, based on the Kaplan-Meier estimates. The S-K lowering effect was rapid, with a statistically significant and clinically meaningful decrease from baseline noted at 1 hour after the first 10 g dose of SZC. The median time to normalisation of S-K values during the acute phase was 2.17 hours after the first dose of SZC.

Patients who achieved normokalaemia after receiving SZC 10 g TID in the acute phase were randomised to 28 days of placebo, SZC 5 g OD, SZC 10 g OD, or SZC 15 g OD dosing during the maintenance phase. SZC was effective in maintaining normokalaemia (S-K between 3.5 mmol/L and 5.0 mmol/L, inclusive), meeting the pre-defined primary efficacy endpoint of mean S-K value during maintenance phase study days 8–29 at all three licensed doses of SZC. Each SZC group had a statistically significantly smaller mean S-K value than the placebo group ($p \leq 0.0001$ for each SZC dose group). The mean S-K value decreased with increasing dose of SZC (5.1 mmol/L for placebo, 4.8 mmol/L for SZC 5 g OD and, 4.5 mmol/L for SZC 10 g OD, and 4.4 mmol/L for SZC 15 g OD). Based on the sequential closed testing procedure, each SZC dose group was superior to placebo for the pre-defined secondary efficacy endpoints of total number of days normokalaemic and proportion of patients normokalaemic at the end of the on-maintenance phase (study day 29)/exit.

In conclusion, SZC was highly effective in reducing S-K in patients with HK, demonstrating significant improvement from baseline in S-K with SZC 10 g TID over the first 48 hours of dosing. The S-K lowering effect was rapid and continued through the initial 48 hours. SZC maintained lower mean S-K values than placebo among patients who achieved normokalaemia in the acute phase, with lower mean S-K values with larger doses of SZC between maintenance phase study days 8 and 29. At the end of the maintenance phase (study day 29/exit), the proportion of patients who remained normokalaemic was statistically significantly larger in each SZC group than in the placebo group.

B.2.6.2 *Study ZS-005*

The study methodology for Study ZS-005 is summarised in B.2.3. The study involved an acute phase with a 1- to 3-day treatment with SZC 10 g TID (n=751), showing similar results on effectiveness and rapid onset of action of SZC. Subsequent to the acute phase, patients (n=746) were enrolled into the open-level label extended dosing phase who were dosed with

SZC at a starting dose of 5 g OD and were titrated to 10 g or 15 g OD or 5 g once every other day depending on their serum potassium levels. Dose titrations occurred according to the protocol-defined dose adjustment rules and the majority received 5 g or 10 g – at some point during the study, 32 (4.3%) patients were titrated to the 5 g dose, 396 (53.1%) patients were titrated to the 10 g dose, and 87 (11.7%) to the 15 g dose (NB. the 15 g is not a licensed dose). The durations of overall exposure were generally comparable among the maximum doses, with mean durations of 269.2 days for 5 g, 290.2 days for 10 g, and 337.7 days for 15 g.

B.2.6.2.1 Primary efficacy outcome

All the 751 patients treated in the acute phase were included in the acute phase safety population. Of these, two patients did not have at least one S-K assessment after administration of acute phase SZC and were excluded from the acute phase ITT population.

In the extended dosing phase, 746 patients were treated, and included in the extended dosing phase safety population. Of these, 12 patients did not have at least one S-K measurement during extended dosing due to early termination from the study and were excluded from the extended dosing phase ITT population.

B.2.6.2.2 Acute phase – primary efficacy outcome

Restoration of normal serum potassium levels (3.5 ≤ S-K^+ ≤ 5.0 mmol/L)

A rapid correction of hyperkalaemia was observed in the acute phase of ZS-005 with 77.9% (95% CI: 74.8%, 80.9%) of patients achieving S-K^+ levels in the range 3.5-5.0 mmol/L within 72 hours and 66.0% responding within 24 hours. More patients achieved S-K^+ levels in the range 3.5-5.5 mmol/L within 72 hours (98.7%; 95% CI: 97.6%, 99.4%) and 24h (92.5%; 95%CI 0.904-0.943) (Table 14).

Table 14: Acute phase: proportion of patients with S-K values between 3.5 and 5.0 mmol/L, inclusive, or between 3.5 and 5.5 mmol/l, inclusive, by acute phase study day – ITT population

Acute phase	SZC 10 g TID (N=749)					
	S-K 3.5–5.0 mmol/L inclusive			S-K 3.5–5.5 mmol/L, inclusive		
	n/N	Proportion	95% CI	n/N	Proportion	95% CI
24 hours	494/748	0.660	0.625, 0.694	692/748	0.925	0.904, 0.943
38 hours	563/748	0.753	0.720, 0.683	732/748	0.979	0.965, 0.988
72 hours/last	583/748	0.779	0.748, 0.809	738/748	0.987	0.796, 0.994

Abbreviations: CI, confidence interval; ITT, intent-to-treat; S-K, serum potassium; SZC, sodium zirconium cyclosilicate; TID, three times a day.

Throughout the study, all potassium samples were measured both by i-STAT and the central laboratory. However, protocol-specified endpoint analyses on the study data were based on S-K values as measured by the central laboratory. When analysing results based on i-STAT measurements, the mean difference between central laboratory and i-STAT measurements for patients/visits with both values was 0.2 mmol/L higher for the central laboratory

measurement. While small differences were apparent, in general, i-STAT (99.9%; 747/748) and S-K (98.7%, 738/748) values yielded similar results for the proportions of patients with potassium values between 3.5 and 5.5 mmol/L following acute phase dosing.

B.2.6.2.3 Extended dosing phase – primary efficacy outcome

A high proportion of patients (88.4%; 95% CI: 85.7%, 90.8%) maintained a mean S-K+ value ≤ 5,1 mmol/L across extended dosing phase days 85–365. The proportions of patients with S-K values ≤ 5.1 mmol/L were relatively constant among the extended dosing phase time points, ranging from 76.7% to 87.2%. This is summarised in Table 15 below.

Table 15: Extended dosing phase: proportion of patients with mean S-K values ≤ 5.1 mmol/L across extended dosing phase days 85–365 and proportions by extended dosing phase day – ITT population

Extended dosing phase	SZC daily (N=734)		
	n/N	Proportion	95% CI
Proportion of patients with mean S-K values ≤ 5.1 mmol/L during ED study days 85–365	571/646	0.884	0.857, 0.908
Proportion of patients by ED study day			
ED study day 8	562/733	0.767	0.734, 0.797
ED study day 15	550/713	0.771	0.739, 0.802
ED study day 22	552/705	0.783	0.751, 0.813
ED study day 29	556/701	0.793	0.761, 0.823
ED study day 57	534/674	0.792	0.760, 0.822
ED study day 85	523/645	0.811	0.778, 0.840
ED study day 113	507/620	0.818	0.785, 0.847
ED study day 141	488/602	0.811	0.777, 0.841
ED study day 176	493/588	0.838	0.806, 0.867
ED study day 211	464/559	0.830	0.796, 0.860
ED study day 239	440/546	0.806	0.770, 0.838
ED study day 267	454/524	0.866	0.834, 0.894
ED study day 295	434/508	0.854	0.821, 0.884
ED study day 330	413/495	0.834	0.799, 0.866
ED study day 365	383/439	0.872	0.838, 0.902
ED study day 365/EOS	607/734	0.827	0.798, 0.854

Abbreviations: CI, confidence interval; ED, extended dosing; EOS, end of study; S-K, serum potassium; SZC, sodium zirconium cyclosilicate.

Proportions of patients with mean S-K values ≤ 5.5 mmol across extended dosing phase days 85–365

The proportions of patients with mean S-K values ≤5.5 mmol/L across extended dosing phase days 85–365, as well as the proportions at each visit during extended dosing, were summarised in Table 16. This is consistent with the S-K HK thresholds used in UK clinical practice and aligns with additional SZC studies. Across extended dosing phase days 85–365, 98.8% (95% CI: 97.6, 99.5) of patients had mean S-K values ≤5.5 mmol/L. The

proportions of patients with S-K values ≤5.5 mmol/L were relatively constant among the extended dosing phase time points, ranging from 92.7% to 96.4%.

Table 16: Extended dosing phase: proportion of patients with mean S-K values ≤5.5 mmol/L across extended dosing phase days 85–365 and proportions by extended dosing phase day – ITT population

Extended dosing phase	SZC daily (N=734)		
	n/N	Proportion	95% CI
Proportion of patients with mean S-K values ≤5.5 mmol/L during ED study days 85–365	638/646	0.988	0.976, 0.995
Proportion of patients by ED study day			
ED study day 8	681/733	0.929	0.908, 0.947
ED study day 15	661/713	0.927	0.905, 0.945
ED study day 22	655/705	0.929	0.908, 0.947
ED study day 29	660/701	0.942	0.921, 0.958
ED study day 57	632/674	0.938	0.917, 0.955
ED study day 85	599/645	0.929	0.906, 0.947
ED study day 113	584/620	0.942	0.921, 0.959
ED study day 141	569/602	0.945	0.924, 0.962
ED study day 176	558/588	0.949	0.928, 0.965
ED study day 211	534/559	0.955	0.935, 0.971
ED study day 239	525/546	0.962	0.942, 0.976
ED study day 267	505/524	0.964	0.944, 0.978
ED study day 295	487/508	0.959	0.938, 0.974
ED study day 330	473/495	0.956	0.933, 0.972
ED study day 365	422/439	0.961	0.939, 0.977
ED study day 365/EOS	688/734	0.937	0.917, 0.954

Abbreviations: CI, confidence interval; ED, extended dosing; EOS, end of study; S-K, serum potassium; SZC, sodium zirconium cyclosilicate.

B.2.6.2.4 Extended dosing phase – secondary efficacy outcome

Proportion of patients with mean S-K values between 3.5 and 5.5 mmol/L inclusive, across extended dosing phase days 85–365

The proportions of patients with mean S-K values between 3.5 and 5.5 mmol/L, inclusive, across extended dosing phase days 85–365, as well as the proportions at each visit during extended dosing, are presented in Table 17. Across extended dosing phase days 85–365, 98.5% (95% CI: 97.2, 99.3) of patients had mean S-K values between 3.5 and 5.5 mmol/L, inclusive.

The proportions of patients with S-K values between 3.5 and 5.5 mmol/L, inclusive, were relatively constant among the extended dosing phase time points, ranging from 91.3% to 95.6%.

Table 17: Extended dosing phase: proportion of patients with mean S-K values between 3.5 and 5.5 mmol/L, inclusive, across extended dosing phase days 85–365 and proportions by extended dosing phase day – ITT population

Extended dosing phase	SZC daily (N=734)		
	n/N	Proportion	95% CI
Proportion of patients with mean S-K values between 3.5 and 5.5 mmol/L during ED study days 85–365	636/646	0.985	0.972, 0.993
Proportion of patients by ED study day			
ED study day 8	891/733	0.929	0.908, 0.947
ED study day 15	661/713	0.927	0.905, 0.945
ED study day 22	654/705	0.928	0.906, 0.946
ED study day 29	660/701	0.942	0.921, 0.958
ED study day 57	625/674	0.927	0.905, 0.946
ED study day 85	593/645	0.919	0.896, 0.939
ED study day 113	579/620	0.934	0.911, 0.952
ED study day 141	567/602	0.942	0.920, 0.959
ED study day 176	550/588	0.935	0.912, 0.954
ED study day 211	531/559	0.950	0.928, 0.966
ED study day 239	522/546	0.956	0.935, 0.972
ED study day 267	500/524	0.954	0.933, 0.970
ED study day 295	483/508	0.951	0.928, 0.968
ED study day 330	469/495	0.947	0.924, 0.965
ED study day 365	419/429	0.954	0.931, 0.972
ED study day 365/EOS	670/734	0.913	0.890, 0.932

Abbreviations: CI, confidence interval; ED, extended dosing; EOS, end of study; S-K, serum potassium; SZC, sodium zirconium cyclosilicate.

Mean and percent change from acute phase baseline in S-K values

Mean decreases and mean percent decreases from acute phase baseline in S-K were observed at each time point during extended dosing. Mean changes from acute phase baseline in S-K ranged from −0.78 to −1.00 mmol/L, corresponding to mean percent changes of −13.61% to −17.63%, respectively. During the first 4 weeks of the extended dosing phase, small mean increases from extended dosing phase baseline in S-K were observed, which is likely to be associated with patients shifting from the acute phase TID dosing regimen to the OD dosing regimen. After the first month of therapy in the extended dosing phase, small mean decreases were observed (≤0.15 mmol/L) from extended dosing phase baseline. Mean percent decreases were ≤2.70%. Following discontinuation of SZC treatment, typically 7 days after last dose, mean S-K increased by 0.35 mmol/L.

Mean change and percent change from acute phase baseline in bicarbonate values

Mean increases and mean percent increases from acute phase baseline in bicarbonate were observed early during treatment, beginning at extended dosing phase day 8. Across the extended dosing time points, mean increases from acute phase baseline in bicarbonate

ranged from 0.76 to 1.22 mmol/L, corresponding to mean percent changes of 4.13% to 6.21%, respectively.

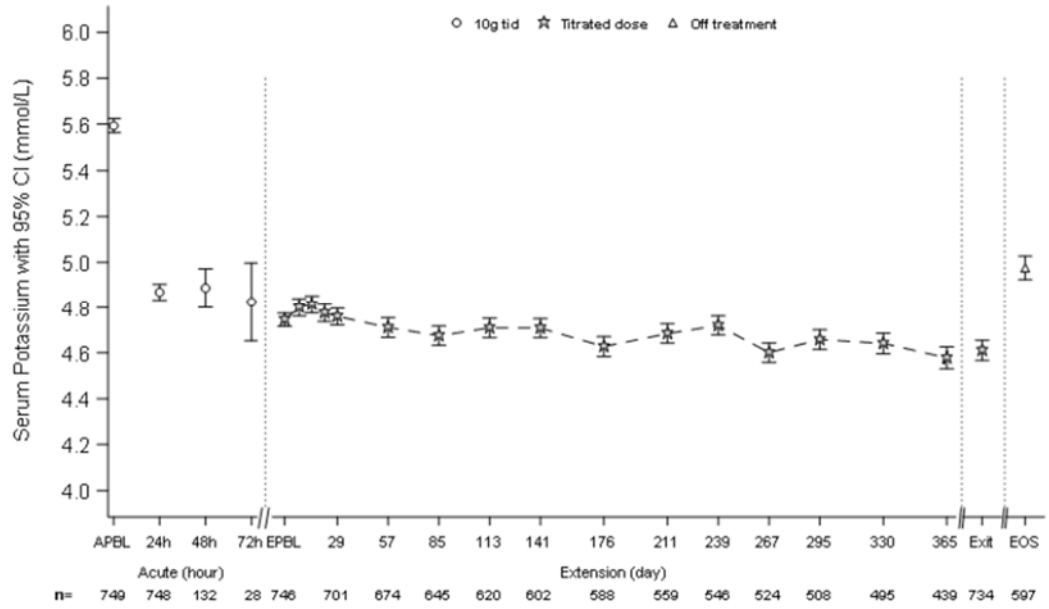
Among patients with metabolic acidosis (defined as baseline bicarbonate value of <22 mmol/L), mean increases and mean percent increases from acute phase baseline in bicarbonate were observed at each time point during extended dosing among patients with metabolic acidosis. Mean changes from acute phase baseline in bicarbonate ranged from [redacted] corresponding to mean percent changes of [redacted], respectively.

B.2.6.2.5 Exploratory endpoints

Extended dosing phase: mean S-K values over time

Mean S-K values were maintained within the normal range throughout the extended dosing phase time points (Figure 12). After discontinuation of SZC, S-K increased at the end of study visit, typically 7 days after last dose. The LS mean S-K value between extended dosing study days 8 and 365/end of study was within the normal range (4.7022 mmol/L).

Figure 12: Extended dosing phase: mean (95% CI) S-K (mmol/L) over time – ITT population



Abbreviations: APBL, acute phase baseline; CI confidence interval; EOS, end of study; EPBL, extended phase baseline; ITT, intent-to-treat; S-K, serum potassium; TID, three times daily.

Extended dosing phase: proportion of patients with normal aldosterone values

The proportion of patients with a normal aldosterone value at acute phase baseline was [redacted] and was relatively constant among the extended dosing phase time points, ranging from [redacted]

Renin-angiotensin-aldosterone system inhibitor use during extended dosing phase

Among the 746 patients in the extended dosing phase safety population, [redacted] were taking RAASi at acute phase baseline. Of the [redacted] patients not taking RAASi at acute phase baseline[redacted] initiated RAASi therapy during the extended dosing phase.

Among the [redacted] patients taking RAASi at baseline, the majority could continue the same dose ([redacted] Increases in RAASi dose occurred in [redacted] decreases occurred in [redacted] discontinued RAASi use altogether. Similar results were observed among patients with diabetes, HF and eGFR <60 mL/min. Of note, as patients could have undergone multiple RAASi regimen adjustments, including dose increases followed by dose decreases, followed by a discontinuation, patients could have been included in multiple subcategories, accounting for the aggregate percentage of >100%.

Among the [redacted] patients who were on RAASi during the extended dosing phase, the mean S-K at acute phase baseline was [redacted] Following acute phase dosing, the mean S-K among these patients at the extended dosing phase baseline was within the normal range ([redacted] Mean S-K values throughout the extended dosing phase time points remained within the normal range among patients taking RAASi medication.

B.2.6.2.6 Conclusion

In this study of patients with HK taking SZC, S-K was rapidly lowered to the normal range, with the majority of the patients responding within 24 hours. The majority of patients maintained normal S-K on daily SZC administration, with 88.4% and 98.8% of patients having mean S-K values ≤ 5.1 and ≤ 5.5 mmol/L, respectively, over extended dosing phase days 85–365.

There were no specific requirements regarding the underlying aetiology of HK in the inclusion criteria and there were few restrictions in the exclusion criteria. Hence, a number of concomitant diseases and treatments were allowed, recognising that many patients with HK suffer from a variety of underlying conditions. Patients were not under any protocol-mandated dietary restrictions and concomitant RAASi use was not restricted. Thus, the population evaluated in this long-term study is likely representative of patients who would receive the drug in clinical practice.

The majority of the patients completed the extended dosing phase of the study. The dropout rate observed in this study was 37.5%, with the 10.9% discontinuing due to withdrawal of consent, 6.8% due to experiencing adverse events and 5.4% progression of CKD. Further evaluation performed comparing the S-K values and changes from baseline demonstrated that the discontinuation rate did not appear to affect the robustness of the results observed in the study.

This long-term, open-label study showed:

- Rapid reduction of S-K into the normokalaemic range within 24–72 hours after initiating SZC 10 g TID
- Maintenance of normokalaemia over 12 months and S-K increased after dosing with SZC was stopped, confirming continued need for S-K control
- Consistent results across subgroups defined by age, baseline eGFR, RAASi use, and presence HF and CKD (see B.2.7.2)
- Although a lower proportion of patients with higher baseline S-K values achieved and maintained normokalaemia ≤5.1 mmol/L during the acute and extended dosing phases,

these patients had the largest reductions in S-K and S-K values were kept ≤5.5 mmol/L in the majority of patients, which is clinically acceptable in the UK.

B.2.7 *Subgroup analysis*

Subgroup analyses were performed to determine the relevance and potential impact of a variety of disease characteristics and comorbidities that might have influenced the primary endpoint. Subgroup analysis for studies ZS-004 and ZS-005 are presented below. Results for ZS-004 and ZS-005 as well as subgroup analyses for ZS-002, ZS-003 and ZS-004E are presented in Appendix E.

B.2.7.1 *Study ZS-004*

B.2.7.1.1 Methodology and statistical analysis, including characteristics of patient included in the analysis

Pre-planned subgroup analyses were conducted for eight subpopulations, to investigate the impact on primary efficacy variables by clinically important baseline subpopulations. The subpopulations were: patients with CKD, HF, or diabetes mellitus; patients receiving RAASi therapy; patients with Acute Phase baseline eGFR <60 mL/min, Acute Phase baseline S-K 5.5 to 6.0 mmol/L, or Acute Phase baseline S-K ≥6.0 mmol/L. Comparisons between treatment group efficacy were assessed using 2-sample t-tests and 95% confidence intervals.

The following subgroup analyses were conducted for all subpopulations:

- Mean, mean change and percent change in S-K value from the Acute Phase baseline to 48 hours after the start of SZC dosing
- Mean, mean change and percent change in S-K^+ levels during Maintenance Phase Study Days 8 and 29

B.2.7.2 *Study ZS-005*

B.2.7.2.1 Methodology and statistical analysis, including characteristics of patients included in the analysis

Pre-planned efficacy analyses within clinically important baseline subpopulations including presence of CKD, diabetes mellitus, and HF; use of RAASi medication; baseline eGFR <60 mL/min; acute phase baseline S-K (<5.5, 5.5 to <6.0, and ≥6.0 mmoL/min); and age (<55, 55 to 64, and ≥65 years) were performed for the primary efficacy variables.

Characteristics of patients included in the analyses are presented below.

Patients with S-K^+ and iSTAT potassium values ≥6 mmol/L

In total, 126 patients had serum potassium levels ≥6 mmol/L and 78 patients with iSTAT potassium ≥6.0 mmol/L[103]. Patient demographics are shown in Table 18 below.

Table 18: Baseline characteristics in patients ≥6.0 mmol/L

	i-STAT K^+ ≥6.0 mEq/L (n=78)	S-K ≥6.0 mEq/L (n=126)
Mean age, y (SD)	63.9 (13.2)	63.2 (12.5)
Male, n (%)	48 (61.5)	79 (62.7)
Race, n (%)		
White	62 (79.5)	97 (77.0)
Black	11 (14.1)	22 (17.5)
Asian	3 (3.8)	3 (2.4)
Ethnicity, n (%)		
Hispanic	28 (35.9)	43 (34.1)
Geography, n (%)*		
United States	62 (79.5)	89 (70.6)
Mean K^+, mEq/L (range)	6.2 (6.0–7.3)	6.3 (6.0–7.6)
eGFR, mL/min/1.73 m^2, n (%)		
<15	9 (11.5)	13 (10.3)
15 to <30	27 (34.6)	46 (36.5)
30 to <45	14 (17.9)	26 (20.6)
45 to <50	4 (5.1)	5 (4.0)
50 to <60	4 (5.1)	12 (9.5)
≥60	19 (24.4)	22 (17.5)
Comorbidity, n (%)		
CHF	34 (43.6)	47 (37.3)
CKD	58 (74.4)	102 (81.0)
Diabetes mellitus	47 (60.3)	78 (61.9)
Hypertension	62 (79.5)	104 (82.5)
Concomitant medications, n (%)		
RAASi	50 (54.1)	87 (69.0)
Diuretics	32 (41.0)	49 (38.9)

Abbreviations: CI, confidence interval; CHF, congestive heart failure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RAASi, renin-angiotensin-aldosterone system inhibitor; SD, standard deviation; S-K, serum potassium.

Patients taking RAASi therapies

In total, [redacted] patients were taking RAASi medication during the acute phase of the study. Patient demographics are shown in Table 19 below.

Table 19: Baseline characteristics in patients taking RAASi medication

	Patients taking RAASi medication [redacted]
Mean age, y (SD)	[redacted]
Male, n (%)	[redacted]
Race, n (%)	
White	[redacted]
Black	[redacted]
Asian	[redacted]
Ethnicity, n (%)	
Hispanic	[redacted]
Geography, n (%)*	
United States	[redacted]
eGFR, mL/min/1.73 m^2, n (%)	
Mean (SD)	[redacted]
<15	[redacted]
15 to <30	[redacted]
30 to <60	[redacted]
≥60	[redacted]
Comorbidity, n (%)	
CHF	[redacted]
CKD	[redacted]
Diabetes mellitus	[redacted]
Hypertension	[redacted]
Concomitant medications, n (%)	
RAASi	[redacted]
Diuretics	[redacted]
S-F, n (%)	
<5.0 mmol/L	[redacted]
5.5 to <6.0 mmol/L	[redacted]
≥6.0 mmol/L	[redacted]

Abbreviations: CHF, congestive heart failure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; ITT, intent-to-treat; RAASi, renin-angiotensin-aldosterone system inhibitor; SD, standard deviation; S-K, serum potassium.

B.2.8 *Meta-analysis*

A meta-analysis of clinical data is appropriate where sufficiently homogeneous trials based on population, clinical trial designs and outcomes are available. While there are four Phase 3 studies and one Phase 2 study evaluating SZC (ZS-002, ZS-003, ZS-004, ZS-004E and ZS-005), the studies are heterogeneous making a meta-analysis infeasible.

Population heterogeneity exists for ZS-003 study compared to other studies, rendering it inappropriate to meta-analyse. In the ZS-003 study, for the relevant treatment arms (5g and 10g, only licenced doses) and placebo arms at baseline, only 25.9%, 19.7% and 15.4% respectively had S-K^+ levels >5.5 mmol/L, which is the threshold at which treatment is initiated for patients with HiK in UK clinical practice. This is substantially lower than the other SZC studies and not entirely surprising given that ZS-003 was a dose ranging study comparing multiple doses in a relatively small patient population.

Clinical trial design heterogeneity exists for ZS-002 as well as ZS-004, and ZS-005, the two studies relevant for the economic model, in particular:

- the duration of treatment with SZC 10g TID in the acute phase was different in the 3 studies (2-4 days in study ZS-002, fixed period of 2 days in study ZS-004, 1-3 days until patients achieve normokalaemia in study ZS-005);
- whilst patients were randomised to a SZC dose or placebo during the maintenance phase of study ZS-004 with no titration permitted, those enrolled in the single arm study ZS-005 were able to increase or decrease the dose of SZC in increments of 5 once daily up to a maximum of 15g daily or a minimum of 5g once every two days;
- the duration of the maintenance/extended phase was much shorter in ZS-004 (28 days) than in ZS-005 (up to 52 weeks);
- No SZC was given during the follow-up period in study ZS-002.

As such the ZS-004 and ZS-005 studies cannot be deemed comparable to meta-analyse.

As for ZS-004E, the extension phase of ZS-004, it has further design differences, and is further complicated by the fact that enrolment was at the investigators decision and did not form part of the original statistical analysis plan for Study ZS-004; 77 patients who completed Study ZS-004 and qualified for entry into this extension study were unable to participate as investigational product was not available.

B.2.9 *Indirect and mixed treatment comparisons*

An indirect or mixed treatment comparison is required where no head-to-head data is available for the intervention versus the relevant comparators. Given that the Phase 3 trial ZS-004 has a valid comparator, an indirect comparison was not deemed necessary.

The feasibility of a network meta-analysis was explored based the published evidence for the temporising agents (e.g. repeat insulin-glucose) and calcium resonium. (Appendix D, Table 9) The relevant aspects are described below:

Insulin-glucose as temporising agent, used in the acute setting (Section B.1.3.5.3):

- In the A&E setting, some patients may receive an additional dose of IV infusion of insulin-glucose to maintain normokalaemia. (Section B.1.3.5.1)
- Three RCTs of temporising agents were identified in the SLR, all had a very small population and only reported outcomes within the first few minutes or hours after administration [107-109]. An indirect comparison at these early timepoints would not be clinically relevant for SZC target population and proposed positioning.[110]

Calcium resonium (calcium polystyrene sulphonate, CPS), used in the acute setting (Section B.1.3.5.3):

- Only one RCT by Nasir et al. comparing CPS 5g TID with SPS 5g TID was retrieved. This trial could not be connected to the ZS trials. In addition, the dose of CPS used in the trial (5g TID) is not relevant to UK clinical practice where a dose of 15g 3-4 times daily is commonly used.[111]

In the absence of relevant evidence from the published literature for an additional dose of insulin-glucose and for calcium resonium a network meta-analysis was deemed infeasible.

B.2.10 *Adverse reactions*

Summary of safety data

ZS-004 study

- The safety profile of SZC in patients with HK has been demonstrated in the placebo-controlled Phase 3 ZS-004 trial. In total, 258 patients participated in the acute phase, where all patients received 10 g SZC three times daily. Following the acute phase, 237 patients continued into the maintenance phase where 85 patients received placebo, 45 patients received 5 g SZC, 51 patients received 10 g and patients received 15 g SZC OD.
- All treatment-emergent adverse events (TEAEs) reported during the acute phase were considered mild or moderate in severity.
- During the maintenance phase, TEAEs associated with gastrointestinal disorders (e.g. constipation) were more common in the placebo group (14.1%) compared to the treatment groups. The incidence of oedema rates was generally similar among the placebo (2.4%), 5 g daily (2.2%) and 10 g daily (5.9%) SZC.
- The overall incidence of serious TEAEs that occurred during the study was low (10 SZC-treated patients during maintenance phase), with no dose-response relationship observed for any specific type of serious adverse event, and none were considered related to study drug.
- Of the 8 SZC-treated patients who were prematurely discontinued from study drug due to adverse events, 4 met the protocol-specified stopping rules for prolonged QTc interval, 2 of which were considered possibly related to study drug. None of the other events that led to premature discontinuation were considered related to study drug.
- One patient died (SZC 10 g daily) of MI, which was deemed not to have ben related to study drug.

ZS-005 study

- The safety profile of SZC in patients with HK, demonstrated in the open-label Phase 3 ZS-005 trial was consistent with previous similar studies of SZC. In total, 751 patients participated in the acute phase, where all patients received 10 g SZC three times daily for up to 3 days. Patients entered the maintenance phase if their serum potassium levels reached 3.5–5.0 mmol/L within 3 days.
- In the maintenance phase, all 746 patients entered the phase on a dose of 10 g SZC OD. Serum potassium levels were monitored and the dose modified accordingly (417 patients, median time to first dose increase = 175 days) to achieve normokalaemia. Of these 55.9%, 32 patients were down-titrated to 5 g every other day, 396 were titrated to the 10 g daily dose, and 87 were titrated to the 15 g daily dose. At least two dose modifications were needed in 16.5% of patients with <4% requiring at least three dose modifications.
- The mean daily dose received was 7.18 g SZC and 37.5% of patients discontinued during the extended phase.

- The overall incidence of TEAEs during acute phase was low (4.1%). The most common TEAEs reported during the acute phase were associated with gastrointestinal disorders, but all were considered mild.
- The overall incidence of TEAEs during the extended dosing phase was 65.5%, the most common were hypertension (11.0%), peripheral oedema (9.7%), and urinary tract infection (7.9%).
- Serious TEAEs occurred in 0.1% in the acute phase and 21.6% in the extended phase. Only two patients had serious events considered related to study drug by the investigator (pulmonary oedema, and cardiac failure congestive).
- Discontinuations due to TEAEs occurred in 0.3% of patients in the acute phase and 13.7% of patients in the extended phase. The most common reasons for discontinuation were cardiac failure congestive (1.5%) and renal failure acute (1.2%). No trend was apparent for the types of serious events reported that led to premature discontinuation.
- A total of 113 (15.1%) patients experienced 139 TEAEs based on the haemodynamic oedema, effusions, and fluid overload Standardised MedDRA Queries (SMQs) during the extended phase. Ten of these events were serious, two led to discontinuation, and one case was considered related to study drug by the investigator.
- 85 patients (11.4%) had a total of 105 TEAEs during the extended phase based on the hypertension SMQ. The majority of these patients had a history of hypertension and/or CKD (78 patients, 91.8%). No patients discontinued the study medication due to hypertension.
- The incidence of HK (S-K value ≥5.0 mmol/L) was 72.8% in the extended phase. During this phase, 1.2% of patients met the stopping criteria for hypokalaemia (i-STAT <3.0 mmol/L) and 0.7% for HK (i-STAT >6.5 mmol/L).

B.2.10.1 *Study ZS-004*

B.2.10.1.1 Extent of exposure

During the acute phase, the majority of patients (96.9%) received three doses of study drug on study days 1 and 2 of the acute phase.

Among the 258 ZS-treated patients in the acute phase safety population, 237 patients continued into the maintenance phase. The mean number of days on treatment were comparable among the groups, ranging from 25.8 to 27.2 days. Data is presented for the 5 and 10 g treatment groups, as these are the clinically relevant and approved doses for use.

B.2.10.1.2 Safety profile

The AEs for the acute phase, are summarised in Table 20. During the maintenance phase, TEAEs associated with gastrointestinal disorders were more common in the placebo group (14.1%) compared to the treatment groups. Constipation was the most common gastrointestinal disorder event reported in the placebo groups (7.1%) and occurred at a higher rate, than in any of the treatment groups. The incidence of oedema rates was generally similar among the placebo (2.4%), 5 g daily (2.2%) and 10 g (5.9%).

None of the severe TEAEs were considered related to the study drug.

Table 20: AEs occurring in 5% or more of patients in any group, and all serious AEs

AEs, n (%)	Open-label SZC 10 g TID (n=258)	Randomised phase		
		Placebo (n=85)	5 g (n=45)	10 g (n=51)
Any event	20 (7.8)	27 (31.8)	24 (53.3)	15 (29.4)
Any treatment-related event	6 (2.3)	7 (8.2)	3 (6.7)	3 (5.9)
Any severe event	0	1 (1.2)	4 (8.9)	1 (2.0)
Death	0	0	0	1 (2.0)
Any serious event	0	0	5 (11.1)	2 (3.9)
Any event leading to premature discontinuation of study drug	1 (0.4)	0	4 (8.9)	0
Gastrointestinal disorder	10 (3.9)	12 (14.1)	3 (6.7)	1 (2.0)
Diarrhoea	3 (1.2)	1 (1.2)	0	0
Constipation	2 (0.8)	6 (7.1)	0	1 (2.0)
Oedema	0	2 (2.4)	1 (2.2)	3 (5.9)
Hypokalaemia	0	0	0	5 (9.8)
URTI	1 (0.4)	1 (1.2)	3 (6.7)	1 (2.0)
Serious AEs[b]				
Any event	0	0	5 (11.1)	2 (3.9)
Cardiac failure	0	0	1 (2.20)	0
MI	0	0	0	1 (2.0)
Small intestinal obstruction	0	0	1 (2.2)	0
Hepatoxicity	0	0	1 (2.2)	0
Cellulitis	0	0	0	1 (2.0)
Pneumonia	0	0	1 (2.2)	0
Confusional state	0	0	1 (2.2)	0

Abbreviations: AE, adverse event; MI, myocardial infarction; SZC, sodium zirconium cyclosilicate; TID, three times daily; URTI, upper respiratory tract infection.
a: Including generalised and peripheral oedema; b: None of the serious adverse events were deemed by the investigator to be related to study treatment.

B.2.10.1.3 Other serious adverse events

During the maintenance phase of the study, 7 patients in the SZC groups (5 x SZC 5 g OD, and 2 x SZC 10 g OD) experienced serious TEAEs (including the 1 patient who died). No dose-response relationship was observed among the SZC dose groups for the overall incidence of serious TEAEs or for any specific type of serious event. None of the serious TEAEs were considered related to study drug administration.

Three patients were prematurely discontinued from study drug during the maintenance phase due to serious AEs, including small intestinal obstruction (1 patient in the SZC 5 g OD group), and confusional state (1 patient in the SZC 5 g OD group).

None of the placebo-treated patients experienced a serious TEAE.

B.2.10.1.4 Summary

Treatment with SZC was well tolerated. Given the age and underlying disease burden of this patient population, the overall incidence of TEAEs was low during acute and maintenance phase treatment. Gastrointestinal disorders were the most common TEAEs reported during the acute phase, and included diarrhoea (1.2%), constipation (0.8%), and nausea (0.8%). All TEAEs reported during the acute phase were considered mild or moderate in severity.

Similar rates of oedema were observed among the placebo (2.4%, 2 patients), SZC 5 g OD (2.2%, 1 patient), and SZC 10 g OD (5.9%, 3 patients) groups. Each of the patients reporting oedema events was receiving multiple types of medication for treatment of hypertension, of which oedema is a common AE. The majority of the patients also had CKD and most had a medical history of oedema. None of the oedema events was considered related to study drug and most were mild or moderate in severity.

The overall incidence of serious TEAEs that occurred during the study was low (10 SZC-treated patients during maintenance phase), with no dose-response relationship observed for any specific type of serious AE, and none were considered related to study drug. The one patient who died (SZC 10 g OD; MI) was a 60-year-old female with a history of Stage 5 CKD, type 2 diabetes mellitus, hypertension, and known cardiovascular disease. Of the 8 SZC-treated patients who were prematurely discontinued from study drug due to AEs, 4 met the protocol-specified stopping rules for prolonged QTc interval, 2 of which were considered possibly related to study drug. None of the other events that led to premature discontinuation was considered related to study drug.

No clinically significant dose-related trends were observed in the evaluation of vital signs.

B.2.10.2 *Study ZS-005*

B.2.10.2.1 Extent of exposure

Acute phase

In total, 751 patients were treated with SZC 10 g TID for 24–72 hours during the acute phase. The mean number of days on treatment was 1.2 and ranged from 1 to 3 days. The overall number of doses received during the acute phase ranged from 1 to 9, with a mean and median of 3.6 and 3.0, respectively.

Extended dosing phase

In total, 746 patients entered the extended dosing phase. 466 (62.5%) completed the 12-month study. The mean and median dose received was 7.18 g and 5.74 g, respectively. The majority of patients (87%) received a mean dose of 5 to <10 g during the extended dosing phase. Four-hundred and seventeen (55.9%) patients had at least one dose modification. Among those, 32 (4.3%) were down-titrated to 5 g every other day, and 396 (53.1%) were

titrated to the 10 g OD. Only 87 (11.7%) were titrated to the 15 g OD. The median time to the first dose increase was 175 days. The duration of overall exposure was generally comparable among the maximum doses, with mean durations of 269.2 days for 5 g, 290.2 days for 10 g and 333.7 days for 15 g. The safety population in the extended dosing phase includes all the patients who received at least one dose of study drug.

B.2.10.2.2 Safety profile

A summary of the AEs is shown in Table 21.

Table 21: Summary of AEs in Study ZS-005

Adverse events, n (%)	Acute phase – 10 g TID (n=751)	Extended dosing phase (n=746)
Any event	31 (4.1)	489 (65.5)
Any treatment-related event	7 (0.9)	90 (12.1)
Any severe event	2 (0.3)	125 (16.8)
Death	0	8 (1.1)
Any serious event	1 (0.1)	161 (21.6)
Any event leading to premature discontinuation of study drug	2 (0.3)	102 (13.7)
TEAEs reported by ≥5% of patients overall		
Anaemia	0	44 (5.9)
Constipation	2 (0.3)	48 (6.4)
Diarrhoea	2 (0.3)	33 (4.4)
Nausea	4 (0.5)	56 (7.5)
Peripheral oedema	0	72 (9.7)
URTI	0	37 (5.0)
Urinary tract infections	4 (0.5)	59 (7.9)
Hypertension	0	82 (11.0)
Hypokalaemia	1 (0.1)	43 (5.8)

Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event; TID, three times daily; URTI, upper respiratory tract infection.

The overall incidence of TEAEs during acute phase was low (4.1%). The most common TEAEs reported during the acute phase were associated with gastrointestinal disorders, but all were considered mild. The overall incidence of TEAEs during the extended dosing phase was 65.5%, the most common were hypertension (11.0%), peripheral oedema (9.7%), urinary tract infection (7.9%), nausea (7.5%), constipation (6.4%), anaemia (5.9%) and upper respiratory tract infection (5.0%). Events leading to premature discontinuation reported in ≥1.0% patients were congestive cardiac failure (1.5%) and acute renal failure (1.2%).

The overall population treated for up to 12 months in this study, had substantial underlying comorbidities (hypertension 82.8%; CKD 68.3%, diabetes mellitus 62.7%, HF 37.9%), with the majority of the patients having more than one comorbid condition.

From the total number of patients that reported TEAEs related to 'haemodynamic, oedema, effusions and fluid overload', most had a history of CKD (92.9%) and over half had a history of HF (53.1%). 97.2% of peripheral oedema reported was mild-to-moderate, and 2.8% was severe. Peripheral oedema was treated in 40 patients (55.6%) with an increase in diuretics in all but two treated cases. One patient discontinued study drug because of peripheral oedema.

Eighty-five patients (11.4%) had a total of 105 TEAEs during the extended dosing phase based on the hypertension SMQ. Among the 85 patients reporting these events, the majority had a history of hypertension or CKD (78 patients, 91.8%). In the overall population, mean blood pressure at baseline was 136/77 mmHg; a mean (standard deviation [SD]) change from baseline of 0.0/−0.6 (19/11) mmHg was reported within the last day of SZC administration. In the patients with an AE of hypertension, mean blood pressure (BP) at baseline was 149/81 mmHg; a mean (SD) change from baseline of −0.6/−1.0 (21/13) mmHg was reported within the last day of SZC administration. No patients discontinued the study medication due to an AE of hypertension.

Hypokalaemia

During the extended phase, hypokalaemia (3.5 mmol/L) was reported by 43 patients (5.8%). 34 (4.6%) had a S-K of 3.0–3.4 mmol/L and 9 (1.2%) with a S-K of 2.5-2.9 mmol/L.

Haemodynamic oedema, effusions, and fluid overload

In total, 113 (15.1%) patients experienced 139 TEAEs based on the haemodynamic oedema, effusions, and fluid overload SMQ during the extended dosing phase, the most common being oedema peripheral (9.7%), followed by oedema (2.0%), fluid overload (1.6%), and local swelling (1.6%). Of the 113 patients reporting these events, most had a history of CKD (105 patients; 92.9%) and over half had a history of heart failure (60 patients; 53.1%). The verbatim terms reported for 12 of these 113 patients specified upper extremity swelling or unilateral oedema. The highest SZC dose received prior to the event was 5 g once every other day for two patients, 5 g OD for 54 patients, 10 g OD for 41 patients, and 15 g OD for 16 patients. Ten of the events in the haemodynamic oedema, effusions, and fluid overload SMQ were serious (pulmonary oedema [3 patients], fluid overload [3 patients], ascites, local swelling, pleural effusion, and generalised oedema [1 patient each]); 1 of these serious events was considered related to study drug by the investigator. Two of the serious fluid overload events resulted in discontinuation from the study. One additional patient had an event of oedema peripheral, considered not related to study drug by the investigator, which led to premature discontinuation from study drug. More than half of the patients (67.3%) required concomitant medication to treat the event.

Hypertension

As hypertension was the most commonly reported TEAE during the extended dosing phase, an additional analysis of these types of events were performed based on the hypertension SMQ. Eighty-five patients (11.4%) had a total of 105 TEAEs during the extended dosing phase based on the hypertension SMQ, the most common of which was the preferred term of hypertension (11.0%). Among the 85 patients reporting these events, the majority had a history of hypertension or CKD (78 patients each; 91.8%).

Among the 85 patients who had a hypertension event during the extended dosing phase, 6 had events that were serious, including hypertension in 4, hypertensive crisis in 1 patient and malignant hypertension in one patient. None of the events reported as part of the hypertension SMQ led to premature discontinuation from study drug.

B.2.10.2.3 Other serious adverse events

During the extended dosing phase, 21.6% of patients reported at least one serious TEAE. Serious AEs were generally consistent with the severe underlying comorbidities of the patient population. The most commonly reported serious TEAEs included pneumonia (1.9%), cardiac failure congestive (1.5%), chest pain (1.5%), osteomyelitis (1.1%), and renal failure acute (1.1%).

Of the 161 patients who experienced serious TEAEs in the extended dosing phase, only 2 had serious events that were considered related to study drug by the investigator (pulmonary oedema and cardiac failure congestive in 1 patient each).

B.2.10.2.4 Summary

The safety profile observed in this study was consistent with results from previous controlled and uncontrolled studies of SZC, in which similar patient populations with similar comorbidities (including CKD, hypertension, heart failure, and diabetes mellitus) were enrolled.

Duration of treatment in the extended dosing phase ranged from 1 to 371 days, with a mean and median duration of 286.2 and 364.0 days, respectively. The majority of patients (87.0%) received a mean dose of 5 to <10 g during the extended dosing phase. More than half (55.9%) of the patients required at least one dose modification, most of which were up-titrations to the 10 g OD dose. At least two dose modifications were observed in 16.5% of patients with <4% requiring at least three dose modifications.

Commonly reported TEAEs during acute phase dosing were associated with gastrointestinal disorders including nausea (0.5%), diarrhoea (0.3%), and constipation (0.3%). During the 12-month extended dosing phase, the overall incidence of TEAEs was 65.5%, the most common (≥5.0%) of which were hypertension (11.0%), oedema peripheral (9.7%), urinary tract infection (7.9%), nausea (7.5%), constipation (6.4%), anaemia (5.9%), and upper respiratory tract infection (5.0%).

A total of 8 (1.1%) patients died during the extended dosing phase, none of which was considered related to study drug by the investigator. Serious TEAEs occurred in 0.1% of patients in the acute phase and 21.6% of patients in the extended dosing phase. The most commonly reported serious TEAEs during extended dosing included pneumonia (1.9%), cardiac failure congestive (1.5%), chest pain (1.5%), osteomyelitis (1.1%), and renal failure acute (1.1%). Two patients experienced serious TEAEs during the extended dosing phase that were considered related to study drug by the investigator (pulmonary oedema in one patient and cardiac failure congestive in one patient); both patients had a medical history of the condition. Discontinuations due to TEAEs occurred in 0.3% of patients in the acute phase and 13.7% of patients in extended dosing phase. The most common events that led to premature discontinuation during extended dosing were cardiac failure congestive (1.5%)

and renal failure acute (1.2%). No trend was apparent for the types of serious events reported or among those that led to premature discontinuation from study drug.

The incidence of TEAEs in the haemodynamic oedema, effusions, and fluid overload SMQ, the cardiac failure SMQ, and the hypertension SMQ that were reported during the extended dosing phase was 15.1%, 15.8%, and 11.4%, respectively. Among patients with TEAEs associated with fluid overload, most had a history of CKD (92.9%) and over half had a history of heart failure (53.1%). Among the 36 patients with cardiac failure-type TEAEs (after exclusion of TEAEs associated with oedema peripheral, oedema, and pulmonary oedema), most had a history of CKD (86.1%) or heart failure (80.6%). Among patients with TEAEs in the hypertension SMQ, 91.8% had a history of hypertension or CKD; none of the hypertension events reported led to premature discontinuation from study drug. The incidence of hypokalaemia (S-K <3.5 mmol/L) was 0.1% in the acute phase and 5.8% in the extended dosing phase. All the events were mild or moderate hypokalaemia, with S-K ranging from 2.6 to 3.3 mmol/L. The incidence of HK (S-K value ≥5.0 mmol/L) was 72.8% in the extended dosing phase; maximum S-K values observed were >5.0 to ≤5.5 mmol/L for 277 (37.1%) patients, >5.5 to ≤6.0 for 194 (26.0%) patients, and >6.0 mmol/L for 72 (9.7%) patients. During extended dosing, the incidence of premature discontinuation from study due to meeting potassium-related stopping criteria was 1.2% for hypokalaemia (i-STAT <3.0 mmol/L) and 0.7% for HK (i-STAT >6.5 mmol/L).

Throughout the study, changes observed in laboratory parameters or vital signs were generally consistent with the underlying comorbidities of the study population. The incidences of potentially clinically significant low magnesium, phosphorus, or calcium values, as well as high calcium or sodium values was <1%. No clinically significant mean changes from acute phase baseline in PR interval, QRS duration, and heart rate were observed during the extended dosing phase. Small mean increases in QTc interval were observed throughout the extended dosing time points relative to acute phase baseline; however, these increases in QTc interval are to be expected with correction of potassium into the normokalaemic range.

B.2.10.3 *Additional studies*

Safety data from studies ZS-002, ZS-003 and ZS-004E are reported in Appendix F.

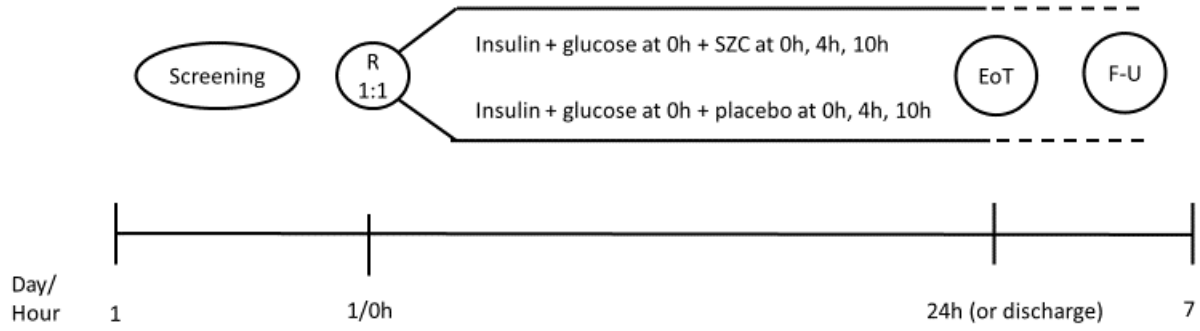
B.2.11 *Ongoing studies*

ENERGIZE NCT03337477

ENERGIZE is a Phase 2, multicentre, randomised, double-blind, placebo-controlled study to evaluate a potassium normalisation treatment regimen with SZC. Insulin and glucose is the standard of care for emergency treatment, among patients with a S-K ≥6.0 mmol/L due to the rapid onset of action. As insulin is a temporising agent with a short duration of effect, additional clinical benefits may be achieved when SZC is added to insulin and glucose, particularly as SZC rapidly binds and eventually displaces potassium from the body, while insulin merely shifts S-K in to the intracellular space. The purpose of this Phase 2 study is to compare the effect of SZC 10 g administered up to three times over 10 hours, versus placebo added to insulin and glucose in the emergency department setting. The target study patient population consists of patients with S-K ≥6.0 mmol/L and suitable for treatment with insulin and glucose to manage HK. The primary endpoint will be the mean absolute change in S-K from baseline until 4 hours after the start of dosing.

The first patient was enrolled in Q4 2017, with the estimated last patient completing Q3 2018, and approximately 132 patients will be recruited. The study design is summarised in Figure 13.

Figure 13: Study design for ENERGIZE NCT03337477



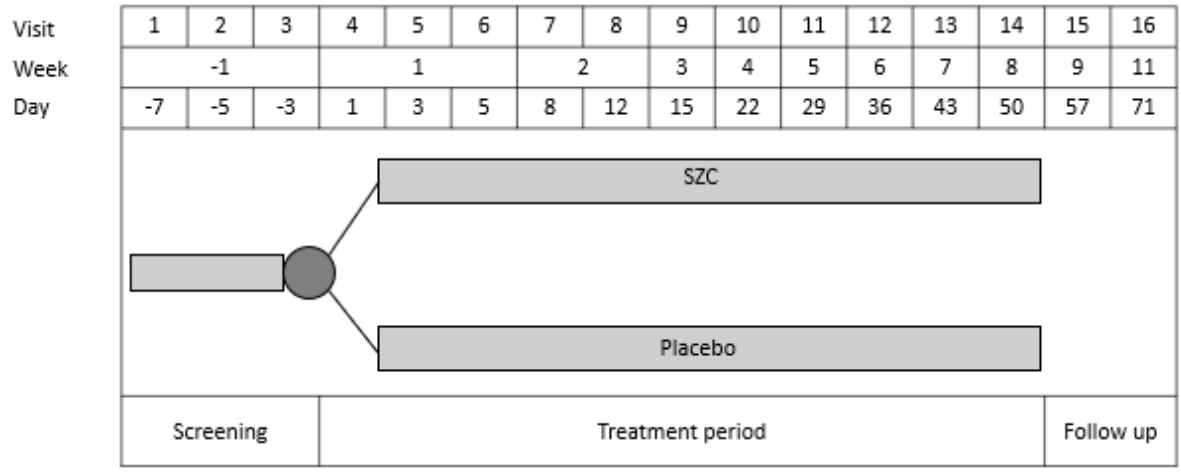
Abbreviations: EoT, end of treatment; F-U, follow-up; R, randomisation; SZC, sodium zirconium cyclosilicate.

DIALIZE NCT03303521

This is a randomised, double-blind, placebo-controlled study to determine the safety and efficacy of SZC in patients with HK and on stable haemodialysis. The study consists of a screening period, an 8-week randomised treatment period and a follow-up period. Stable haemodialysis patients with persistent pre-dialysis HK will be enrolled in the study across research sites in the US, EU and Japan. The primary objective is to assess the efficacy of SZC in the treatment of HK in patients on haemodialysis and approximately 180 patients with ESRD receiving haemodialysis three times a week, will be recruited.

The study started in Q4 2017 and is expected to end by Q4 2018 and approximately 180 patients will be recruited. The study design is outlined below in Figure 14.

Figure 14: Study design for DIALIZE NCT03303521



Abbreviation: SZC, sodium zirconium cyclosilicate.

B.2.12 *Innovation*

The introduction of SZC is a first-in-class potassium binder, with a proven clinical and favourable tolerability profile demonstrated across four Phase 3 RCTs, and represents a step change in the management of patients with HK.

HK is currently an under-recognised and debilitating condition in the long term, and is typically caused as a direct result of underlying comorbidities, such as CKD and HF and worsening renal function. Evidence from the UK, Europe, and the US has consistently demonstrated a statistically significant increased risk of cardiovascular events and death as a result of HK; with an increasing risk as S-K levels increases. [17,44,46,59]

Due to the comorbid nature of the patients, the majority (70–80%) of patients receive treatment with evidence-based cardiorenal protective medications such as RAASi. While these treatments are associated with a risk reduction in CV events, death, and progression to renal replacement therapy (RRT), they are also associated with an increased risk of developing HK.[29,112] As such, NICE guidelines recommend that RAASi treatment should not be initiated in patients with a serum potassium is >5 mmol/L and to completely discontinue if it rises >6 mmol/L.[7] In addition, ESC-HF guidelines recommend that ACEi/ARB therapy should be reduced or discontinued if serum potassium rises >5.5 mmol/L [113]. Therefore, clinical options are limited and current standard of care is to down-titrate or discontinue RAASi/MRA therapy; leading to a suboptimal number of patients receiving adequate treatment with life-saving treatment. [30]

Given that HK is associated with an increased risk of cardiovascular events and death, and that the current standard of care is to reduce exposure to other cardiorenal protective medicines, there is a great unmet need to introduce a rapid, effective, and well tolerated pharmacological intervention to control potassium levels, while allowing patients to continue and optimise treatment on RAASi/MRA therapy.

There has been a lack of pharmacological interventions for over 60 years, with the only alternative pharmacological treatment option being calcium resonium up until just recently. However, there is a lack of clinical evidence to support the use of calcium resonium in clinical practice and it is typically poorly tolerated by patients. Alternatively, patients are advised to adopt a low potassium diet which is deemed to be an unhealthy dietary restriction, has a negative impact on the patients' QoL, and as a consequence is known to have low adherence.

SZC is a fast-acting (within 1 hour), efficacious and well-tolerated pharmacological intervention that allows for:

- Sustained control of potassium levels without the need to adopt a restrictive low-potassium diet
- Management of the underlying comorbid disease without the need to alter cardio-renal protective agents such as RAASi therapy

This dual effect of SZC means that patients will have a reduced risk of hospitalisation, morbidity and mortality, and clinicians will no longer face the dilemma of whether to alter medications treating the patient underlying disease or waiting to see whether a poorly adhered to diet may reverse the patient's HK.

In summary, SZC is the only potassium-binding agent with a rapid onset of action (within 1 hour) and would represent a complete change in the management of patients with HK, which will lead to an improvement in outcomes in patients with complex medical needs.

B.2.13 *Interpretation of clinical effectiveness and safety evidence*

HK, while often asymptomatic, can lead to fatal cardiac arrhythmias such as asystole or ventricular fibrillation. It is common in patients with CKD and a GFR <60 mL/min/m^2 and in those with HF and diabetes mellitus. The mainstay of treatment for these conditions, are RAASi therapies, and whist these treatments improve mortality and morbidity, they are often not tolerated and down-titrated or discontinued due to HK. Data demonstrates that patients on suboptimal doses of these medications have increased morbidity and mortality. Therefore, there is a distinct need to introduce an effective, well-tolerated, and easy to administer medication to allow patients to continue taking RAASi therapy, whilst effectively controlling potassium levels and reducing the risk of cardiovascular events and death.

Acute treatments for HK involve moving potassium into cells, which is temporising and can lead to rebound HK. The current mainstay for long-term management of HK is modification of life-saving RAASi therapy and a low potassium diet, which is poorly adhered to and adversely impacts patient QoL.

SZC is a novel potassium binder, which differs in mode of action, to other potassium binders such as calcium resonium and patiromer. It is highly selective for potassium and begins exchanging Na and H ions in the stomach and small intestine, which explains its rapid onset of action. It also does not cause other electrolyte imbalances, such as hypomagnesaemia, as other potassium binders have been shown to cause.

The two phase 3 clinical trials presented, demonstrate that SZC is efficacious in adult patients with HK, both in the acute and 12-month setting, and treatment up to 12 months is well tolerated. While the overall incidence of TEAEs was around 65% in the long-term study, most events were considered by the investigator to be unrelated to study drug. There was no effect on mean BP in the 12-month trial, including in those where BP was reported as an AE. Oedema rates were low and comparable to placebo in ZS-004, in the 5 g and 10 g doses of SZC and while oedema was reported in the long-term trials, it was in patients with risk factors for oedema, such as CKD and HF.

SZC demonstrated a rapid onset of action and clinically relevant decreases in potassium level. Furthermore, those with a higher potassium level had a larger decrease in potassium. The onset of action is unique to SZC. Other potassium binders take >7 hours to act, and whilst they may lead to small decreases in S-K level, these may not be clinically meaningful. SZC would meet an unmet need, complementing insulin-glucose in the acute setting and avoiding complete discontinuation of RAASi therapy. In addition, SZC rapidly reduces potassium levels to reduce hospital stays, morbidity and mortality.

The studies had broad inclusion criteria and did not have any dietary restrictions or limitations of concomitant medications, demonstrating that it is efficacious, even when patients' diets are liberalised and RAASi treatments are maintained or up-titrated. Once again, this contrasts to other potassium binders, such as calcium resonium or patiromer, where studies conducted included treatments, alongside dietary restriction of potassium.

The patient populations in the studies were also reflective of clinical practice, including all adults with HK without restricting the patients, to certain comorbidities. Hence, there was a cross section of comorbidities that were consistent between all the studies with approximately 2/3 of patients in all the trials, having CKD and around 1/3 having heart failure. In addition, the majority of patients treated in study ZS-005, had a S-K level between 5.5 and 6.0 mmol/L, which is also reflective of UK clinical practice. SZC trials also included doses that are currently licensed for use. This contrasts to the studies conducted for other licensed potassium binders, which used twice daily doses while the license is for OD dosing, which may affect its external validity.

In conclusion, SZC is a novel potassium binder, with a rapid onset that is both efficacious and well tolerated. It is suitable for use in the acute, life-threatening situation alongside IV treatments, as well as in the longer-term chronic setting, to allow for optimal management of these patients and liberalisation of poorly adhered to dietary restrictions.

B.2.13.1 *Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology*

The efficacy and safety of SZC in the acute corrective and maintenance therapy for adults with HK, has been conclusively demonstrated in four, multicentre, international phase 3 trials. These trials included patients from the USA, Australia and South Africa, as well as in Europe and the UK. Data have been reported for a follow-up of up to 12 months.

From feedback from UK clinicians, patients were generally representative of patients who would present with HK in the UK, including the comorbidities and proportions of patients on RAASi therapies.[29]

SZC pharmacological properties

There are several key aspects of the pharmacological properties of SZC which support its use in clinical practice:

- SZC has a unique and first-in-class, mode of action, where it mimics the selectivity filter of physiological potassium channels. As such, it works throughout the entire gastrointestinal tract, which results in early capture of potassium and is not dependent on a concentration gradient, unlike exchange resins[1,2]
- Due to its mode of action, it has a rapid onset of action compared with exchange resins, such as calcium resonium and patiromer, as it binds potassium in the small intestine rather than the large intestine[2]
- It also explains its selectivity and does not cause other electrolyte abnormalities, such as hypomagnesaemia, which can also cause cardiac arrhythmias.[2] Electrolyte abnormalities can be cause of exchange resins[114,115]

SZC also benefits from minimal drug to drug interactions and can be taken with other medications unlike other exchange resins, where there must be a separation.[1,114,115] Furthermore, it is consumed in small volumes and is tasteless and odourless. This compares to calcium resonium which according to UK clinical feedback, is poorly tolerated by patients.[29]

Efficacy

SZC has four large, well-designed, multicentre and international trials, including more than 1,700 patients, that demonstrated the efficacy of SZC using the doses that are licensed for use in the UK. To the best of our knowledge, we are the only recent potassium binder where the clinical dosing regimen used in the trials, is the same as the UK marketing authorisation licence.[95,99,103,105,116-118]

SZC has a rapid onset of action, producing both a clinically relevant and statistically significant reduction at 1 hour (-0.23; 95% CI -0.28, -0.17), with a median time to normalisation of 2.2 hours. In both studies ZS-004 and ZS-005, in a total of 988 patients, 66% had normalised S-K values at 24 hours and 75.3% – 88.0% at 48 hours, when normokalaemia was defined as 3.5 – 5.0.[99] As such, expert clinical feedback has supported its use in the acute setting, where it could be used together or following treatment with insulin/glucose and salbutamol as an alternative to repeat treatments with insulin/glucose and calcium resonium.[29]

Furthermore, SZC maintains normokalaemia long-term, showing a significant difference compared to placebo up to 28 days, and demonstrates efficacy at maintaining normokalaemia up to 12 months, which is consistent across all subgroups including patients with CKD, HF, diabetes mellitus and those taking RAASi therapy.[103,105,119]

In the [redacted] patients taking RAASi at baseline in 005, [redacted] could continue the same dose ([redacted]). Increases in RAASi dose occurred in [redacted], decreases occurred in [redacted] discontinued RAASi use altogether. Similar results were observed among patients with diabetes, HF and eGFR <60 mL/min. Furthermore, SZC was efficacious in this group, demonstrating a baseline S-K of 5.6 mmol/L, decreasing to 4.8 mmol/L in the acute phase, and 4.6 mmol/L at day 365, on a mean dose of 7.4 g (± 2.7).[103]

SZC also showed efficacy irrespective of baseline S-K levels, with a larger decrease in those with higher S-K levels. In ZS-005, 100% of the 126 patients with a S-K >6.0, had a K^+ <5.5 mmol/L at 72 hours, with 57.9% with a S-K <5.1. The mean S-K change at 24, 48 and 72 hours was −1.12, −1.35 and −1.73 and in 004, the mean S-K reduction in those with K >6.0, was 1.5 mmol/L at 48 hours. Both studies showed the magnitude of K^+ reduction was proportional to the starting baseline K^+ level, suggesting that the efficiency of SZC increases with the severity of HK.[101,103]

Safety and tolerability

In all four Phase 3 trials, SZC was well tolerated with minimal serious AEs. The most common TEAEs reported during the acute phase were gastrointestinal disorders, but all were considered mild and in study ZS-004, it was mostly reported in the placebo arm in ZS-004, at 14.1% vs 6.7% and 2.0% for the 5 and 10 g doses respectively.[95,99,103]

In the 12-month, single-arm, maintenance phase trials, the most common TEAEs reported in ZS-004E and ZS-005, were hypertension (11–12.2%), peripheral oedema (8.1–9.7%) and urinary tract infections (7.9–8.9%).[103] The sodium content of SZC in total is 400 mg in every 5 g dose. This is equivalent to the amount of sodium in one soluble paracetamol tablet,

which contacts 392 mg of sodium. Furthermore, it is unknown whether the full amount of Na in SZC gets released and whether all of it absorbed, so the absolute maximum amount of Na that a patient could potentially absorb from the 5 g is 400 mg and it could potentially be less. Of note, thePhase 2 trial did not report a change 24-hour urinary sodium excretion between placebo and any SZC dose [3,99].

In ZS-004, oedema rates between placebo and the 5 g and 10 g doses were similar, at 2.4%. 2.2% and 5.9% respectively.[99] Over 12 months, peripheral oedema was reported in 9.7% as a TEAE. From these patients, most had a history of CKD (92.9%) and over half had a history of HF (53.1%). Furthermore, 97.2% of the peripheral oedema reported was mild-to-moderate and was treated in 55.6% of patients with an increase in diuretics. Only one patient discontinued the study drug, due to peripheral oedema. A total of 11.4% of patients reported hypertension over 12 months. However, among these patients, 91.8% had a history of hypertension, and in these patients, there was a mean (SD) change from baseline of −0.6/−1.0 (21/13) mmHg. In the overall population, the mean BP change from baseline was −0.6/−1.0 (21.13) mmHg. No patients discontinued due to an AE of hypertension. Hence overall, rates of oedema and hypertension were low, and only one case of peripheral oedema was thought to be secondary to the SZC and the patient was discontinued. There was no change in mean BP, over 12 months of treatment. This data demonstrates that the rates of reported oedema were similar up to 28 days in placebo versus the treatment groups, and only one patient discontinued treatment due to oedema, in a group of patients who have multiple comorbidities that predispose them to developing oedema. Furthermore, there was no change in mean BP and no discontinuations due to hypertension.[99,103]

B.2.13.2 *Strengths and limitations of the clinical evidence base for the technology*

The key strengths and limitations are summarised below.

Strengths

- The inclusion criteria for all SZC trials were broad, hence representing the typical patient with HK – a comorbid patient, on treatments that predispose these patients to developing HK. Therefore, the trial population is representative of the patient population likely to be seen in UK clinical practice.
- More than 70% patients were receiving treatment with RAASi therapy and therefore is reflective of the patient population in UK clinical practice. In addition, subgroup analyses of these patients show a statistically significant improvement in S-K levels during the extension/maintenance treatment phase, which was consistent with the general population
- The placebo-controlled arms, up to 28 days, were also reflective of standard of care – as in these arms, treating clinicians could down-titrate RAASi treatment to control HK. Even in this setting, treatment with SZC was more efficacious than standard of care
- The SZC trial programme is comprehensive, including >850 patients with long-term maintenance treatment, with consistent results in both trials ZS-004E and ZS-005. Furthermore, this long-term data includes a UK site, hence UK patients have been treated with SZC

- There was a statistically and clinically meaningful reduction in HK up to 12 months, irrespective of underlying comorbidities and maintenance of RAASi therapies. This demonstrates that SZC is a pharmacological intervention, which would result in a step change in the current standard of care and will result in long-term improvements in outcomes
- The dosing regimen included in the SZC clinical trial programme is aligned with the licence and SmPC and therefore data on efficacy and tolerability are robust and likely to represent the effect which will be observed in patients in routine clinical practice
- Unlike other licensed potassium binders, there is no restriction on dosing windows with other medications and can be stored without the need for refrigeration, which offers convenience and flexibility for patients who often have multiple medications
- It does not cause other significant electrolye abnormalities that require monitoring, unlike other licensed potassium binders

Limitations

- Patients were enrolled, on the definition that HK was >5.0 mmol/L. While UK clinicians will treat HK once S-K is >5.5 mmol/L, this is relevant to clinical practice as NICE guidelines recommend that RAASi are not routinely offered to patients with CKD if their pre-treatment S-K concentration is >5.0 mmol/L,[7] and similarly ESC-HF guidelines recommend caution in commencing RAASi in patients with S-K >5.0 mmol/L, and stopping RAASi if potassium rises to >5.5 mmol/L[8]
  - Nevertheless, >50% patients enrolled in the clinical trials had a baseline potassium level >5.5 mmol/L and therefore the majority of the patient population represent those that are likely to be routinely treated in UK clinical practice
- Studies ZS-004E and ZS-005 did not include a placebo arm. However, this decision was made due to safety concerns of not treating patients with HK.
  - However, there is placebo-controlled data up to 28 days and is reflective of standard of care in the UK
- Premature discontinuations occurred in 37.5% of patients in the long-term trials.
  - However, the majority of these were not due to AEs (6.8%) and were predominantly due to consent being withdrawn (10.9%). Therefore, it is likely that compliance may be increased in UK clinical practice

B.3. Cost-effectiveness

B.3.1 *Published cost-effectiveness studies*

An economic systematic literature review (SLR) was conducted to identify existing cost-effectiveness studies conducted in the management of HK in adults on 27 April 2018. In line with guidance from the Centre for Reviews and Dissemination (CRD), the population, interventions, comparators, outcomes and study type principle was used to define the following review question:[120]

- What cost-effectiveness analyses have been conducted in the treatment of HK?

For this economic SLR, a single search strategy was used to identify cost-effectiveness, HRQoL (Section B.3.4), and cost and resource use studies (Section B.3.5). Please see Appendix G for the methods used to identify all relevant studies, and a description and quality assessment of the cost-effectiveness studies identified.

Five cost-effectiveness studies were identified. The NICE STA user guide[121] recommends that an overview of each cost-effectiveness study is required only if it is relevant to decision-making in England. Therefore, extraction was only performed for cost-effectiveness studies from a UK perspective (n=3) and a detailed summary is provided in Table 22.

A tabulated summary of the two excluded US cost-effectiveness studies is presented in Table 23.

Table 22. Summary list of published UK cost-effectiveness studies

Study	Bennett H, 2017 (a)[122]	Bennett H, 2017 (b)[123]	Sutherland C, 2017[124]
Summary of model	Objective was to estimate costs and health outcomes associated with effective K^+ management, independent of pharmacological treatment costs, in HF or CKD patients with or without RAASi therapy from a UK NHS perspective Two hypothetical scenarios were assessed: NK group: lifetime maintenance of normokalaemia. K^+ remained at a constant value of 4.5 mEq/L for the duration of the modelled horizon HK group: fluctuating K^+ levels resulting in HK rates consistent with clinical practice. K^+ sampled from a normal distribution (mean 4.5 ± SD 0.5 mEq/L). A patient-level simulation model was developed to characterise the natural history of HF and CKD. HF progression was modelled according to transitions between NYHA classes I–IV. CKD progression was modelled through CKD stages, via continuous eGFR decline, leading to ESRD and the initiation of RRT. Lifetime-horizon Discount rate of 3.5% Time-dependent K^+ trajectories were simulated using mixed-effects regression equations. K^+ profiles were superimposed on the HF and	Objective was to explore the impact of ESRD on health economic outcomes associated with managing HK, independent of pharmacological K^+ management costs, in CKD patients from a UK NHS perspective Two scenarios were compared: NK group: maintenance of normokalaemia, via a stable K^+ of 4.5 mEq/L HK group: fluctuating K^+ levels, sampled from a normal distribution (mean 4.5 ± SD 0.5 mEq/L) A patient-level simulation model was developed to characterise the natural history of CKD. CKD progression was modelled through CKD stages, via continuous eGFR decline, (3.52 mL/min/1.73m^2/year), until the incidence of ESRD (defined as eGFR <15 mL/min/1.73 m^2) Lifetime and pre-ESRD time-horizon Discount rate of 3.5% Prior to the onset of ESRD, simulated time-dependent trajectories of K^+ were linked to the incidence of cardiovascular events, hospitalisation and mortality via published rates IRRs for each event were applied to baseline event rates, which were defined by CKD stage	Objective was to evaluate the cost and health benefits that patiromer may provide from a UK NHS perspective The cost-effectiveness of patiromer vs no patiromer was assessed while considering RAASi discontinuation Markov model was developed using monthly cycles with the following health states: CKD stages 3-4; CKD progression; hyperkalaemia (hospitalisation); CV event (hospitalisation); post-CV event; death Lifetime-horizon Discount rate of 3.5% Parameter values for mortality, morbidity, costs and utilities were derived from published literature and publicly available data in the UK Life-expectancy calculated based on national lifetables Utilities calculated as a function of age based on a previously published algorithm It was assumed that the RAASi-enabling effect would continue as long as patiromer was given and thereafter a proportion would discontinue RAASi Uncertainty of the base-case results examined via univariate sensitivity

Study	Bennett H, 2017 (a)[122]	Bennett H, 2017 (b)[123]	Sutherland C, 2017[124]
	CKD model components and were linked to mortality, hospitalisation and MACE incidence via published rates Incidence rate ratios and HRs relating K^+ to event risk were sourced from published literature and applied to baseline risks defined by CKD stage or NYHA class Costs and utilities were derived from published literature No sensitivity analyses were conducted	Costs and utilities were derived from published literature No sensitivity analyses were conducted	analysis and probabilistic sensitivity analysis Univariate sensitivity analyses demonstrated that the RRs of progression to ESRD, cost of ESRD and inputs related to mortality (i.e. RR of death with RAASi, etc.) had the greatest impact on the ICER
Patient population (average age in years)	Patients with HK in HF or CKD, with or without RAASi therapy Modelled patients were initiated with baseline age 60 years and eGFR <50 mL/min/1.73 m^2	Patients with CKD Modelled patients were initiated with baseline age 60 years, eGFR <50 mL/min/1.73 m^2 50% of the simulated cohort were female	Population under evaluation from the OPAL-HK trial
QALYs (intervention, comparator)	Discounted results – lifetime horizon CKD patients: NK group: 6.65 QALYs, 9.07 LYs HK group: 6.30 QALYs, 8.57 LYs HF patients: NK group: 5.63 QALYs, 7.75 LYs HK group: 4.29 QALYs, 5.92 LYs	Discounted results – lifetime horizon NK group: 6.65 QALYs, 9.07 LYs HK group: 6.26 QALYs, 8.51 LYs Discounted results – pre-ESRD time horizon NK group: 5.47 QALYs, 7.03 LYs HK group: 5.27 QALYs, 6.78 LYs	Patiromer: 5.80 QALYs, 7.60 LYG No patiromer: 5.58 QALYs, 7.34 LYG
Costs (currency) (intervention, comparator)	Discounted results – lifetime horizon CKD patients: NK group: £69,606 HK group: £65,231 HF patients:	Discounted results – lifetime horizon NK group: £69,606 HK group: £64,458 Incremental (NK-HK): £5148	Base-case results (discounted), CKD stage 3–4 with HK on RAASi Patiromer case cost: £84,281 No patiromer case cost: £80,160 Event costs

Study	Bennett H, 2017 (a)[122]	Bennett H, 2017 (b)[123]	Sutherland C, 2017[124]
	NK group: £7881 HK group: £6374	Discounted results – pre-ESRD time horizon NK group: £38,050 HK group: £37,667 Incremental (NK-HK): £383 Net monetary benefit at £20,000/QALY – lifetime horizon NK group: £63,346 HK group: £60,749 Net monetary benefit at £20,000/QALY – pre-ESRD time horizon NK group: £71,426 HK group: £67,646	MI: £8938 Stroke: £14,099 CHF hospitalisation: £2692 HK: £2824 Constipation: £220 Diarrhoea: negligible Monthly costs: CKD management: £147 ESRD (PD): £1,934 ESRD (HD): £2,315 ESRD (transplant): £1,435 Patiromer: £304 RAASi and other meds: £15
ICER (per QALY gained)	Not reported	Net monetary benefit at £20,000/QALY – lifetime horizon Incremental (NK-HK): £2597 Net monetary benefit at £20,000/QALY – pre-ESRD time horizon Incremental (NK-HK): £3,750	ICER Patiromer versus no patiromer £18,807 per QALY gained £15,486 per LYG

bbreviations: CHF, congestive heart failure; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HD, haemodialysis; HF, heart failure; HK, hyperkalaemia; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IRR, incident rate ratio; LY, life year; LYG, life years gained; MACE, major adverse cardiovascular events; MI, myocardial infarction; NHS, National Health Service; NK, normokalaemia; NYHA, New York Heart Association; PD, peritoneal dialysis; QALY, quality-adjusted life-year; RAASi, renin-angiotensin-aldosterone system inhibitor; RR, relative risk; RRT, renal replacement therapy; SD, standard deviation.

Table 23. Summary of US cost-effectiveness studies

Study	Bounthavong M, 2017[125]	Little D, 2014[126]
Year	**2017**	**2014**
Summary of model	• Objective was to estimate the clinical and economic outcomes of using patiromer with spironolactone in patients with NYHA Class III–IV HF receiving an ACEi and otherwise unable to add spironolactone due to HK from a US payer perspective • The cost-effectiveness of spironolactone / ACEi + patiromer versus ACEi only was assessed. Spironolactone/ACEi + patiromer were assumed to be administered for the first 3 years. It was also assumed that 15% of patients in the cohort would discontinue due to intolerance at 2 months • A Markov model was developed with the following health states: stable HF; hospitalisation; death. • 10-year time horizon • Discount rate of 3.0% • Clinical inputs derived from RALES trial (spironolactone versus placebo in patients with NYHA Class III–IV HF on an ACEi). However, to reflect current treatment practices and align with current literature, the modelled baseline survival was adjusted upward to 40% survival at 5 years based on contemporary survival data in NYHA functional Class III–IV patients from the Swedish Heart Failure Registry • RALES mortality risk was adjusted to RR=0.81 based on current survival data • Utilities were derived from the literature and adjusted for NYHA classification • The wholesale acquisition cost was used for drug costs, and hospitalisation costs were estimated from a national survey • Deterministic and scenario analyses were performed	• Objective was to assess the cost-utility of SPS against a theoretical “drug X” binding resin in the treatment of chronic HK in RAASi-treated outpatients with CHF, proteinuric CKD, or both from a US perspective • A decision-tree model was developed with the key events being colonic necrosis and death with Drug X or SPS • 1-year time horizon • Discounting was deemed unnecessary due to the short time horizon • Clinical inputs and utilities were obtained from existing literature • Cost inputs were drug costs based on wholesaler price and colectomy costs based on inflated Medicare costs • Deterministic and probabilistic sensitivity analyses were performed
Patient population (average age in years)	Population details not provided	Population was adult (≥18 years) outpatients with mild-to-moderate chronic HK (K^+ ≥ 5.2 and < 7.0 mEq/L), due to RAASi for CHF with or without CKD, RAASi for proteinuric kidney disease (including

		diabetic nephropathy), or HK due to CKD, who were candidates for chronic treatment with oral potassium-binding resins
QALYs (intervention, comparator)	• Spironolactone/ACEi + patiromer: 2.54 QALYs • ACEi only: 2.27 QALYs	• SPS base-case: 0.7193 QALYs • Drug X base-case: 0.7197 QALYs
Costs (currency) (intervention, comparator)	<u>Spironolactone/ACEi + patiromer</u> • Drug cost: $16,200 • Hospital cost: $14,800 • Total: $31,000 <u>ACEi only</u> • Drug cost: $0.00 • Hospital cost: $15,800 • Total: $15,800	• SPS base-case: $3926.82 • Drug X base-case: $14,616.96
ICER (per QALY gained)	<u>ICER</u> Spironolactone/ACEi + patiromer versus ACEi • $56,300 per QALY gained	<u>ICER</u> Drug X versus SPS • $26,088,369.00 per QALY gained (based on hypothetical drug cost of $40.00)

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; CHF, congestive heart failure; CKD, chronic kidney disease; HF, heart failure; HK, hyperkalaemia; ICER, incremental cost-effectiveness ratio; K^+, potassium; NYHA, New York Heart Association; QALY, quality-adjusted life-year; RAASi, renin-angiotensin-aldosterone system inhibitor; RR, relative risk; SPS, sodium polystyrene sulfonate.

B.3.2 *Economic analysis*

The economic SLR found three cost-effectiveness studies to inform the economic analysis. Two studies by Bennett et al.[122,123] estimated the costs and outcomes associated with effective management of HK from the UK NHS perspective. Both studies used a newly developed patient simulation model to characterise the natural history of CKD or HF in one study[122] and CKD only in the other study[123] over a lifetime horizon. The progression of CKD was modelled in both studies through CKD stages, via continuous eGFR decline until the incidence of ESRD, while the progression of HF was modelled according to transitions between New York Heart Association (NYHA) classes I–IV. In these studies, two hypothetical scenarios were explored: 1) patients with normokalaemia (NK group) 2) patients with HK (HK group) being entered into the patient simulation model. Simulated time-dependent trajectories of K^+ were linked to cardiovascular events, hospitalisation and mortality via published rates.

In the third UK study, Sutherland et al.[124] investigated the cost-effectiveness of using patiromer versus no patiromer in treating CKD patients with RAASi-induced HK, from the perspective of the UK NHS. A Markov model was developed to estimate outcomes over a lifetime-horizon for those continuing RAASi or discontinuing RAASi in both patiromer and no patiromer arms. Population characteristics were based on the OPAL-HK trial, which included patients with CKD stage 3–4 with HK and on RAASi.

Based on these three studies, a patient-level simulation model was deemed a more appropriate model structure than a Markov model to capture the transience and complexity of HK management in patients with CKD or HF, while enabling the modification of RAASi therapies including down-titration or discontinuation. As discussed in Section B.3.2.2, a Markov model aiming to capture all the aforementioned clinically relevant components would have resulted in an unreasonable number of health states.

B.3.2.1 *Patient population*

In line with the licensed indication and the decision problem for SZC, the patient population included in the model comprises adults with HK.

As discussed in Section B.1.3.1.2, HK is usually a consequence of an underlying health condition, the most common of which that are likely to result in impaired excretion are CKD and HF. Therefore, in line with underlying health conditions observed clinical practice and in the clinical trial programme for SZC, patients in the model have HK and an underlying condition of:

- Non-dialysed CKD stage 3a–5 (see Table 24), or
- NYHA functional class I, II, III or IV (see Table 25)

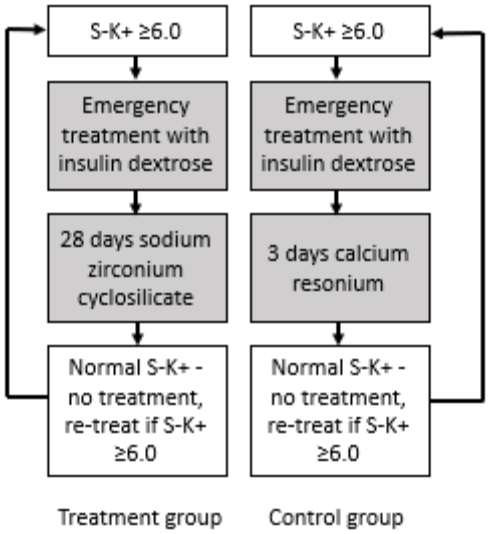
The patient population is assumed to enter either the:

- Acute setting (when S-K ≥6.0 mmol/L), or
- Chronic setting (when S-K ≥5.5 mmol/L).

The positioning of SZC within these settings is illustrated in Figure 15 for the acute setting and Figure 16 for the chronic setting. This is based on the treatment pathway described in Figure 6. Since patient demographics and management differ between the two settings, the cost-effectiveness of SZC is evaluated for each setting separately. As such, the evaluation considers the cost-effectiveness of SZC in two distinct populations:

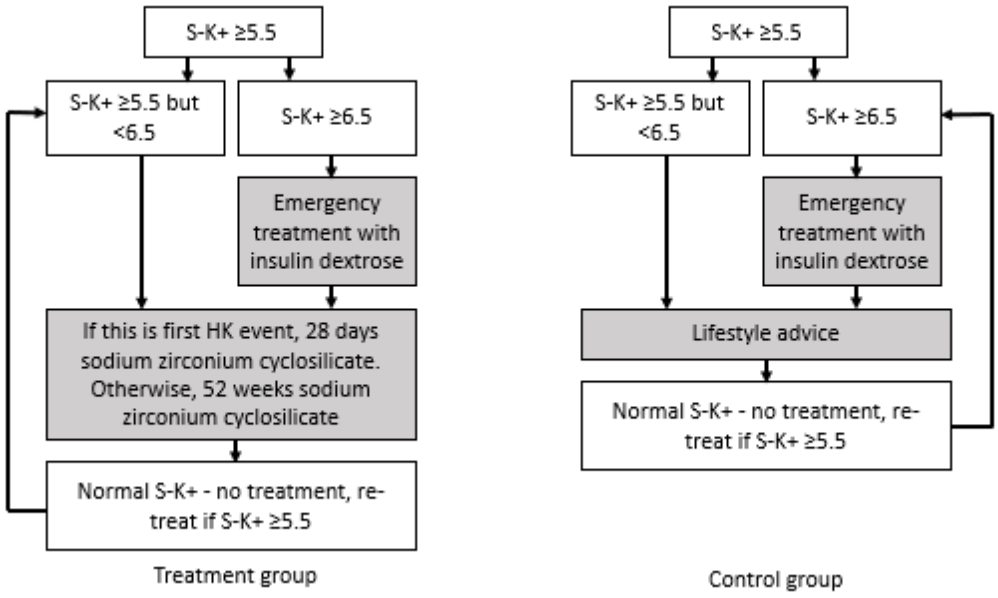
1. Patients with HK, with underlying CKD or HF, in the acute setting
2. Patients with HK, with underlying CKD or HF, in the chronic setting

Figure 15. Schematic treatment pathway in acute setting



Abbreviation: S-K, serum potassium.

Figure 16. Schematic treatment pathway in chronic setting



Abbreviation: HK, hyperkalaemia; S-K, serum potassium.

Table 24. CKD staging definitions[127]

CKD stages	eGFR lower bound	eGFR upper bound
3a	≥45 mL/min/1.73 m^2	<60 mL/min/1.73 m^2
3b	≥30 mL/min/1.73 m^2	<45 mL/min/1.73 m^2
4	≥15 mL/min/1.73 m^2	<30 mL/min/1.73 m^2
5	≥0 mL/min/1.73 m^2	<15 mL/min/1.73 m^2

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Table 25. HF staging definitions[128]

NYHA classification	Patient symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea (shortness of breath)
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea (shortness of breath)
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnoea
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases

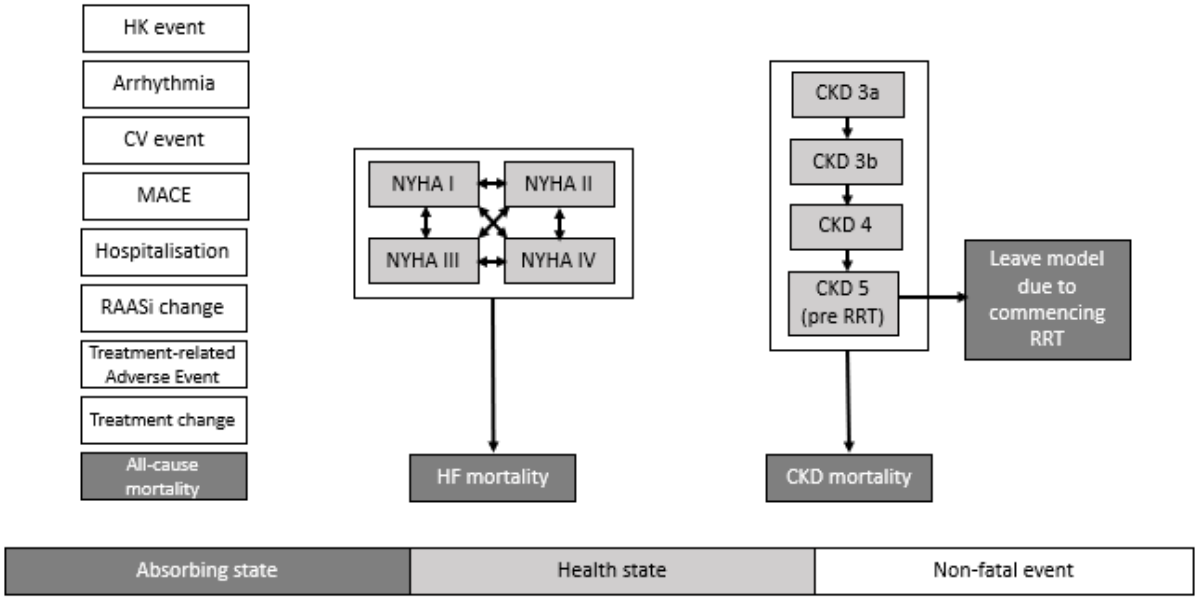
Abbreviations: HF, heart failure; NYHA, New York Heart Association.

B.3.2.2 *Model structure*

As discussed in Section B.1.3.1.2, clinical outcomes in HK depend significantly on individual S-K profiles. As such, a patient-level simulation model was deemed to be an appropriate structure. The justification for the structure is to capture the complexity of disease (especially the association between long-term control of individual S-K levels and short-term acute events) and enable the simulation of multiple co-existing and competing conditional risks. Such complexity would lead to an unduly large number of health states were a Markov modelling approach adopted. The structure has been validated by clinical experts.[29]

The model was designed to compare SZC against standard of care in the target patient population. The model was developed as a patient-level, fixed-time increment stochastic simulation in Microsoft® Excel. The model's core calculations are undertaken within Visual Basic for Applications. Figure 17 represents a simplified flow diagram depicting the health states and events captured by the model.

Figure 17. Flow diagram summarising the SZC model health states (shaded) and events (unshaded)



Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; HF, heart failure; HK, hyperkalaemia; MACE, major adverse cardiac event; NYHA, New York Heart Association; RAASi, renin-angiotensin-aldosterone system inhibitor; RRT, renal replacement therapy; SZC, sodium zirconium cyclosilicate.

Cohorts of simulated patients with advanced CKD or HF enter the model at their first HK event. As can be seen, the progression of HF patients is modelled via transitions between NYHA classifications (I–IV), while the progression of CKD patients is modelled via the decline of eGFR on a continuous scale. For CKD patients, progression through CKD stages are tracked until the onset of ESRD and the initiation of RRT. The structures of the CKD and HF component of the model are based on well-documented existing models.[129 43]

As patients progress through the model, economically and clinically relevant events for each treatment arm are estimated: acute HK events, cardiovascular events, MACE, hospitalisation, changes in RAASi therapy, adverse events and treatment changes (i.e. down-titration and discontinuation).

Patients exit the model due to death. In addition, patients exit the model following the introduction of RRT. The rationale for patients exiting at RRT is that:

- According to UK clinical experts,[29] the management of S-K following the initiation of RRT differs from that prior to RRT, and there is no NICE guidance setting out the consensus of treatment in this area. The SmPC[1] highlights that there is no data to support the use of SZC in this population. As such the effect of RRT both in terms of costs and consequences is highly uncertain
- Since RRT is not management for HK, this should be regarded as an 'unrelated future cost' with respect to SZC. NICE guidance is to ignore unrelated future costs[130], as there is no agreed methodology for calculating them
- The inclusion of RRT obscures the decision problem of an intervention positioned prior to RRT, since RRT is not a cost-effective intervention. As such, the inclusion of RRT and non-cost-effective use of interventions not in control of the manufacturer should not

influence the decision to be made about SZC for the treatment of HK. This position is supported in the clinical literature[123,131]

Inputs to the model are included based on a hierarchy of evidence consistent with NICE's Reference Case. Where possible, direct trial evidence is used to inform parameters. If this evidence is not available, validated published literature sources and national-level guidelines (such as NICE clinical guidelines) are used. Finally, if there are no other sources available, cohort data and expert opinion are used to inform parameters.

Costs and utilities (or utility decrements) are applied by health state, treatment status, and at the incidence of each event. Patients are simulated until death or RRT; after all individuals have progressed through the model, the process ends and all relevant statistics are presented for each modelled arm.

The time horizon for the model is lifetime (80 years) or until RRT initiation to reflect all important differences in costs and outcomes between the technologies being compared. As a standard modelling assumption, no patient can survive past age 100, therefore an 80-year time horizon was selected to ensure that any adult aged >20 years initiated into the model would end as a result of transitioning into an absorbing state. The cycle length is 4 weeks (28 days) to reflect the design of the ZS-004[99] and ZS-005[103] trials (one cycle and 13 cycles respectively). However, in order to capture short-term events that may occur during the acute setting, the first 4-week period is broken into shorter cycle lengths, described in Table 26. Due to the varying cycle lengths, no half-cycle correction was required, and as such this is not applied in the model.

Table 26. Summary of cycle lengths applied from start of simulation

Cycle	Description	Cycle length
1	Day 1	1 day
2	Day 2	1 day
3	Day 3	1 day
4	Day 4–14	11 days
5	Day 15–28 (Week 3–4)	2 weeks
6+	Week 5+	4 weeks

The key features of the economic analysis with justification are presented in Table 27. There have been no previous technology appraisals for management of HK in this population, and as such no comparison of model features can be made.

B.3.2.2.1 Key features of the de novo analysis

Table 27. Features of the economic analysis

	Current appraisal	
Factor	**Chosen values**	**Justification**
Time horizon	Lifetime (80 years from first event), unless RRT is initiated in which case model ends at RRT	NICE reference case. No patient may survive after 100 years. Model terminates at RRT as: • RRT leads to great increase in uncertainty, as highlighted in the SmPC[1] • RRT is likely to be considered an unrelated future cost • RRT obscures decision problem See Section B.3.2.2 for a more detailed discussion of this
Cycle length	28 days after initial acute management	Reflects the design of the ZS-004[99] and ZS-005[103] trials
Were health effects measured in QALYs; if not, what was used?	Yes	NICE reference case
Discount of 3.5% for utilities and costs	Yes	NICE reference case. The impact of alternative discount rates has been tested in sensitivity analyses
Perspective (NHS/PSS)	UK NHS PSS	NICE reference case
Treatment waning effect?	N/A	Treatment effect is based on direct data from the ZS-004 and ZS-005[103] trials, and treatment ceases after the duration of ZS-005 (52 weeks). An assumption is made that subsequent re-treatment (if required) would be equivalent to first-time treatment. Therefore, no extrapolation is required considering waning.
Source of utilities	No HRQoL data was collected in ZS-004[99] and ZS-005[103] trials (see Section B.2.6) therefore source of utility is published literature	NICE reference case
Source of costs	Sources of cost data included the BNF for drug costs, published literature and national cost databases (NHS Reference Costs)	NICE reference case

Abbreviations: BNF, British National Formulary; HRQoL, health-related quality of life; NHS, National Health Service; PSS, personal social services; QALY, quality-adjusted life-year; RRT, renal replacement therapy.

B.3.2.3 *Intervention technology and comparators*

In line with the decision problem (Section B.1.1), the model evaluates the use of SZC against standard care in the acute and chronic settings as per Figure 15 and Figure 16 respectively.

- In the acute setting, standard care consists of two rounds of insulin glucose and intermittent use of calcium resonium for the correction of S-K whilst the intervention arm includes one round of insulin glucose followed by SZC.
- In the chronic setting, no targeted therapy is administered for standard care. Insulin glucose may be given to both standard care and SZC arms if S-K levels get extremely high (>6.5 mmol/L).

In both treatment arms and settings, lifestyle interventions for the background maintenance of S-K (for example, dietary intervention and modification of concomitant medications such as RAASi) are also part of the management of HK.

B.3.3 *Clinical parameters and variables*

B.3.3.1 *How are clinical data incorporated into the model?*

The key clinical data are the relationship between S-K levels and treatment. The only evidence available on this topic is from the two trials, ZS-004[99] for standard care and SZC and ZS-005[103] for long-term use of SZC. Changes in S-K levels were reported for the first 28 days in ZS-004[99] and 52 weeks for ZS-005[103], therefore the changes in S-K levels are based on a pooled analysis of ZS-004 and ZS-005 for the first 28 days, and on ZS-005 only for day 29 to week 52 (Section B.3.3.2.2).

S-K levels were linked to a number of outcomes including mortality, risk of MACE and risk of hospitalisation. Linking these outcomes to the S-K levels is typically done through literature sources, as there are no national-level guidelines on this topic. This is in line with the hierarchy of evidence adopted as part of the model structure (Section B.3.2.2).

Costs and clinical outcomes are not extrapolated beyond the trial period as the longest any patient can be on SZC in the model is 52 weeks, consistent with ZS-005[103]. However, as patients in the model can have multiple re-treatments an assumption is made that the efficacy of the drug seen in the trials remains the same for repeat treatment. This assumption is justified as there is no evidence from the trials that a previous HK event affects response to SZC, and this evidence is extended to make the same assumption about standard care treatment. Costs of underlying medical conditions (such as HF and CKD) are extrapolated beyond the trial period using sources from the targeted literature review to estimate long-term costs and clinical outcomes.

B.3.3.2 *Transition probabilities*

B.3.3.2.1 Baseline demographics

To reflect the population for which the efficacy of SZC has been derived, baseline characteristics were based on results from ZS-004[99] and ZS-005[103], where possible. Table 28 provides the baseline characteristics of patients entering the model which could be derived from ZS-004[99] and ZS-005.[103] While direct trial data was preferred where it was available, in line with the NICE reference case,[130] not all demographic data used in the model was available from ZS-004[99] and ZS-005.[103].

Table 29 provides the baseline characteristics of patients entering the model which could not be derived from ZS-004[99] and ZS-005;[103] as such retrospective, observational studies in CKD and HF patients from the British Society for Heart Failure National Heart Failure Audit, CPRD (an English NHS observational data and interventional research service for primary care) and the PRAISE study (a large trial in over 1,000 HF patients) were used. These sources were selected as they were the largest and most nationally representative data available.

Patients simulated in the model are split by CKD (64%) and HF (36%) using a random number generator based on the observed split between patients in ZS-005.[103] Baseline characteristics for each patient entering the model are calculated by simulating from the probabilistic distribution, mean and standard errors described in Table 28 and Table 29.

Table 28. Baseline demographics of cohort entering the model

Patient characteristic	CKD		HF			
	Mean	**SE**	**Mean**	**SE**	**Distribution**	**Source**
Proportion with CKD	1.00	N/A	0.00	N/A	N/A	Pooled from ZS-004[99] and ZS-005[103]
Age (years)	63.56	0.65	65.07	1.25	Normal	
Proportion female	0.37	0.02	0.37	0.05	Beta	
eGFR (mL/min/1.73 m^2)	31.63	0.88	68.14	3.22	Normal	
Weight (kg)	89.44	1.24	82.23	2.49	Normal	
SBP (mmHg)	141.20	0.96	132.13	2.32	Normal	
Hb (g/dL)	11.79	0.09	13.25	0.20	Normal	
WBC count (109/L)	7.28	0.11	7.66	0.28	Normal	
Lymphocytes (103/µL)	1.72	0.03	2.04	0.09	Normal	
Sodium (mmol/L)	137.71	0.16	137.55	0.36	Normal	

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HF, heart failure; SBP, systolic blood pressure; SE, standard error; WBC, white blood cell.

Table 29. Baseline demographics of cohort entering the model (other sources)

Patient characteristic	CKD			HF			
	Mean	SE	Source	Mean	SE	Source	Dist.
Morbidity profile							
Duration of disease, years	0	0	Assumption	0	0	Assumption	N/A
Ejection fraction, mL	N/A	N/A	N/A	21	0.18	PRAISE[129]	Normal
Ischaemic aetiology, %	N/A	N/A	N/A	0.64	0.01		Beta
NYHA Class I, %	N/A	N/A	N/A	10	N/A	British Society for Heart Failure National Heart Failure Audit, 2015/16[112]	N/A
NYHA Class II, %	N/A	N/A	N/A	10	N/A		N/A
NYHA Class III, %	N/A	N/A	N/A	43	N/A		N/A
NYHA Class IV, %	N/A	N/A	N/A	37	N/A		N/A
Comorbidity/clinical history (proportion)							
Cancer	0.0920	0.0007	CPRD	0.0982	0.0020	CPRD[55]	Beta
PVD	0.0241	0.0003	CPRD	0.0298	0.0012	CPRD[55]	Beta
Modifiable risk factors							
BMI, kg/m^2	28.53	0.0270	CPRD	28.37	0.1092	CPRD[55]	Normal

Patient characteristic	CKD			HF			
	Mean	SE	Source	Mean	SE	Source	Dist.
Total cholesterol, mg/dL*	193.86	0.1655	CPRD	168.92	0.7734	CPRD[55]	Normal
Uric acid, mg/dL	N/A	N/A	N/A	8.9	0.078	PRAISE[129]	Normal
Concomitant therapies (proportion, unless otherwise stated)							
RAASi, %	0.357	N/A	ZS-005 [103]CSR. Table 11.3	0.702	N/A	ZS-005[103] CSR. Table 11.3	N/A
K^+ sparing diuretics	N/A	N/A	N/A	0.0300	0.0050	PRAISE[129]	Beta
Diuretics	0.4019	0.0011	CPRD	0.6144	0.0033	CPRD[55]	Beta
Beta blocker	N/A	N/A	N/A	0.4478	0.0034		Beta
Calcium channel blocker	0.2749	0.0010	CPRD	N/A	N/A	N/A	Beta
Statin	N/A	N/A	N/A	0.4153	0.0034	CPRD[55]	Beta
Proportion of RAASi users on ACE	N/A	N/A	N/A	0.8192	0.0033	CPRD[55]	Beta
Proportion of RAASi users on ARB				0.1904	0.0044	CPRD[55]	Beta
Allopurinol				0.1000	0.0090	PRAISE[129]	Beta
ICD				0.0000	0.0000		Beta
BICD				0.0000	0.0000		Beta
Diuretic dose, mg/kg				1.4500	0.0400		Normal

*Total cholesterol measurements converted as follows: 1 mmol/L = 38.67 mg/dL.
Abbreviations: ACE, angiotensin-converting-enzyme; ARB, angiotensin II receptor blocker; BICD, biventricular implantable cardioverter defibrillator; BMI, body mass index; CKD, chronic kidney disease; CPRD, Clinical Practice Research Datalink; ICD, implantable cardioverter defibrillator; Dist., distribution; HF, heart failure; N/A, not applicable; NYHA, New York Heart Association; PVD, peripheral vascular disease; RAASi, renin-angiotensin-aldosterone system inhibitor; SE, standard error.

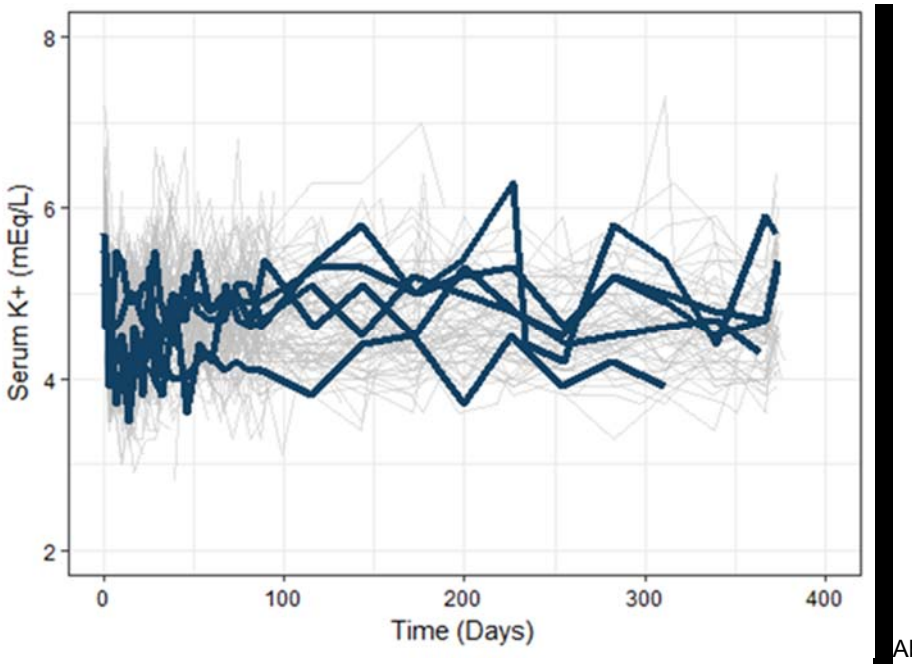
B.3.3.2.2 S-K profile

S-K levels are important in the model as they are associated with health outcomes, in addition to triggering a number of economically relevant events such as an acute HK episode. S-K levels are taken directly from trial data, and there is a significant clinical literature linking S-K levels to long-term clinical outcomes.

S-K levels fluctuate over time, with each patient exhibiting a unique S-K trajectory (Figure 18). To reflect this within the model, trial-, treatment- and patient-specific S-K profiles are simulated using mixed effects regression models. These models comprise a fixed effect representing a time-varying, population-averaged mean level of S-K and a random effect representing patient-specific mean S-K levels that may be systematically higher or lower

than the population-averaged mean level. The fixed effect therefore represents the improvement in S-K levels that occurs across the whole population, and importantly captures the treatment effect of SZC in reducing S-K. The random effect is used to obtain estimates of S-K variability that occurs from patient to patient and to acknowledge unobserved heterogeneity in the patient population. This ensures that measurements taken from the same patient are more likely to be similar than measurements taken from different patients. The inclusion of patient-specific random effects increases the accuracy of the models, ensuring that key statistical assumptions are satisfied, and validity of inferences obtained from the models.

Figure 18. Illustrative patient-level S-K trajectories



Abbreviations: K+, serum potassium; S-K, serum potassium.

Table 30 and Table 31 show the parameters associated with the mixed effect models used in the cost-effectiveness model for SZC and standard care respectively.

For SZC, parameters were estimated from pooled data from the ZS-004[99] and ZS-005[103] trials in order to take all the relevant evidence into account for patients who received doses of up to 10 g OD in the maintenance phase as per the SmPC[1], see Section B.2.2.1 for details. Pooled data was used as patients in ZS-005[103] received the same treatment as those in ZS-004[99] for the first 28 days, therefore the first 28 days could be pooled across both trials patients included in the analysis received the same as per protocol dose of SZC in the acute phase (i.e. 10 g TID for 1–3 days: 2 days in ZS-004[99] and 1–3 days in ZS-005[103]) and in the maintenance phase (5 g or 10 g OD for 28 days in ZS-004[99] and 5 g once every other day, OD or 10 g ODfor up to 12 months).

Should SZC be discontinued for any reason (including due to reaching the end of a course of treatment), S-K profile reverts to the standard care profile.

Table 30. Pre-defined S-K profile for SZC: mixed-effects model parameters

	Fixed component	Time-dependent component	Patient component (SD)	Observation component (SD)	Source
Day 0–3	[redacted]	[redacted]	[redacted]	[redacted]	Pooled data from ZS-004[99] and ZS-005[103]
Day 4–14	[redacted]	[redacted]	[redacted]	[redacted]	
Day 15–28	[redacted]	[redacted]	[redacted]	[redacted]	
Day >28	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: N/A, not applicable; SD, standard deviation; S-K, serum potassium; SZC, sodium zirconium cyclosilicate.

Table 31. Pre-defined S-K profile for standard care: mixed effects model parameters

	Fixed component	Time-dependent component	Patient component (SD)	Measurement component (SD)	Source
Day 0–3	[redacted]	[redacted]	[redacted]	[redacted]	Control arm of ZS-005[103]
Day 4–14	[redacted]	[redacted]	[redacted]	[redacted]	
Day 15–28	[redacted]	[redacted]	[redacted]	[redacted]	
Day >28	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: N/A, not applicable; SD, standard deviation; S-K, serum potassium.

Every cycle of the model generates a new S-K level for each patient. This S-K value is the sum of three components:

- The cohort-averaged mean S-K level in that time period, associated with the global time trend. This is fixed, depending on the time since HK event.
- A patient-specific component, obtained as a random draw from a normal distribution with mean 0 and a standard deviation taken from the pooled ZS-004[99] and ZS-005[103] trial data. This is randomly drawn at each HK event, and again at day 4 following HK event.
- A measurement-specific component, obtained as a random draw from a normal distribution with mean 0 and a standard deviation taken from the pooled ZS-004[99] and ZS-005[103] trial data. This is randomly drawn each cycle.

As an example, the S-K of a patient taking SZC on day 1 following an HK event will be [redacted] (fixed) plus [redacted] (time-dependent, fixed) plus a random draw from a normal distribution of mean 0.322 and standard deviation [redacted] (patient component), plus a random draw from a normal distribution of mean [redacted] and standard deviation [redacted] (observation component). The next day, that patient's S-K will have the same fixed component, the time-dependent component will increment by one (to [redacted]), the patient component will remain the same and the observation component will be redrawn from the same distribution.

Patients enter the model at day 0 with an S-K ≥6.0 mmol/L in the acute setting and ≥5.5 mmol/L in the chronic setting based on the above sampling method for S-K. These

thresholds are defined based on national clinical guidelines and UK expert opinion[132]. Patients are resampled in the event that the S-K value is not within the pre-defined thresholds prior to initiating the model.

RAASi status change

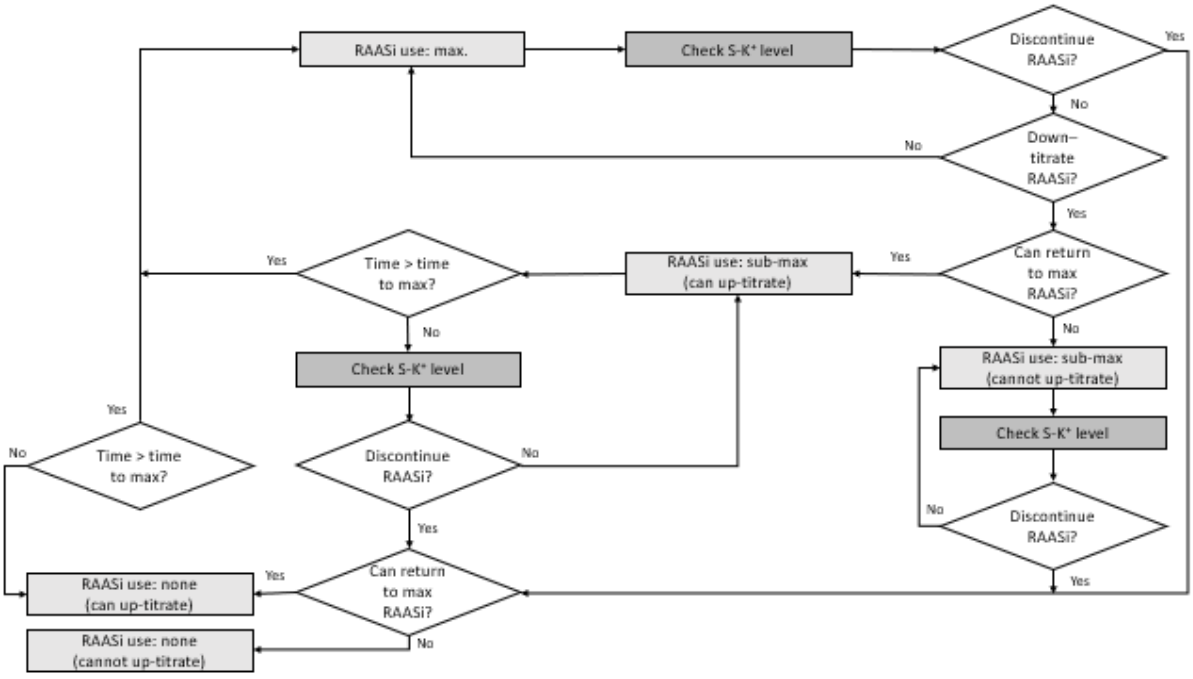
Alongside S-K, RAASi use is a key clinical parameter used to estimate disease progression, cardiovascular events, hospitalisation, and death in the CKD and HF populations. Three RAASi states are modelled:

- RAASi "max" – RAASi use in line with guidelines[8]
- RAASi "sub-max" – RAASi use in line with the mean dose at baseline observed in the CPRD cohort,[60] intended to represent imperfect RAASi use
- No RAASi use

Approximately 70.2% of patients simulated in the model are using RAASi at baseline, based on the observed data from ZS-005[103] trial. Patients are randomly allocated to RAASi / no RAASi using a random number generator. For those not initiating the model on RAASi, it is assumed they will never initiate RAASi. This is justified as NICE CG182[7] states that RAASi should not be prescribed in patients with S-K >5.0, which will cover all patients simulated in the model. All patients who initiate the model on RAASi initiate at "max". This is an assumption as there is no data on the proportion of patients at less than optimal RAASi dosing at the moment of a HK event, but is conservative as it is unfavourable to treatment.

At any stage of the model, patients can discontinue RAASi. In addition, patients can down-titrate from "max" to "sub-max" and up-titrate from "none" or "sub-max" to "max". The process for RAASi change is illustrated in Figure 19.

Figure 19. Logical process followed to model changes in RAASi use (up to one change per cycle)



Abbreviations: S-K, serum potassium; RAASi, renin-angiotensin-aldosterone system inhibitor.

Table 32 to Table 34 describe the proportion of patients discontinuing and down-titrating in the acute and chronic settings. These proportions depend on the S-K level and RAASi state.

In the acute setting, all patients in both treatment groups immediately discontinue RAASi and never re-start. This is based on both clinical experts' input[132] and the NICE clinical guidelines CG182.[7] Note that in the acute setting sub-max RAASi is never reached, therefore no sub-max state is presented in this setting. In the chronic setting, the proportion of patients discontinuing and down-titrating depends on whether the patient begins the cycle at "max" or "sub-max" RAASi. Patients treated with standard care will discontinue RAASi if their S-K is ≥6.0, as per the NICE clinical guidelines CG182[7] and in line with the acute setting assumption. Finally, based on clinical experts' input,[132] patients will discontinue 20% of the time if their S-K is ≥5.5–6.0, and down-titrate the remaining 80% of the time. If the patient is at sub-max RAASi then down-titration is already occurring and will continue. This is a significantly more conservative approach than recommended in CG182,[7] but is thought to better represent clinical practice. In the SZC arm, no special assumptions are made regarding RAASi discontinuation / down-titration (see Section B.3.3.3).

It is possible to return to max RAASi in the chronic setting only; returns occur in 49.7% of eligible cycles. This is justified based on Luo et al.[43] This paper contains data for CKD up-titration following discontinuation only, so an assumption is made that all HF and CKD up-titration following down-titration probabilities will be the same. It is assumed a patient is eligible to return to max RAASi if they are in the chronic setting, have not left the model due to death or RRT and at least three cycles (12 weeks) have elapsed from the discontinuation / down-titration and the current cycle. The timing requirement is based on published literature,[117] the value for the timing requirement itself (three cycles) is based on clinical expert input.[132]

Table 32. RAASi discontinuation and down-titration, by S-K category – acute setting, max RAASi

S-K category (mmol/L)	SZC				Standard care					
	Proportion of patients discontinuing		Proportion of patients down-titrating		Proportion of patients discontinuing		Proportion of patients down-titrating			
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Distribution	Source
<5.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	Beta	Clinical expert input[132]
5.5–6.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	Beta	
≥6.0	1.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0	Beta	

Abbreviations: S-K, serum potassium; RAASi, renin-angiotensin-aldosterone system inhibitor; SE, standard error; SZC, sodium zirconium cyclosilicate.

Table 33. RAASi discontinuation and down-titration, by S-K category – chronic setting, max RAASi

S-K category (mmol/L)	SZC				Standard care					
	Proportion of patients discontinuing		Proportion of patients down-titrating		Proportion of patients discontinuing		Proportion of patients down-titrating			
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Distribution	Source

<5.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	Beta	Clinical expert input[132]
5.5–6.0	0.0	0.0	0.0	0.0	0.2	0.0	0.8	0.0	Beta	
≥6.0	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0	Beta	

Abbreviations: S-K, serum potassium; RAASi, renin-angiotensin-aldosterone system inhibitor; SE, standard error; SZC, sodium zirconium cyclosilicate.

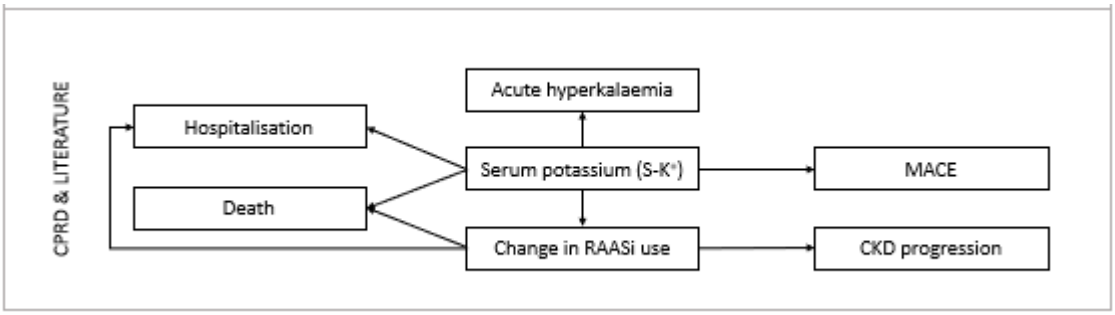
Table 34. RAASi discontinuation and down-titration, by S-K category – chronic setting, sub-max RAASi

S-K category (mmol/L)	SZC				Standard care					
	Proportion of patients discontinuing		Proportion of patients down-titrating		Proportion of patients discontinuing		Proportion of patients down-titrating			
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Distribution	Source
<5.5	0.0	0.0	N/A	N/A	0.0	0.0	N/A	N/A	Beta	Clinical expert input[132]
5.5–6.0	0.0	0.0	N/A	N/A	0.2	0.0	N/A	N/A	Beta	
≥6.0	0.0	0.0	N/A	N/A	1.0	0.0	N/A	N/A	Beta	

Abbreviations: S-K, serum potassium; RAASi, renin-angiotensin-aldosterone system inhibitor; SE, standard error; SZC, sodium zirconium cyclosilicate.

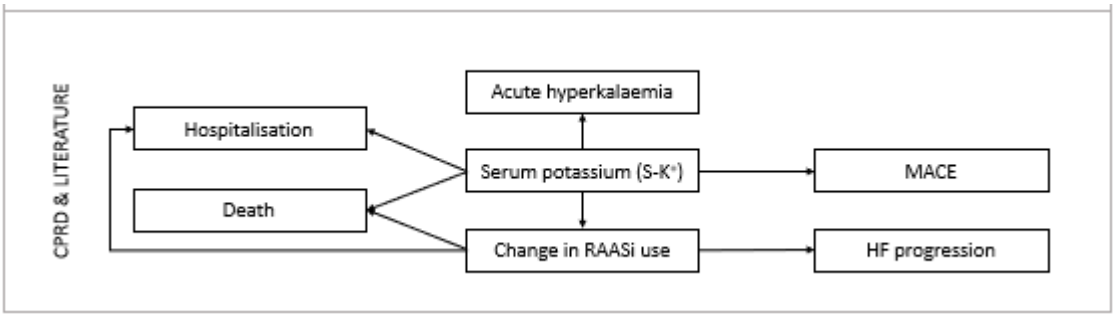
B.3.3.2.3 Adverse events

Over the course of the simulation, patients experience changes in S-K and RAASi profile which affect the probability of key clinical events including acute HK events, MACE, hospitalisation and death (see Figure 20 and Figure 21). **Figure 20. Modelled relationships between S-K levels, RAASi use and events in the CKD population**



Abbreviations: CKD, chronic kidney disease; CPRD, Clinical Practice Research Datalink; MACE, major adverse cardiac event; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium.

Figure 21. Modelled relationships between S-K levels, RAASi use and events in the HF population



Cardiovascular events (dotted line) will vary according to several other factors so are included only for illustrative purposes

Abbreviations: CPRD, Clinical Practice Research Datalink; HF, heart failure; MACE, major adverse cardiac event; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium.

HK events

S-K level defines HK, therefore for the purposes of the model a HK event is defined as S-K level going above a certain threshold. Patients may have up to one HK event per cycle (see Section B.3.3.2.3) and patients initiate the model with an HK event to represent the trigger for a decision to prescribe SZC. Two types of HK event are modelled “Severe”, which is an acute event requiring hospitalisation for monitoring as a precaution following insulin dextrose and “Less severe”, which represents the threshold for re-treatment without hospitalisation. The thresholds selected in the model vary depending on whether the acute or chronic setting is run (Table 35).

Table 35. S-K thresholds for HK events

	S-K thresholds		
	Acute setting	**Chronic setting**	**Source**
“Severe” HK event	≥6.0	≥6.5 mmol/L	Renal Association[133]
“Less severe” HK event	N/A	5.5–6.5 mmol/L	Clinical expert input[132]

Abbreviations: HK, hyperkalaemia; S-K, serum potassium.

Treatment-related adverse events

Ten AEs are included in the model, based on events recorded in the ZS-005[103] trial with an incidence of ≥5% in either arm. The proportion of the treatment arm experiencing these events is taken from the ZS-005[103] trial, while the proportion of the standard care arm experiencing these events is taken from Nasir et al.[111] It was not possible to use the proportion of the standard care arm experiencing AEs from the trial, as treatment for the first 3 days of the trial was non-randomised and therefore unrepresentative of the standard care arm modelled. Table 36 shows the proportion of these AEs each cohort will experience.

The ZS-005 [103] CSR distinguishes between treatment-related AEs (TRAEs) and TEAEs. As a conservative assumption, it is assumed that all AEs with an incidence of ≥5% in either arm are TRAE for the purposes of modelling. As AEs are assumed to be treatment related, they can occur only when treatment is being given. For standard care, this is only for the 3 days immediately following an HK event in the acute setting and never in the chronic setting. For SZC, it is only possible for AEs to occur when on treatment, which varies depending on setting.

Table 36. Proportion of cohort experiencing adverse events

	SZC (while on treatment)		Standard care (3 days following HK event only)		
	Mean	**SE**	**Mean**	**SE**	**Distribution**
Oedema	0.116	0.012	0.060	0.034	Beta
Worsening hypertension	0.109	0.011	0.000	0.000	Beta
Constipation	0.064	0.009	0.120	0.046	Beta
Diarrhoea	0.044	0.007	0.020	0.020	Beta
Nausea	0.075	0.010	0.180	0.054	Beta
Hypomagnesaemia	0.012	0.004	0.000	0.000	Beta
Anorexia	0.000	0.000	0.140	0.049	Beta
Hypokalaemia	0.015	0.004	0.000	0.000	Beta
Anaemia	0.059	0.009	0.000	0.000	Beta
UTI	0.079	0.010	0.000	0.000	Beta

Abbreviations: HK, hyperkalaemia; UTI, urinary tract infection; SE, standard error; SZC, sodium zirconium cyclosilicate.

B.3.3.2.4 CKD risk equations

In the CKD cohort, eGFR decline is related to RAASi use (see Table 37). It was not possible to estimate annual eGFR decline from the trials, as the trials were ongoing for only 52 weeks. Therefore Evans et al.[134] (identified in a poster by Bennett et al. (a)[122] retrieved in the economic SLR) was used. RRT is initiated if eGFR ≤8.5 mL/min/1.73 m^2, which is the recommended level according to the Renal Association.[133]

Table 37. Natural history of eGFR decline in CKD

	Annual eGFR decline (mL/min/1.73 m^2)			
Health state	**Mean**	**SE**	**Distribution**	**Justification**
CKD; RAASi “max” or “sub-max”	2.34	0.023	Normal	Evans et al. 2012, as per placebo months 24–48[134]
CKD; no RAASi use	3.52	0.035	Normal	Evans et al. 2012, as per irbesartan months 24–48[134]

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RAASi, renin-angiotensin-aldosterone system inhibitor; SE, standard error.

Event risk in CKD is related to eGFR (Table 38), S-K (Table 39) and RAASi use status (Table 40). It was not possible to use the trials for these data because the trials were S-K based, not eGFR based, and therefore were not powered to detect AEs associated with eGFR levels. Therefore, literature sources were identified in a targeted literature review and selected on the basis of containing the most relevant information. In Table 38 the cardiovascular AE is defined in a slightly different way to Table 39. Therefore, it is assumed the increase in risk due to S-K levels for MACE is the same as for cardiovascular events, and that the increase in risk due to eGFR levels for cardiovascular events is the same as for MACE. This is justified as the definition of cardiovascular events in Go et al,.[135] is very similar to the definition of MACE in Luo et al.[43]

Table 38. Baseline cardiovascular, hospitalisation and mortality event rate in CKD patients, by CKD stage

	CKD subgroup – mean annual event rate (SE)						
	1–2	**3 a**	**3b**	**4**	**5**	**Dist.**	**Source**
Cardiovascular event*	0.0211 (0.0012)	0.0365 (0.0012)	0.1129 (0.0012)	0.218 (0.0024)	0.366 (0.0048)	Normal	Go et al.[135]
Hospitalisation	0.1354 (0.0045)	0.1722 (0.0045)	0.4526 (0.0067)	0.8675 (0.0090)	1.4461 (0.0090)	Normal	
Mortality (all-cause)	0.0076 (0.0002)	0.0108 (0.0004)	0.0476 (0.0007)	0.1136 (0.0018)	0.1414 (0.0031)	Normal	

* Defined as hospitalisation for coronary heart disease, heart failure, ischaemic stroke, and peripheral arterial disease.
Abbreviations: CKD, chronic kidney disease; Dist., distribution.

Table 39. Incidence rate ratio for MACE, hospitalisation and mortality in CKD patients, by S-K subgroup

	S-K subgroup – incidence risk ratio (SE)								
	<3.5	**3.5–3.9**	**4.0–4.4**	**4.5–4.9**	**5.0–5.4**	**5.5–5.9**	**≥6.0**	**Dist.**	**Source**
MACE	1.89 (0.09)	1.27 (0.04)	1.04 (0.01)	1*	1.01 (0.02)	1.12 (0.04)	1.88 (0.12)	Normal	Luo et al.[43]
Hospitalisation (eGFR <30)	1.93 (0.45)	1.65 (0.22)	0.93 (0.09)	1*	1.00 (0.10)	1.34 (0.18)	3.65 (0.58)	Normal	
Hospitalisation (eGFR 30–40)	1.77 (0.34)	1.35 (0.16)	0.99 (0.08)	1*	0.96 (0.09)	1.07 (0.14)	1.82 (0.44)	Normal	
Hospitalisation (eGFR 40–50)	2.24 (0.38)	1.23 (0.13)	1.08 (0.07)	1*	1.07 (0.09)	1.23 (0.18)	1.91 (0.56)	Normal	
Hospitalisation (eGFR 50–60)	2.06 (0.27)	1.13 (0.08)	1.01 (0.05)	1*	1.00 (0.07)	0.81 (0.11)	1.07 (0.30)	Normal	
Mortality (all-cause)	3.05 (0.29)	1.49 (0.08)	1.06 (0.04)	1*	1.14 (0.06)	1.6 (0.13)	3.31 (0.46)	Normal	

*Index.
Abbreviations: Dist., distribution; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular event; S-K, serum potassium.

Table 40. Odds ratios for RAASi use risk relating to event risk in CKD patients

Parameter	Odds ratio mean	Standard error	Distribution	Source
Mortality – RAASi vs no RAASi	0.870	0.069	Normal	Xie et al.[136]
Mortality – "sub-max" RAASi vs no RAASi	0.935	0.069	Normal	Assumption – 50% of impact of "max" RAASi with same standard error
Hospitalisation – RAASi vs no RAASi	1	0	Normal	Assumption – no literature source identified so null value used
Hospitalisation – "sub-max" RAASi vs no RAASi	1	0	Normal	Assumption – no literature source identified so null value used

Abbreviation: CKD, chronic kidney disease; RAASi, renin-angiotensin-aldosterone system inhibitor.

B.3.3.2.5 HF risk equations

NYHA classification transition probabilities are unrelated to RAASi use (see Table 41). It was not possible to use the trials for these data because the trials were S-K based, not NYHA-based, and therefore were not powered to detect AEs associated with NYHA levels. Therefore, literature sources were identified in the SLR, and selected based on containing the most relevant information. In keeping with the hierarchy of evidence, observational datasets were only used where there was no appropriate literature source, which in the HF cohort was MACE risk and demographics (Table 43) and death demographics (but not risk equations, which were taken from the Seattle Heart Failure Model (SHFM), as shown in Table 45).

Table 41. Probabilities of changes in NYHA classification per cycle

	NYHA I	NYHA II	NYHA III	NYHA IV	Source
NYHA I	0.7956	0.1245	0.0738	0.0061	Yao et al.[137]
NYHA II	0.0710	0.8448	0.0765	0.0077	
NYHA III	0.0047	0.0893	0.8845	0.0216	
NYHA IV	0.0000	0.1064	0.1064	0.7872	

Abbreviation: NYHA, New York Heart Association

Event risk for the heart failure population depends on RAASi use and NYHA stage for hospitalisation (Table 42), and CPRD risk equations for the risk of MACE (Table 43), modified by S-K levels as taken from Luo et al[43] (Table 44).

Table 42. Per-cycle probability of hospitalisation for heart failure in HF patients

	Mean	SE	Distribution	Source
NYHA I	0.015	0.0015	Normal	Ford et al.[138]
NYHA II	0.024	0.0024	Normal	

NYHA III	0.024	0.0024	Normal	
NYHA IV	0.154	0.0154	Normal	
Odds ratio RAASi vs no RAASi	0.670	0.0330	Normal	Flather et al.[139]
Odds ratio "sub-max" RAASi vs no RAASi use	0.882	0.033	Normal	Assumption based on ATLAS[22], which recorded 24% fewer hospitalisations for heart failure with high dose vs low dose lisinopril

Abbreviation: HF, heart failure; NYHA, New York Heart Association; RAASi, renin-angiotensin-aldosterone system inhibitors; SE, standard error.

Table 43. CPRD risk equation for annual risk of MACE in HF patients

Coefficient	Mean	Distribution	Source
Intercept	−3.119	See Appendix N – distribution sampled from Cholesky decomposition of covariance matrix	CPRD[55]
Age (years)	0.014		CPRD[55]
Female	−0.078		CPRD[55]
Disease duration (days)	0.000		CPRD[55]
History of MACE	0.310		CPRD[55]
History of cancer	0.148		CPRD[55]
History of PVD	0.274		CPRD[55]
Ln(WBC)	0.186		CPRD[55]
Diuretic use	0.527		CPRD[55]
Beta blocker use	0.225		CPRD[55]

Abbreviation: CPRD, Clinical Practice Research Datalink; MACE, major adverse cardiac event; PVD, peripheral vascular disease; S-K, serum potassium; WBC, white blood cell count.

Table 44. Incident rate ratio for MACE in HF population by S-K levels

Coefficient	Mean	SE	Distribution	Source
S-K <3.5	1.890	0.090	Normal	Luo et al. [43]
S-K <4.0	1.270	0.040	Normal	Luo et al. [43]
S-K <4.5	1.040	0.010	Normal	Luo et al. [43]
S-K <5.0	1.000	0.000	Normal	Luo et al. [43]
S-K <5.5	1.010	0.020	Normal	Luo et al. [43]
S-K <6.0	1.120	0.040	Normal	Luo et al. [43]
S-K ≥6	1.880	0.012	Normal	Luo et al. [43]

Abbreviation: HF, heart failure; MACE, major adverse cardiac event; SE, standard error; S-K, serum potassium.

Finally, mortality risk for HF patients is estimated from the implementation of the SHFM[129]. This is a multivariate Cox model for survival among HF patient. Coefficients for this model are given in Table 45. In addition, mortality risk is modified depending on S-K profile, based on published data from Krogager et al.[57] and described in Table 46. These HRs modify the all-cause mortality risk, described below.

Table 45. SHFM hazard ratios for survival in HF patients

	Mean	SE	Distribution	Source
Age (parameter is age divided by 10)	1.090	0.0561	Normal	Levy et al., 2006 [129]
Male gender	1.089	0.1467	Normal	
NYHA (1–4)	1.600	0.3806	Normal	
100/Ejection fraction	1.030	0.0102	Normal	
Ischaemic aetiology (No/Yes)	1.354	0.1615	Normal	
SBP (parameter is mmHg divided by 10)	0.877	0.0286	Normal	
Diuretic dose (mg/kg)	1.178	0.0431	Normal	
Allopurinol use (No/Yes)	1.571	0.2395	Normal	
Statin use (No/Yes)	0.630	0.1449	Normal	
If sodium<138, 138-sodium	1.050	0.0235	Normal	
Cholesterol (100/mg/dL)	2.206	0.9212	Normal	
If haemoglobin <16, 16-haemoglobin	1.124	0.0375	Normal	
If haemoglobin >16, haemoglobin-16	1.336	0.1931	Normal	
Lymphocytes (%/5)	0.897	0.0523	Normal	
Uric acid (mg/dL)	1.064	0.0219	Normal	
ACE use (No/Yes)	0.770	N/A	Normal	
Beta blocker use (No/Yes)	0.660	N/A	Normal	
ARB use (No/Yes)	0.850	N/A	Normal	
K-sparing diuretic use (No/Yes)	0.740	N/A	Normal	
ICD (No/Yes)	0.730	N/A	Normal	
BICD (No/Yes)	0.790	N/A	Normal	

Abbreviations: ACE, angiotensin-converting-enzyme; ARB, angiotensin II receptor blocker; BICD, biventricular implantable cardioverter defibrillator; HF, heart failure; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association; SBP, systolic blood pressure; SE, standard error; SHFM, Seattle Heart Failure Model.

Table 46. S-K hazard ratios for survival in HF patients

S-K level	Mortality – all-cause (SE)	Mortality – adjusted (SE)	Distribution
<3.5	2.19 (0.59)	1.91 (0.52)	Normal
3.5–3.8	1.91 (0.40)	1.84 (0.39)	Normal
3.9–4.2	Index	Index	Normal
4.3–4.5	1.1 (0.23)*	1.24 (0.26)*	Normal
4.6–5.0	1.47 (0.27)	1.55 (0.29)	Normal
5.1–5.5	2.28 (0.55)	2.00 (0.49)	Normal
>5.5	6.6 (1.70)	5.60 (1.51)	Normal

*Nonsignificant – value of 1.00 (0.00) assumed in model.
Abbreviations: S-K, serum potassium; SE, standard error.

Discontinuation

Patients on SZC will discontinue this treatment if they die or initiate RRT. In addition, patients may discontinue for other reasons not directly accounted for in the model. The rate of discontinuation depends on whether the patient is simulated as part of the acute or chronic setting, and is described in Table 47.

Table 47. Annual discontinuation rate by scenario

	Annual discontinuation rate	Source
Acute scenario	0.853	Annualised discontinuation rate from ZS-004[99]
Chronic scenario	0.375	Discontinuation rate in ZS-005[103]

Other-cause mortality

The model assumes that in addition to any condition-specific mortality, all patients have an additional probability of death in the model (i.e. other-cause mortality).

Other-cause mortality is included, based on ONS life tables[140] (see Appendix N), which estimate general all-cause mortality for England and Wales by each year of age, from birth to 100. A random number generator is used to determine the probability of death during each cycle.

It is unlikely but possible that the probability of death due to comorbidities is lower than the probability of death due to all-cause mortality; if this occurs, the probability of all-cause mortality is applied to retain clinical plausibility.[132]

No patient is able to live past 100 years to align with general modelling conventions.

B.3.3.3 *Clinical expert assessment of applicability of clinical parameters*

Seven clinical experts (2 cardiologists, 3 nephrologists, 2 A&E physicians) were approached and asked to provide expert clinical input to support modelling parameters. Of these, all 7 agreed to participate. The method used to collect the opinions was structured interview, with interviewer responses prescribed by the interview protocol. Interviews were conducted in person, in a one-on-one format to avoid biases associated with focus groups. Iterative techniques were not used, as a diversity of opinions was sought.

Results from this expert engagement are included in Appendix N, and referenced where applicable in this document[132].

B.3.4 *Measurement and valuation of health effects*

B.3.4.1 *Health-related quality of life data from clinical trials*

No HRQoL data were collected in the ZS-004[99] and ZS-005[103] studies; therefore, utility data were sourced from published literature.

B.3.4.2 *Mapping*

No HRQoL data were collected in the ZS-004[99] and ZS-005[103] studies to map onto a generic outcome measure; therefore, utility data was sourced from published literature.

B.3.4.3 *Health-related quality of life studies*

A summary of the six studies identified in the SLR is presented in Table 48.

In Bennett et al.(a),[122] utility values were obtained from published literature. The utility scores for HF were obtained from a study by Göhler et al.,[141] which used EuroQol-5D (EQ-5D) data from the eplerenone post-acute MI HF efficacy and survival study trial to estimate utilities as a function of NYHA classification. Utilities for CKD stages 3 and 4 were from Gorodetskaya et al.[142] where utilities were based on the Time Trade-Off (TTO) questionnaire administered in 205 patients with CKD. The utility values were presented by eGFR level, which is the basis to define the stages of CKD. Although not reported in Bennett et al.(a),[122] utility scores for CKD stages 1 and 2 were also reported in Gorodetskaya et al.[142] (utility = 0.90). Utility scores for CKD stage 5 was from Lee et al.[143] and based on the EQ-5D index. In this study[143], the EQ-5D questionnaire was administered to patients identified from a renal unit departmental database in the UK and grouped into four cohorts: 1) those who had received a functioning graft following transplant, 2) those undergoing peritoneal dialysis, 3) those receiving haemodialysis and 4) those awaiting initiation of dialysis. As these utilities from all three sources were relevant and consistent with NICE reference case,[130] they are used in the economic model and are reported in the summary table in section B.3.4.10.

Additionally, disutility values relating to hospitalisations were documented in Bennett et al. (a). [122] The disutility score for hospitalisations was sourced from Göhler et al.,[141] which used EQ-5D data, and was included in the economic model.

In Bennett et al.(b),[123] utilities were also based on published studies and the sources were identical to those used in Bennett et al (a) [122] presented above.

In Sutherland et al.,[124] it was reported that utility data were derived from published literature that was publicly available in the UK. However, no further description was provided regarding the literature. Annual utility scores were reported for: end-stage renal disease with either haemodialysis (ESRD-HD); peritoneal dialysis (ESRD-PD); or transplant (ESRD – transplant); MI; stroke; hospitalisation due to CHF; HK; constipation; and diarrhoea. These health states were without additional information on the origin of the data, the population in which the health effects were measured, elicited and valued is unknown. Therefore, their relevance to the NICE reference case cannot be verified.

In Bounthavong et al.,[125] utility scores, independent of treatment, were estimated from QoL assessments made during the CARE-HF trial, including HF patients with HK and weighted by NYHA class from Yao et al.[137] Utility scores were derived from the EQ-5D results at baseline and 90 days.

In Lee et al.[144], five scenarios related to the health status of HF were developed including a scenario for stable chronic heart failure (SCHF) plus HK. Utility estimates were obtained using results from Visual Analogue Scale (VAS), TTO, and EQ-5D-5L in the Korean general population. Utility scores for a range of health statuses were given in both a combined form and aggregated by age and gender. Repeated Measure Analysis of Variance was used to compare the utility values among the different questionnaires. Utility values measured by EQ-5D-5L were valued using the Korean tariffs from the National Evidence-based Healthcare Collaborating Agency; as such, these are less relevant for NICE reference case.[130]

The utility scores used in the study conducted by Little et al.[126] were obtained from a weighted average of utility scores from a range of databases. In order to help determine a baseline utility, the mean of utility scores for NYHA class II and III CHF, type 2 diabetes, and stage 3 CKD from a range of sources was calculated. Similarly, an average of utility scores for metastatic colon cancer and moderate-severe Crohn's disease and mild Crohn's disease to help determine the utility of colonic necrosis. As the actual calculation to determine the utilities was not stated, and the results from the Health Utilities Index Mark 3 (HUI3), Quality of Well Being – Self Assessment (QWB-SA), 36-item short form (SF-36), TTO and the Assessment of Quality of Life (AQoL) questionnaires were combined, the utility scores used in the study are not consistent with the NICE reference case.[130]

Table 48. Summary of the HRQoL studies identified in the published literature

Study	Bennett H, 2017 (a) [122]	Bennett H, 2017 (b)[123]	Sutherland C, 2017[124]
Population in which health effects were measured	Patients with HK in HF or CKD with or without RAASi therapy	Patients with CKD	Patients from the OPAL-HK trial: CKD stage 3–4 with HK on RAASi
Information on recruitment	N/A	N/A	Not reported
Interventions and comparators	Normokalaemia: K^+ remained at a constant value of 4.5 mEq/L for the duration of the modelled horizon Hyperkalaemia: fluctuating K^+ levels resulting in HK rates consistent with clinical practice. K^+ sampled from a normal distribution (mean 4.5 ± SD 0.5 mEq/L)	Normokalaemia: maintenance of normokalaemia, via a stable K^+ of 4.5 mEq/L Hyperkalaemia: fluctuating K^+ levels, sampled from a Normal distribution (mean 4.5 ± SD 0.5 mEq/L)	Patiromer No patiromer (while considering relevant proportions in each arm that discontinued RAASi therapy)
Sample size	N/A	N/A	Unclear
Response rates	N/A	N/A	N/A
Description of health states	HF health states: • NYHA classes I – IV CKD health states: • CKD stages 3a, 3b, 4, 5 • Transplant • Dialysis	CKD health states: • CKD stages 3a, 3b, 4, 5 • Transplant • Dialysis	CKD health states: • CKD (stages 3–4) • CKD progression • Hyperkalaemia (hospitalisation) • CV event (hospitalisation) • Post-CV event • Death
Adverse reactions	N/A	N/A	N/A
Appropriateness of health states given the	Appropriate	Appropriate	Appropriate

Study	Bennett H, 2017 (a) [122]	Bennett H, 2017 (b)[123]	Sutherland C, 2017[124]
condition and treatment pathway			
Method of elicitation	Health-related utilities published by Gorodetskaya et al.,[142] Lee et al.[143] and Göhler et al.[141] were used: • In Gorodetskaya et al.,[142] HRQoL was measured using TTO in patients with CKD • In Lee et al.,[143] HRQoL was measured using the EQ-5D in patients with end-stage renal failure • In Göhler et al. [141] HRQoL was measured using the EQ-5D in patients with NYHA classes I–IV • Published studies were also used for disutilities[141,145-149]	Health-related utilities published by Gorodetskaya et al. and Lee et al. [143] were used: • In Gorodetskaya et al. [142] HRQoL was measured using TTO in patients with CKD • In Lee et al. [143] HRQoL was measured using the EQ-5D in patients with end-stage renal failure • Published studies were also used for disutilities[145-147,149]	Unclear, no reference is provided Utilities were calculated as a function of age based on a previously published algorithm
Method of valuation	• Gorodetskaya et al. [142]: TTO • Lee et al. [143]: EQ-5D index using utility weights from a general population survey in the UK • Göhler et al. [141] :EQ-5D. The EQ-5D score was weighted by the appropriate preference weight based on the patient's specific region of origin (United States—31%, Western Europe— 52%, Latin America—14%).	• Gorodetskaya et al. [142]: TTO • Lee et al. [143]: EQ-5D index using utility weights from a general population survey in the UK	Not reported
Mapping	N/A	N/A	N/A
Uncertainty around values	Not reported in the poster of the study, however 95% CI was reported alongside the mean utility score in Göhler et al. [141]	Some standard errors and standard deviations were reported alongside the means (see results below).	Not reported
Consistency with reference case	EQ-5D is the preferred measure of HRQoL TTO is also consistent with NICE reference case	EQ-5D is the preferred measure of HRQoL TTO is also consistent with NICE reference case	Unclear as there is no information reported on the methods used to obtain the utilities

Study	Bennett H, 2017 (a) [122]	Bennett H, 2017 (b)[123]	Sutherland C, 2017[124]
Results with CIs • Utility scores • Disutility scores	Utility scores: CKD stage 3: 0.870 (SE = 0.034)[142] CKD stage 4: 0.850 (SE = 0.029)[142] CKD stage 5: 0.570 (SD = 0.33)[143] Dialysis: 0.452[143] Transplant (procedure and maintenance): 0.710 (SD = 0.27)[143] Organ transplant service: 0.710[143] NYHA I: 0.855 (95% CI 0.845, 0.864)[141] NYHA II: 0.771 (95% CI 0.761, 0.781)[141] NYHA III: 0.673 (95% CI 0.665, 0.690)[141] NYHA IV: 0.532 (95% CI 0.480, 0.584) Disutility scores: Acute HK (K^+≥6.0 mEq/L): 0 [Assumption] Arrhythmia: −0.025[149] CV event: −0.321[145-147] (weighted by prevalence) Dialysis complications: −0.060[148] Hospitalisation: −0.024[141]	Utility scores: CKD 3 a: 0.870 (SE = 0.034)[142] CKD 3b: 0.870 (SE = 0.034)[142] CKD 4: 0.850 (SE = 0.029)[142] CKD 5 (pre-RRT): 0.570 (SD = 0.33)[143] Dialysis: 0.452[143] Transplant: 0.710 (SD = 0.27) [143] Disutility scores: Acute HK (K^+≥6.0 mEq/L): 0 [Assumption] Arrhythmia: −0.025[149] CV event, year 1: −0.321[145-147] CV event, year 2+: −0.321[145-147] Dialysis complications: −0.060[148] Hospitalisation: −0.024[141]	Disutility scores: ESRD – PD: −0.2770 ESRD – HD: −0.2640 ESRD – transplant: −0.0530 CV event - MI: −0.1000 CV event – stroke: −0.1000 CHF hospitalisation: −0.1000 Hyperkalaemia: −0.0098 AE – Constipation: −0.00167 AE – Diarrhoea: −0.00417
Appropriateness of the study for cost-effectiveness analysis	Appropriate but there are no comparative treatment arms	Appropriate but there are no comparative treatment arms	Appropriate

Study	Bounthavong M, 2017[125]	Lee J, 2016[144]	Little D, 2014[126]
Population in which health effects were measured	HF patients	Korean general population	Adult (≥18 years) outpatients with mild-to-moderate chronic HK (K^+ ≥5.2 and <7.0 mEq/L), due to RAAS inhibition for CHF with or without CKD, RAAS inhibition for proteinuric kidney disease (including diabetic nephropathy), or HK due to CKD, who were candidates for chronic treatment with oral potassium-binding resins
Information on recruitment	Patients from the RALES trial with NYHA Class III–IV HF on an ACEi (angiotensin receptor blockers not studied)	Face-to-face interviews were carried out for 100 people selected from the general population through	N/A

Study	Bounthavong M, 2017[125]	Lee J, 2016[144]	Little D, 2014[126]
		proportional allocation by age and gender	
Interventions and comparators	Spironolactone + ACEi + patiromer ACEi only	None	Sodium polystyrene sulfonate Theoretical "drug X" binding resin treatment for chronic HK
Sample size	Not reported	100	N/A
Response rates	N/A	N/A	N/A
Description of health states	HF health states: Stable HF Hospitalisation Death	HF health states: SCHF Hospitalisation due to acute exacerbation SCHF + cough SCHF + hypotension SCHF + HK (HK)	Health states: Survival Colonic necrosis No colonic necrosis Death
Adverse reactions	N/A	N/A	N/A
Appropriateness of health states given the condition and treatment pathway	Seems appropriate	Appropriate	No appropriate as they appear to be too simplistic
Method of elicitation	EQ-5D	VAS TTO EQ-5D-5L	HUI-3 QWB-SA SF-36 TTO AQoL
Method of valuation	The EQ-5D index was used to produce a utility score	The utilities measured by EQ5D-5L were computed using the Korean tariffs by National Evidence-based Healthcare Collaborating Agency	To determine the utility scores used in the study, a weighted average was taken using utility scores from HUI-3, QWB-SA, SF-36, TTO and AQoL questionnaires
Mapping	N/A	N/A	N/A
Uncertainty around values	95% CI and lower and upper bound are provided for the utility scores by NYHA class	Standard deviations are reported alongside the means	Not reported
Consistency with reference case	EQ-5D is the preferred measure of HRQoL and the utilities from the original data source are based on the EQ-5D from the CARE-HF trial	Not consistent with NICE reference case	A combination of instruments was used to derive a utility and it is unclear how the utility was derived. Therefore, it doesn't appear consistent with the reference case

Study	Bounthavong M, 2017[125]	Lee J, 2016[144]	Little D, 2014[126]
Results with CIs • Utility scores • Disutility scores	Utility scores: Stable HF: 0.597 Disutility scores: Hospitalisation: −0.100	SCHF+HK mean utility scores: VAS: • Overall:0.338 • 19–39 years old: 0.335 • 40–59 years old: 0.341 • Male:0.330 • Female: 0.346 TTO: • Overall:0.548 • 19–39 years old: 0.537 • 40–59 years old: 0.560 • Male:0.558 • Female: 0.539 EQ-5D-5 L: • Overall:0.589 • 19–39 years old: 0.593 • 40–59 years old: 0.585 • Male:0.600 • Female: 0.579	Utility scores: Death: 0 Colonic necrosis: 0.624 No colonic necrosis: 0.8
Appropriateness of the study for cost-effectiveness analysis	Appropriate	Not appropriate	Not appropriate

Abbreviations: ACEi, ACE inhibitors; AE, adverse event; AQoL, assessment of quality of life; CHF, congestive heart failure; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EQ-5D-5L, EuroQoL five dimensions; ESRD, end-stage renal disease; HD,– haemodialysis; HF, heart failure; HK, hyperkalaemia; HUI3, health utilities index 3 level; K^+, potassium; MI, myocardial infarction; N/A, not applicable; NYHA, New York Heart Association; PD, peritoneal dialysis; QWB-SA, quality of well-being self-administered scale; SCHF, stable chronic heart failure; SF-36, 36-Item short form health survey; TTO, time trade off; VAS, visual analogue scale.

B.3.4.4 *Key differences*

No significant differences were identified between the trial data and the data identified in the literature.

B.3.4.5 *Adverse reactions*

Two important sources of AE were included in the model. TRAEs (typically favouring standard care) were relatively common and relatively low-impact. S-K-related AEs (MACE, hospitalisation and death) typically favoured SZC and were relatively less common and relatively high-impact. Table 51 summarises these disutilities, and the associated probabilities are given in Section B.3.3.2.

Disutilities related to AEs were applied by assigning a utility decrement to the baseline utility, conditional on experiencing any particular AE. The length of time a disutility was applied to a particular baseline utility depended on what AE was experienced. The total disutility experienced, however, is the same for the treatment and standard care arms – the reason for this modelling assumption is to allow for the possibility of multiple incidents of the same

AE in the standard care arm as treatment in the standard care arm lasts significantly less than one cycle.

It was not possible to use trial data to estimate the disutility of AEs, since the trial was designed to measure S-K levels and therefore not powered to detect the effect of an AE on utility above the confounding effect of HF and CKD progression. Consequently, utilities identified from the SLR (or from a targeted literature review when the SLR didn't identify relevant studies) have been included as estimates of the per cycle disutility of an event.

No disutility is assumed for an acute HK event, since the disutility associated with this event is assumed to be included in the hospitalisation and any subsequent adverse events. Table 51 summarises these disutilities.

B.3.4.6 *Health-related quality of life data used in cost-effectiveness analysis*

Patients' QoL in each health state depends on expected baseline utility in the general population, which varies by age and sex (Table 49) and a condition-specific utility score, which varies by NYHA in the HF population and CKD stage in the CKD population (Table 50). The patient's health state utility is defined as their baseline utility multiplied by their condition-specific utility, less adverse event disutility. The risk of events of importance to patients (death, MACE, hospitalisation) is predicted by S-K levels and their disease progression (see Section B.3.3.2), but SZC does not affect the progression of the underlying HF or CKD.

Other than utility decreasing over time due to age, utility is assumed to be constant over the course of the disease for a given disease state. Disease-specific health state utility values have been adjusted to account for baseline utility. The patient's health state utility in the model is defined as their baseline utility multiplied by their condition-specific utility. No health effect with a prevalence of >5% in the literature or trials was excluded from the economic model.

A conservative assumption was made, that despite the fact that SZC would prevent the requirement for calcium resonium (in the acute setting) and a low potassium diet (in the chronic setting), no disutilities were applied to standard care for these treatment alternatives despite significant literature and clinical expert opinion suggesting that both are not well tolerated by patients and impact patient QoL negatively.

Table 49. Summary of utility values for baseline utility for cost-effectiveness analysis[150]

Age	Male mean	Male SE	Female mean	Female SE	Distribution
0	0.000	0.007	0.000	0.007	Normal
1–24	0.934	0.007	0.934	0.007	Normal
25–34	0.922	0.005	0.922	0.005	Normal
35–44	0.922	0.005	0.922	0.005	Normal
45–54	0.905	0.006	0.905	0.006	Normal
55–64	0.849	0.010	0.849	0.010	Normal
65–74	0.804	0.010	0.804	0.010	Normal
75–99	0.785	0.010	0.785	0.010	Normal
100	0.734	0.013	0.734	0.013	Normal

Abbreviation: SE, standard error

Table 50. Summary of utility values for disease-specific utility for cost-effectiveness analysis

Health state	Utility	SE	Distribution	Source
NYHA I	0.855	0.005	Beta	Göhler et al.[141]
NYHA II	0.771	0.005	Beta	
NYHA III	0.673	0.006	Beta	
NYHA IV	0.532	0.027	Beta	
CKD 3 a	0.870	0.034	Beta	Gorodetskaya et al.[142]
CKD 3b	0.870	0.034	Beta	
CKD 4	0.850	0.029	Beta	
CKD 5 (pre-RRT)	0.570	0.057	Beta	Lee et al.[143]

Abbreviations: CKD, chronic kidney disease; NYHA, New York Heart Association; RRT, renal replacement therapy; SE, standard error.

Table 51. Summary of AE disutilities

Health state	No. cycles applied for	Utility	SE	Dist.	Source
Oedema	13 (1 year)	−0.0029	0.000	Beta	Sullivan et al.[149]
Constipation	13 (1 year)	−0.0056	0.001	Beta	
Diarrhoea	13 (1 year)	−0.0008	0.001	Beta	
Nausea	13 (1 year)	−0.0037	0.001	Beta	Kristiansen et al.[151]
Hypomagnesaemia	13 (1 year)	−0.0028	0.002	Beta	Nafees et al.[152]
Anorexia	13 (1 year)	−0.0029	0.001	Beta	Sullivan et al. [149]
Hypokalaemia	13 (1 year)	0.0000	0.000	Beta	Assumption – no study identified
Anaemia	13 (1 year)	−0.0015	0.001	Beta	Sullivan et al. [149]
UTI	13 (1 year)	−0.0004	0.001	Beta	Sullivan et al. [149]
MACE event	1	−0.050	0.040	Beta	Palmer et al.[153]
Hospitalisation	1	−0.024	0.007	Beta	Göhler et al.[141]

Abbreviations: AE, adverse event; Dist., distribution; HK, hyperkalaemia; MACE, major adverse cardiac event; SE, standard error; UTI, urinary tract infection.

B.3.4.7 *Clinical expert assessment of applicability of health state utility values*

See Section B.3.3.3 for details.

B.3.5 *Cost and healthcare resource use identification, measurement and valuation*

B.3.5.1 *Resource identification, measurement and valuation studies*

A summary of the costs parameters identified in the published literature and used to estimate cost-effectiveness is presented in Table 52. Additional details are provided in Appendix I.

Table 52. Summary of costs parameters used in the cost-effectiveness

Parameter	Annual cost (mean)	Cost (SE)	Source (primary source)	Cross-reference
CKD stage 3a	£3401.11	NR	Bennett et al. (a) (NICE CG182) [7,122]	Appendix I and Table 57
CKD stage 3b	£3401.11	NR	Bennett et al. (a) (NICE CG182) [7,122]	Appendix I and Table 57
CKD stage 4	£3401.11	NR	Bennett et al. (a) (NICE CG182) [7,122]	Appendix I and Table 57
CKD stage 5 (pre-RRT)	£5311.08	NR	Bennett et al. (a) (NICE CG182) [7,122]	Appendix I and Table 57
HF – NYHA I, II, III, IV	0	0	Bennett et al. (a) (assumption) [7,122]	Appendix I and Table 57
Acute HK event	£2966.60	NR	Bennett et al. (a) (NHS reference costs 2014-2015)[122]	Appendix I and Table 62
Hospitalisation	£2444.80	NR	Bennett et al. (a and b) (Colquitt et al.)[122,123,154]	Appendix I and Table 67

Abbreviations: CKD, chronic kidney disease; HF, heart failure; HK, hyperkalaemia; NR, not reported; NYHA, New York Heart Association; RRT, renal replacement therapy; SE, standard error.

No healthcare resource use was reported in the identified published literature.

As many sources retrieved in the SLR used a different cost-year to the model and submission, all costs retrieved in the SLR were inflated to a 2017 cost-year using standard sources for the inflation tables (see Appendix N).

B.3.5.2 *Appropriateness of NHS Ref costs/PbR tariffs*

NHS Reference Costs are appropriate for costing discrete events that occur on the HK treatment pathway, for example AE costs (Table 66) and resource use during an acute HK event (Table 62-Table 64). However, NHS Reference Costs and Payment-by-Results tariffs are not appropriate for costing the time-in-state costs associated with HF and CKD, since they are not associated with a single event or intervention undertaken by the NHS. For these costs, literature values have been sought and included in the model as per the hierarchy of evidence adopted in the model (see Section B.3.2.2).

B.3.5.3 *Clinical expert assessment of applicability of cost and healthcare resource use values*

Clinical expert opinion was used to estimate healthcare resource use. As a micro-costing approach was adopted for several parameters, clinical estimates of the required resources for each setting were required as there was no plausible published literature identified in either the systematic literature search or ad-hoc searches to populate the model. See Section B.3.3.3 for details. Table 53 identifies all parameters where clinical expert opinion was sought regarding resource use.

Table 53. Parameters where clinical expert opinion was sought

Parameter	Estimated cost / resource use	Standard error	Distribution	Reference
HF, NYHA I, II, III, IV	£0.00	£0.00	N/A	Table 57
S-K, all levels of S-K	£0.00	£0.00	N/A	Table 57
ACEi (assumed to be ramipril for costing)	90%	N/A	N/A	Table 58 – Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; ESC, European Society of Cardiology; HF, heart failure; MRA, mineralocorticoid-receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitor. Table 61
ARB (assumed to be candesartan cilexetil for costing)	10%	N/A	N/A	Table 58 – Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; ESC, European Society of Cardiology; HF, heart failure; MRA, mineralocorticoid-receptor antagonist; RAASi, renin-angiotensin-

				aldosterone system inhibitor. Table 61
MRA (assumed to be spironolactone for costing)	Varies depending on setting and population	N/A	N/A	Table 58 – Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; ESC, European Society of Cardiology; HF, heart failure; MRA, mineralocorticoid-receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitor. Table 61
Resource use of "Less severe" HK event	£177.02 – based on micro-costing, see reference	£4.95	Gamma	Table 63
Resource use of "Severe" HK event	£2,227.34 – based on micro-costing, see reference	£222.73	Gamma	Table 64
RAASi discontinuation cost	£481.48 – based on micro-costing, see reference	£0.00	Gamma	Table 65
RAASi re-continuation cost	£129.72 – based on micro-costing, see reference	£0.00	Gamma	Table 65
RAASi down-titration cost	£722.22 – based on micro-costing, see reference	£0.00	Gamma	Table 65

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, antiontensin II receptor blocker; HF, heart failure; HK, hyperkalaemia; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium.

B.3.5.4 *Intervention and comparators costs and resource use*

Costs for SZC and standard care are summarised in Table 54 and described in more detail below. Table 56 summarises these costs.

Table 54. Cost per day for SZC, calcium resonium and lifestyle management

Day	SZC cost / day	Acute setting treatment (calcium resonium) cost / day	Chronic setting treatment (lifestyle advice) cost / day
1	[redacted]	£14.38	£0.00
2	[redacted]	£14.38	£0.00
3	[redacted]	£14.38	£0.00
4+	[redacted]	£0.00	£0.00

Abbreviation: SZC, sodium zirconium cyclosilicate.

B.3.5.4.1 SZC

The cost for a 5 g sachet of SZC is [redacted]. The cost for a 10 g sachet is [redacted]. The cost of a course of SZC was the cost per sachet multiplied by the actual doses given in the ZS-005[103] trial. The actual drug cost per day therefore varied, but on average on day 4+ was calculated to be [redacted] / day.

Table 55. Dosing schedule for SZC in model-based on actual doses given in ZS-005 trial

Day	5 g daily	5 g every other day	10 g daily	10 g three times a day	Cost / day
1	0%	0%	0%	100%	[redacted]
2	82%	0%	0%	18%	[redacted]
3	96%	0%	0%	4%	[redacted]
4+	62%	1%	37%	0%	[redacted]

Abbreviation: SZC, sodium zirconium cyclosilicate.

It is assumed that costs associated with prescribing SZC are included in the initial management costs following an HK event.

B.3.5.4.2 Standard care

The cost of standard care consists of a 3-day corrective period of treatment with calcium resonium for the correction of S-K in the acute setting only, followed by an ongoing S-K management period. In the acute setting, the cost of the initial 3-day management period is assumed to be £43.13, calculated based on 100% of the standard care cohort being treated with 15 g calcium resonium 3-4 times daily at a price of £82.16 / 300 g (BNF)[155,156], which is approximately £14.38 per day.

No therapy is administered for standard care in the chronic setting, so the cost is assumed to be nil.

Due to a lack on information, no costs were included for repeat insulin glucose nor low potassium diet; both of which SZC would displace. As such, the cost of standard of care may be underestimated.

Table 56. Total costs for treatment in model-based on setting and model progression

	SZC		Standard care	
	Acute	Chronic	Acute	Chronic
First HK event	[redacted]	[redacted]	£43.13	£0.00
Subsequent HK events	[redacted]	[redacted]	£43.13	£0.00

Abbreviations: HK, hyperkalaemia; SZC, sodium zirconium cyclosilicate.

B.3.5.5 *Health state costs and resource use*

As the model structure is individual patient-level, it is possible for a patient in the model to be accruing costs from several long-term sources at once. In the model, each of these costs is added at each cycle to represent background resource use managing these long-term sources.

As the trials were not designed to identify the effect of CKD and HF stage above the impact of HK generally, it was not possible to use the trials to estimate costs for time-in-state.

Consequently, existing NICE guidelines or other national body guidelines are used in the estimation of these values, in keeping with the model's hierarchy of evidence. It was not possible to use these values for the parameter RAASi therapy time-in-state costs ("sub-max" level), and no literature was found to support parameterisation, and so the CPRD dataset was used to give estimated values.

B.3.5.5.1 CKD and HF costs

Costs associated with each stage of CKD are taken from NICE CG182[7] as described in Table 57.

Table 57. Time-in-state costs

State	Annual cost (mean)	Annual cost (SE)	Distribution	Source
CKD 3 a	£3510.96	£351.10	Gamma	NICE CG182[7]
CKD 3b	£3510.96	£351.10	Gamma	
CKD 4	£3510.96	£351.10	Gamma	
CKD 5 (pre-RRT)	£5477.78	£547.78	Gamma	
HF, NYHA I, II, III, IV	£0.00	£0.00	N/A	Assumption – no literature source found so conservative assumption made
S-K, all levels of S-K	£0.00	£0.00	N/A	Assumption – no literature source found so conservative assumption made

Abbreviations: CKD, chronic kidney disease; HF, heart failure; N/A, not applicable; NYHA, New York Heart Association; RRT, renal replacement therapy; SE, standard error; S-K, serum potassium.

B.3.5.5.2 RAASi therapy costs

The main costs associated with ongoing RAASi therapy are the use of ACEi, ARBs and MRA drugs. The effectiveness of RAASi therapy is estimated assuming no MRA use (the source their effectiveness is based on, Xie et al.,[136] did not consider MRA use, see Section B.3.3.2, Table 40), but the cost of RAASi includes an MRA component as a conservative assumption and to better reflect national guidelines and research databases. In the model these drugs can be prescribed at two levels, corresponding to "max" and "sub-max" levels referred to elsewhere. The weighted annual cost is therefore calculated as £45.88 for "max" RAASi (Table 58) and £24.91 for "sub-max" RAASi (Table 59) in the CKD population, and £57.85 for "max" (Table 60) and £35.59 for "sub-max" (Table 61) in the HF population. In the base case of the model the average annual "max" cost is £50.15 and the average annual "sub-max" cost is £28.72.

Table 58. RAASi therapy time-in-state costs ("max" level, CKD population)

Event	Percentage of cohort	Average daily dose (mg)	Cost per mg	Source
ACEi (assumed to be ramipril for costing)	90%	10.00	£0.0041	ESC recommendations[8]
ARB (assumed to be candesartan cilexetil for costing)	10%	32.00	£0.0020	ESC recommendations[8]
MRA (assumed to be spironolactone for costing)	50%	50.00	£0.0033	ESC recommendations[8]

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; ESC, European Society of Cardiology; MRA, mineralocorticoid-receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitor.

Table 59. RAASi therapy time-in-state costs ("sub-max" level, CKD population)

Event	Percentage of cohort	Average daily dose (mg)	Cost per mg	Source
ACEi (assumed to be ramipril for costing)	90%	5.99	£0.0041	CPRD mean dose at baseline [60]
ARB (assumed to be candesartan cilexetil for costing)	10%	10.06	£0.0020	CPRD mean dose at baseline [60]
MRA (assumed to be spironolactone for costing)	30%	44.59	£0.0033	CPRD mean dose at baseline [60]

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; CPRD, Clinical Practice Research Datalink; MRA, mineralocorticoid-receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitor.

Table 60. RAASi therapy time-in-state costs ("max" level, HF population)

Event	Percentage of cohort	Average daily dose (mg)	Cost per mg	Source
ACEi (assumed to be ramipril for costing)	90%	10.00	£0.0041	ESC recommendations[8]
ARB (assumed to be candesartan cilexetil for costing)	10%	32.00	£0.0020	ESC recommendations[8]
MRA (assumed to be spironolactone for costing)	70%	50.00	£0.0033	ESC recommendations[8]

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; ESC, European Society of Cardiology; HF, heart failure; MRA, mineralocorticoid-receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitor.

Table 61. RAASi therapy time-in-state costs ("sub-max" level, HF population)

Event	Percentage of cohort	Average daily dose (mg)	Cost per mg	Source
ACEi (assumed to be ramipril for costing)	90%	5.99	£0.0041	CPRD mean dose at baseline [60]
ARB (assumed to be candesartan cilexetil for costing)	10%	10.06	£0.0020	CPRD mean dose at baseline [60]
MRA (assumed to be spironolactone for costing)	50%	44.59	£0.0033	CPRD mean dose at baseline [60]

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; CPRD, Clinical Practice Research Datalink; HF, heart failure; MRA, mineralocorticoid-receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitor.

B.3.5.6 *Adverse reaction unit costs and resource use*

B.3.5.6.1 HK event costs

Acute HK events are triggered once S-K goes above 6.0 in the acute setting and 5.5 in the chronic setting. The cost of an HK event is described in Bennett et al.,[122] which was identified in the SLR. Bennett et al.[122] estimate the cost of an HK event as £2,967, based on NHS Reference Costs for an inpatient admission for HF and CKD. However, in the chronic setting patients with S-K levels between 5.5 and 6.4 mmol/L would be unlikely to be admitted to hospital, and therefore a micro-costing approach was adopted to more accurately describe the cost of an HK event in both settings.

There is a single cost associated with HK events in the acute scenario simulation ("Severe") and two costs associated with HK events in the chronic scenario simulation ("Less severe" and "Severe"). "Severe" HK events require hospitalisation as per Bennett et al. [122] but "Less severe" HK events require only the immediate re-initiation of treatment without any hospital admission.

The costing for the "Severe" event is based on clinical estimates of resource use rates[132] given by Nottingham University Hospital NHS Trust's 'Guideline for the Management of Acute Hyperkalaemia in Adults'. The price estimated by this micro-costing approach for a standard care HK event based on resource use of nine major parameters is £2,954, which is entirely consistent with Bennet et al.'s £2,967.

The costing for the "Less severe" event is based on clinical estimates of which of these parameters would still be important in the event of no hospitalisation (that is, in the chronic setting when S-K is between 5.5 and 6.5 mmol/'/L). The clinicians described how only an outpatient visit would be relevant in that situation, and therefore that the cost of these "Less severe" events would be minimal.

Table 62 summarises this information, and Table 63 and Table 64 give detail on each state. Nationally representative value sets are used for all costings.

Table 62. Summary of cost of HK events

	SZC		Standard care			
Event	**Cost (mean)**	**Cost (SE)**	**Cost (mean)**	**Cost (SE)**	**Dist**	**Source**
"Less severe" HK event	£177.02	£17.70	£177.02	£17.70	Gamma	Table 63
"Severe" HK event	£2227.34	£222.73	£2954.41	£295.44	Gamma	Table 64

Abbreviations: Dist, distribution; HK, hyperkalaemia; SE, standard error.

Table 63. "Less severe" HK event costs

Event	Cost (mean)	Source	Resource use (SZC)	Resource use (standard care)	Source
ECG	33.78	NHS reference costs[157]	1	1	Clinical expert input[132]
U&E test	£6.24	NICE NG45[158]	2	2	Clinical expert input[132]
Outpatient visit	£137.00	PSSRU 2017[159]	1	1	Clinical expert input[132]

Abbreviations: GP, general practitioner; HK, hyperkalaemia; SZC, sodium zirconium cyclosilicate; U&E, urea and electrolytes (blood test).

Table 64. "Severe" HK event costs

Event	Annual cost (mean)	Source	Resource use (SZC)	Resource use (Standard care)	Source
Inpatient day	£727.00	PSSRU 2017[159]	3	4	Clinical expert input[132]
ECG	£33.78	NHS references costs 2010/11[157]	1	1	Nottingham University Hospital; NHS Trust. Guideline for the Management of Acute Hyperkalaemia in Adults [160]
U&E test	£6.24	NICE guidelines [NG45][158]	1	1	
Insulin	£69.12	BNF	1	2	
Glucose	£2.00	BNF	2	2	
Calcium gluconate	£1.00	NHS eMIT[161]	2	2	
Salbutamol	£0.13	NHS eMIT[161]	2	2	
Ambulance transport	£247.50	NHS references costs 2010/11[157]	1	1	
Emergency (A&E)	£148.36	NHS references costs 2010/11[157]	1	1	

Abbreviations: A&E, accident and emergency; BNF, British National Formulary; ECG, echocardiogram; eMIT, electronic market information tool; HK, hyperkalaemia; NHS, UK National Health Service; PSSRU, Personal Social Services Research Unit; SZC, sodium zirconium cyclosilicate; U&E, urea and electrolytes (blood test).

B.3.5.6.2 RAASi alteration costs

Altering the dose of RAASi is associated with a one-off cost in the model. The cost varies depending on what alteration is being made to the RAASi dose.

Assumptions around what resource use is needed at each stage are listed in Table 65, and were validated by clinical experts' opinion[132]. Expert opinion was that up-titration would happen exclusively in primary care, but that down-titration and discontinuation could happen in either primary care or secondary care. To represent this, clinical expert opinion confirmed that a 50% primary and 50% secondary split would be appropriate as an assumption[132]. When care occurred in a secondary setting, it was further assumed to be split equally between inpatient and outpatient days[132]. Nationally representative sources of costs are used for all values, in line with the discussion in Section B.3.2.2. The calculated costs are £481.48 for a discontinuation, £129.72 for a re-continuation and £722.22 for a down-titration.

Table 65. RAASi alteration event costs

Event	Annual cost (mean)	Source	Down-titration of RAASi		Discontinuation of RAASi		Return to max RAASi	
			Patients affected	Resource use for these patients	Patients affected	Resource use for these patients	Patients affected	Resource use for these patients
GP visit	£37.00	PSSRU 2017[159]	0%	1.50	100%	1.00	100%	3.00
U&E test	£6.24	NICE NG45[158]	100%	3.00	100%	2.00	100%	3.00
Outpatient visit	£137.00	PSSRU 2017[159]	50%	1.13	0%	0.63	0%	0.00
Inpatient day	£727.00	PSSRU 2017[159]	50%	1.13	0%	0.63	0%	0.00

Abbreviations: GP, general practitioner; PSSRU, Personal Social Services Research Unit; RAASi, renin-angiotensin-aldosterone system inhibitor; U&E – Urea and electrolytes (blood test).

B.3.5.6.3 Adverse-event costs

The proportions of patients expected to experience each AE (Section B.3.3.2.3) are used in conjunction with AE costs, to derive an average per-patient cost associated with treatment-related AEs for SZC and the comparators. The model inputs are defined as the annual cost of AEs, conditional on experiencing that event. The cost of adverse events is assumed to be equal across treatment arms.

Table 66. Adverse-event costs

Event	Cost (mean)	Cost (SE)	Dist	Source
Oedema (generalised and peripheral)	£244.82	£24.48	Gamma	Day Case: DZ20E, DZ20F. Pulmonary Oedema without Interventions, with different CC scores
Worsening hypertension	£413.09	£41.31	Gamma	Day Case: EB04Z. Hypertension
Constipation	£392.25	£39.23	Gamma	Day Case: FZ91K/FZ91L/FZ91M. Non-Malignant Gastrointestinal Tract Disorders without Interventions, with different CC scores
Diarrhoea	£392.25	£39.23	Gamma	Day Case: FZ91K/FZ91L/FZ91M. Non-Malignant Gastrointestinal Tract Disorders without Interventions, with different CC scores
Nausea	£196.12	£19.61	Gamma	Day Case: FZ91K/FZ91L/FZ91M. Non-Malignant Gastrointestinal Tract Disorders without Interventions, with different CC scores
Hypomagnesaemia	£330.85	£33.09	Gamma	Day Case: KC05J/KC05K/KC05L/KC05M/KC05N. Fluid or Electrolyte Disorders, without Interventions, with different CC scores
Anorexia	£381.32	£38.13	Gamma	Day Case: FZ49F/FZ49G/FZ49H. Nutritional Disorders without Interventions, with different CC scores
Hypokalaemia	£330.85	£33.09	Gamma	Assumption – same as hypomagnesaemia
Anaemia	£395.63	£39.56	Gamma	Day Case: SA01G, SA01H, SA01J, SA01K. Acquired pure red cell aplasia or other aplastic anaemia, with different CC score
Urinary tract infection	£284.97	£28.50	Gamma	Day Case: LA04S/LA04R/LA04Q/LA04P. Kidney or Urinary Tract Infections, without Interventions, with different CC scores

Abbreviations: CC, complications and comorbidities; Dist, distribution; SE, standard error.

B.3.5.6.4 Other event costs

Event costs not otherwise described are shown in Table 67. Each event cost applies only to the cycle in which it occurs and, does not have any associated ongoing cost.

It was not possible to identify the cost of these events from the trial, and existing national body guidance did not give values which were applicable to the HK population. Consequently, values were taken from the SLR for the cost of hospitalisation (Table 52 and Appendix I) and from a targeted literature search for the cost of MACE events as these were not reported in the SLR conducted.

Table 67. Other event costs

Event	Annual cost (mean)	Annual cost (SE)	Distribution	Source
MACE	£4952.05	£700.04	Gamma	Kent et al.[162]
Hospitalisation	£2521.53	£252.15	Gamma	Colquitt et al.[154]

Abbreviations: SE, standard error

Abbreviations: MACE, major adverse cardiovascular event; SE, standard error.

B.3.5.7 *Miscellaneous unit costs and resource use*

No additional costs and healthcare resource use were applied in the model.

B.3.6 *Summary of base-case de novo analysis inputs and assumptions*

B.3.6.1 *Summary of base-case de novo analysis inputs*

As described throughout this document, two base-case settings are considered – acute and chronic settings. Table 68 summarises the variables which differ in the two settings, and Figure 15 and Figure 16 summarised this information schematically. Table 69 summarises the variables which are constant across all base-case model scenarios, and varied individually in sensitivity analysis.

Table 68. Summary of variables which differ between acute and chronic scenario

Parameter	Value in acute setting	Value in chronic setting	Source
Maximum duration of initial treatment	28 days	28 days	Clinical opinion defining scenario, based on ZS-004[99] trial
Maximum duration of repeat treatment	28 days	52 weeks	Clinical opinion defining scenario, based on ZS-005[103] trial
S-K threshold to initiate treatment (mEq/L)	6.0*	5.5*	Acute: UK Renal Association guidelines[133] Chronic: Clinical engagement[132]
S-K threshold to initiate re-treatment (mEq/L)	6.0*	5.5*	
S-K threshold defining “Less severe” HK event	N/A	5.5*	Clinical expert input[132]
S-K threshold defining “Severe” HK event	6.0*	6.5*	Clinical expert input[132]
RAASi continuation assumptions	All discontinue and never re-start	All discontinue if S-K ≥6.0 mmol/L SZC continues at “max”, standard care cycles through “max”, “sub-max” and “none”	Acute: NICE CG182[7] Chronic: Clinical expert input[132]
Annual probability of discontinuation	0.853*	0.375*	Acute: ZS-004[99] trial, adjusted from 28 day rate (0.152) to annual probability. Chronic: ZS-005[103] trial

* Varied by an illustrative +/- 10% in sensitivity analysis. All other values fixed. Abbreviations: HK, hyperkalaemia; RAASi, renin-angiotensin-aldosterone system inhibitors; S-K, serum potassium; SZC, sodium zirconium cyclosilicate.

Table 69. Summary of structural parameters which are constant across all base-case model scenarios

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Time horizon	Sooner of 80 years or initiation of RRT	N/A		Fixed	Section B.3.2.2, Table 27
Cycle length	28 days	N/A		Fixed	Section B.3.2.2, Table 27
Cohort size	60,000	N/A		Fixed	N/A
Discount rate (costs)	3.5%	0.0%	6.0%	Fixed	Section B.3.2.2, Table 27
Discount rate (benefits)	3.5%	0.0%	6.0%	Fixed	Section B.3.2.2, Table 27
Proportion of cohort female	0.37	0.00	1.00	Beta	Section B.3.3.2.1, Table 28
Age at baseline	64.10	57.69	70.51	Normal	
eGFR at baseline	44.66	40.20	49.13	Normal	
eGFR threshold for RRT initiation	8.60	7.74	9.46	Normal	
Proportion CKD	0.64	0.00	1.00	Fixed	
Proportion RAASi use	0.702	0.00	1.00	Beta	

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; OWSA, one-way sensitivity analyses; PSA, probabilistic sensitivity analysis; RAASi, renin-angiotensin-aldosterone system inhibitor; RRT, renal replacement therapy.

Table 70. Summary of transitional probabilities which are constant across all base-case model scenarios

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Proportion NYHA I	0.10	Varied as a group – NYHA I varies from 0% to 100% while NYHA IV varies by 1-NYHA I		Beta	Section B.3.3.2.1, Table 41
Proportion NYHA II	0.10			Beta	
Proportion NYHA III	0.43			Beta	
Proportion NYHA IV	0.37			Beta	
Proportion of treated patients: oedema (generalised and peripheral)	0.116 on treatment 0.06 on standard care	Varied as a group – proportion experiencing adverse events increased and decreased by 10% for treatment and standard care arm separately		Beta	Section B.3.3.2.3, Table 36
Proportion of treated patients: constipation	0.064 on treatment 0.120 on standard care			Beta	

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Proportion of treated patients: diarrhoea	0.044 on treatment 0.020 on standard care			Beta	
Proportion of treated patients: nausea	0.075 on treatment 0.180 on standard care			Beta	
Proportion of treated patients: hypomagnesaemia	0.012 on treatment 0.000 on standard care			Beta	
Proportion of treated patients: anorexia	0.000 on treatment 0.140 on standard care			Beta	
Proportion of treated patients: hpokalaemia	0.015 on treatment 0 on standard care			Beta	
Proportion of treated patients: anaemia	0.059 on treatment 0.000 on standard care			Beta	
Proportion of treated patients: urinary tract infection	0.079 on treatment 0.000 on standard care			Beta	
Weeks to return to RAASi max, if returning	12.0	10.8	13.2	Normal	Section B.3.3.2.2

Abbreviations: NYHA, New York Heart Association; OWSA, one-way sensitivity analyses; PSA, probabilistic sensitivity analysis; RAASi, renin-angiotensin-aldosterone system inhibitor.

Table 71. Summary of utility parameters which are constant across all base-case model scenarios

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Health state utility: CKD 3a	0.87	0.78	0.96	Beta	Section B.3.4, Table 50
Health state utility: CKD 3b	0.87	0.78	0.96	Beta	

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Health state utility: CKD 4	0.85	0.77	0.94	Beta	
Health state utility: CKD 5 (pre-RRT)	0.57	0.51	0.63	Beta	
Health state utility: NYHA I	0.86	0.77	0.94	Beta	
Health state utility: NYHA II	0.77	0.69	0.85	Beta	
Health state utility: NHYA III	0.67	0.61	0.74	Beta	
Health state utility: NYHA IV	0.53	0.48	0.59	Beta	
Disutility: MACE event	−0.050	−0.045	−0.055	Beta	Section B.3.4.5, Table 51
Disutility: hospitalisation	−0.02	−0.02	−0.03	Beta	
Disutility: oedema	-0.0029	Varied as a group – disutility of experiencing adverse events increased and decreased by 10% for treatment and standard care arm separately		Beta	
Disutility: constipation	−0.0056			Beta	
Disutility: diarrhoea	−0.0008			Beta	
Disutility: nausea	−0.0037			Beta	
Disutility: hypomagnesaemia	−0.0028			Beta	
Disutility: anorexia	−0.0029			Beta	
Disutility: hypokalaemia	0.0000			Beta	
Disutility: anaemia	−0.0015			Beta	
Disutility: urinary tract infection	−0.0004			Beta	

Abbreviations: CKD, chronic kidney disease; MACE, major adverse cardiac event; NYHA, New York Heart Association; OWSA, one-way sensitivity analyses; PSA, probabilistic sensitivity analysis; RAASi, renin-angiotensin-aldosterone system inhibitor; RRT, renal replacement therapy.

Table 72. Summary of cost parameters which are constant across all base-case model scenarios

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Cost of SZC	See reference	N/A	N/A	Fixed	Section B.3.5.4, Table 55
Cost of standard care	See reference	N/A	N/A	Fixed	
Event cost: 'high severity' HK event – treatment (£)	2228.27	2005.44	2451.10	Gamma	Section B.3.5.6, Table 64
Event cost: 'low severity' HK event – treatment (£)	177.02	159.32	194.72	Gamma	Section B.3.5.6, Table 63

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Event cost: 'high severity' HK event – standard care and following discontinuation (£)	2955.34	2659.81	3250.87	Gamma	Section B.3.5.6, Table 64
Event cost: 'low severity' HK event – standard care and following discontinuation (£)	49.48	44.53	54.43	Gamma	Section B.3.5.6, Table 63
Annual cost of RAASi: maximum dose (£)	50.15	45.14	55.17	Gamma	Section B.3.5.5, Table 58
Annual cost of RAASi: sub-maximum dose (£)	28.72	25.85	31.59	Gamma	SectionB.3.5.5, Table 59
Event cost: RAASi discontinuation (£)	481.48	433.33	529.63	Gamma	Section B.3.5.6.2, Table 65
Event cost: RAASi down-titration (£)	722.22	650.00	794.44	Gamma	Section B.3.5.6.2, Table 65
Event cost: return to maximum RAASi use (£)	129.72	116.75	142.69	Gamma	Section B.3.5.6.2, Table 65
Event cost: MACE event	4952.05	4456.85	5447.26	Gamma	Section B.3.5.6.2, Table 66
Event cost: Hospitalisation	2521.53	2269.38	2773.68	Gamma	Section B.3.5.6.3, Table 66
Event cost: Oedema	244.82	Varied as a group – cost of experiencing adverse events increased and decreased by 10% for treatment and standard care arm separately		Gamma	
Event cost: Constipation	392.25			Gamma	
Event cost: Diarrhoea	392.25			Gamma	
Event cost: Nausea	196.12			Gamma	
Event cost: Hypomagnesaemia	330.85			Gamma	
Event cost: Anorexia	381.32			Gamma	
Event cost: Hypokalaemia	330.85			Gamma	
Event cost: Anaemia	395.63			Gamma	
Event cost: Urinary tract infection	284.97			Gamma	
Annual cost CKD 3 a	3510.96	3159.86	3862.06	Gamma	Section B.3.5.5.1, Table 57
Annual cost CKD 3b	3510.96	3159.86	3862.06	Gamma	
Annual cost CKD 4	3510.96	3159.86	3862.06	Gamma	

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Annual cost CKD 5 (pre-RRT)	5477.78	4930.00	6025.56	Gamma	

Abbreviations: CKD, chronic kidney disease; HK, hyperkalaemia; MACE, major adverse cardiac event; OWSA, one-way sensitivity analyses; PSA, probabilistic sensitivity analysis; RAASi, renin-angiotensin-aldosterone system inhibitor; RRT, renal replacement therapy; SZC, sodium zirconium cyclosilicate.

A summary of the scenario analyses performed on the base-case is provided in Table 73.

Table 73. Summary of scenario analysis inputs

Parameter	Purpose	Base-case	Scenarios	Reference to section in submission
RAASi usage	To assess the impact of varying the RAASi usage on outcomes.	70.2%	80.0% as per UK clinical expert opinion	Section B.3.3.2.2
Population split	To assess the impact of a different population mix of HF and CKD.	Population split as per trials – 35.70% HF, 64.30% CKD	Population split as per literature source[163] - 10.95% HF, 89.05% CKD	Section B.3.3.2.1
Length of stay following acute HK event	To assess the impact of varying the cost of HK event on the model results.	3 days for standard care, 2 days for SZC	2 days for both standard care and SZC	Section B.3.5.6.1
Price of standard care treatment.	To assess the most conservative, extreme assumption of zero cost for standard care.	Calcium resonium costs £43.13	Calcium resonium costs £0.00	Section B.3.5.4.2
RAASi discontinuation assumptions (chronic setting only)	To assess the impact of varying the RAASi usage in the chronic setting on outcomes.	20% discontinue and 80% down-titrate when S-K is between 5.5 and 6.0	100% discontinue, 0% down-titrate when S-K is between 5.5 and 6.0	Section B.3.3.2.2
			50% discontinue, 50% down-titrate when S-K is between 5.5 and 6.0	

Initial treatment length (chronic setting only)	To assess the impact of using a longer initial treatment length in the chronic setting.	28 days at initial HK event	52 weeks at initial HK event	Section B.3.5.6.1
Data source for RAASi mix	To assess the impact of using trial data source to estimate mix of RAASi drugs used in “max” and “sub-max” settings.	RAASi mix based on ESC guidelines	RAASi mix based on ZS-005 trial	Section B.3.5.5.2

Abbreviations: HK, hyperkalaemia; S-K, serum potassium; RAASi, renin-angiotensin-aldosterone system inhibitor; SZC, sodium zirconium cyclosilicate.

B.3.6.2 *Assumptions*

Table 74 contains a list of all assumptions made in the de novo economic model along with justifications.

Table 74. Model assumptions and justifications

Assumption	Justification
Time horizon	
The model ends at renal replacement therapy.	According to UK clinical experts,[132] the management of S-K following the initiation of RRT differs from that prior to RRT, and there is no NICE guidance setting out the consensus of treatment in this area. The SmPC[1] highlights that there is no data to support the use of SZC in this population. As such the effect of RRT both in terms of costs and consequences is highly uncertain. Since RRT is not management for HK, this should be regarded as an ‘unrelated future cost’ with respect to SZC. NICE guidance is to ignore unrelated future costs[130], as there is no agreed methodology for calculating them. In addition, the inclusion of RRT obscures the decision problem of an intervention positioned prior to RRT, since RRT is not a cost-effective intervention. As such, the inclusion of RRT and non-cost-effective use of interventions not in control of the manufacturer should not influence the decision to be made about SZC for the treatment of HK. This position is supported in the clinical literature.[123,131]
Duration of disease before model commences equal to 0 years.	No other available evidence to inform this assumption.
Patients cannot age past 100.	Standard modelling assumption.

An other-cause mortality is applied in addition to condition-specific mortality.	Standard modelling assumption. As a significant fraction of all-cause mortality is due to cardiovascular disease this assumption is likely unfavourable to treatment.
Clinical progression of disease	
There is no general factor of eGFR decline in HF population.	Clinical expert input.[132]
No difference in costs, utilities and outcomes between first and subsequent HK events.	Those included in the trial may already have had an HK event, therefore if there is a relationship between number of HK events and outcomes this should already be accounted for in the data based on the trial.
HK event probability independent of number of historic HK events.	There is some clinical consensus that an HK event makes subsequent HK events more likely[132], but no literature evidence. If one was to assume HK event probability did depend on historic HK events, this would only favour SZC; as such, the results may be considered conservative.
If there is no statistically significant relationship between S-K+ and survival, the relationship is assumed not to exist.	See Table 46. The most important clinical relationship in the model is that between S-K+ levels and major adverse events, especially death. Clinical expert input[132] confirms that this relationship is extremely well demonstrated in the literature. Therefore a deliberately conservative interpretation of this evidence was taken, in order to highlight the strength of this literature.
Adverse events last 13 cycles on SZC (at 1/13 of the utility decrement per cycle) and 1 cycle on standard care.	As patients can have up to one HK event per cycle it is possible for a patient experiencing an adverse event from the treatment of a prior HK event to randomly be assigned to the same adverse event on their next acute event. As there is no literature on how – for example – nausea might compound, it is more appropriate to ensure that patients do not experience multiple copies of the same adverse event at the same time. This assumption marginally favours SZC as the costs associated with an adverse event could be discounted if they fall over a year-end during one of the 13 cycles, but making the assumption allows adverse events to occur only on treatment which greatly favours standard care – especially in the chronic setting where no treatment-related adverse events can ever occur.
Condition-specific utility assumed to be constant.	The model contains transition probabilities driving movement from less-severe to more-severe disease states, therefore it is likely that condition-specific decline of utility is already correctly accounted for.
Cost of NYHA levels assumed to be 0 for all levels.	Based on an assumption in a poster - Bennett et al. (a)[122] – but not thought to have a significant impact on results as all patients will always be in one of the four NYHA classes until death and so no incremental cost would be generated in any event until patient death in one arm versus the comparator.
Cost of S-K+ levels assumed to be 0 for all levels.	Based on an assumption in a poster - Bennett et al. (a)[122] – but thought to be conservative as SZC should lower S-K+ levels below standard care. However as above, the assumption actually made results in no incremental cost generated until death in one arm.

RAASi use	
Resource use associated with down-titration, discontinuation and return to max RAASi.	Clinical expert input.[132]
Mix of drugs used in RAASi therapy assumed to be only Ramipril, Candesartan cilexetil, and Spironolactone.	There is no source for actual mix of drugs used in the UK, but these three drugs are representative of ACEi, ARB and MRA drugs respectively, for which there is data. This assumption is likely to have a minimal impact on results, and is thought to be representative of clinical practice.
Proportion of drugs used on RAASi therapy in sub-max RAASi use compared to max RAASi use.	Based on CPRD mean dose.
Odds ratio for sub-max RAASi vs no RAASi contributing to mortality assumed to be 50% of max RAASi vs sub-max RAASi in CKD population.	While there is a strong literature source supporting (Xie et al.[136]) the max vs no RAASi scenario, there is no literature supporting the sub-max vs no RAASi scenario and therefore plausible assumption was made based on other associations observed and clinical judgement.
Odds ratio for RAASi use of any sort contributing to hospitalisation in CKD population.	Assumed to be 0 as there is no literature source and this is the most conservative assumption which is still clinically plausible.
Odds ratio for RAASi use of any sort contributing to hospitalisation in HF population.	Assumed to be 0.882 based on a trial in an HF but not HK population in the absence of any direct evidence.
If a patient does not initiate model on RAASi, they will never begin RAASi.	There are clinical reasons why RAASi might not be appropriate, and therefore it would be invalid to assume that all patients in the model could transition to being on RAASi. If one was to assume some patients not initiating RAASi were to begin RAASi, this would only favour SZC; as such, the results may be considered conservative.
All patients initiate model at “max” RAASi.	No data was found on this topic, even at low qualities of evidence. Consequently, this was informed based on clinical judgement.
Adverse events	
No cost associated with prescribing SZC or calcium resonium.	Cost is included for secondary care hospital appointment, which is assumed to cover the cost of prescribing the drugs.
100% of patients in acute setting are treated with calcium resonium. No cost for repeat insulin glucose or low potassium diet.	Clinical expert input[132] suggests that the proportion of patients treated with calcium resonium varies, but is higher in settings where immediate acute management of S-K+ outweighs the patient dislike of calcium resonium. Overall, the treatment cost for standard care can be considered conservative as repeat insulin glucose and low potassium diet costs are not included.
All adverse events assumed to only possibly occur on treatment	This is a conservative assumption as there is no data identified on the adverse events of lifestyle interventions (for example, a low potassium diet)
For determining MACE risk, three sources with similar definitions of MACE / cardiovascular disease are	No data were found on this topic, even at low qualities of evidence. Consequently, it was thought appropriate to make this assumption to avoid having to use less

assumed equivalent (see Table 44–Table 46)	representative sources and thereby require more extreme assumptions
Costs and utility of death state assumed to be 0	Standard modelling assumption
Disutility of HK event assumed to be 0	HK events are assumed to generate disutility through hospitalisation and an increased risk of death and MACE, therefore this assumption avoids double counting.
Disutility of hypokalaemia assumed to be 0	No study was identified describing the disutility of hypokalaemia, so zero was selected as a Schelling point. Low K+ levels are associated with some adverse outcomes in the general population, but it is unclear how well these data generalise to the HK population
Disutility of calcium resonium and low potassium diet assumed to be zero	Conservative assumption in light of no other data to inform disutilitiy; despite the fact it is well documented that quality of life is negatively affected by both interventions.
Cost of hypokalaemia assumed to be equal to hypomagnesaemia	No reference cost was identified giving the cost of hypokalaemia, therefore it was assumed to be equivalent to the other metabolic disorder adverse event, hypomagnesaemia

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; CPRD, Clinical Practice Research Datalink; eGFR, estimate glomerular filtration rate; ESRD, end-stage renal disease; HF, heart failure; HK, hyperkalaemia; ICER, incremental cost-effectiveness ratio; MACE, major adverse cardiac event; MRA, mineralocorticoid receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitor; RRT, renal replacement therapy; S-K, serum potassium; SZC, sodium zirconium cyclosilicate.

B.3.7 *Base-case results*

B.3.7.1 *Base-case incremental cost-effectiveness analysis results*

Base-case results of the chronic scenario are presented in Table 76, and results for the acute scenario are presented in Table 75.

Over a lifetime horizon, the acute cohort receiving SZC accrued [redacted] QALYs at a cost of [redacted]. Patients receiving standard care accrued [redacted] QALYs at a cost of [redacted]. Therefore, SZC dominates standard care, in that SZC is both less costly and more effective than standard care.

Over a lifetime horizon, the chronic cohort receiving SZC accrued [redacted] QALYs at a cost of [redacted]. Patients receiving standard care accrued [redacted]QALYs at a cost of [redacted]. Therefore, in the chronic setting, the ICER for SZC versus standard care is £21,835.

Table 75. Base-case results – acute scenario

Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
SZC	[redacted]	4.35	[redacted]				
Standard care	[redacted]	4.27	[redacted]	-1,060	0.08	0.05	Dominates

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life-years gained; QALYs, quality-adjusted life years; SZC, sodium zirconium cyclosilicate.

Table 76. Base-case results – chronic scenario

Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
SZC	[redacted]	5.99	[redacted]				
Standard care	[redacted]	4.74	[redacted]	16,688	1.25	0.76	21,835

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life-years gained; QALYs, quality-adjusted life years; SZC, sodium zirconium cyclosilicate.

B.3.7.2 *Clinical outcomes from the model and disaggregated results of the base-case analysis*

A summary of the clinical outcomes and disaggregated results of the base-case incremental cost-effectiveness analysis can be found in Table 77 and Table 78 for the acute and chronic case respectively. Note that the definition of 'hospitalisation' excludes hospitalisations during acute HK events in order to disaggregate this result. Note also that the potentially counterintuitive result of increased MACE and hospitalisation events in the SZC arm of the model is explained by increased life-expectancy, allowing for more S-K-unrelated medical events.

Table 77. Disaggregated clinical outcomes and costs per patient for acute setting

	SZC		Standard care	
	Incidents	Cost	Incidents	Cost
Intervention costs	–	[redacted]	–	£331
Adverse events	0.27	£89	0.00	£11
Acute HK event	7.25	£17,592	8.15	£20,368
MACE	1.36	£6192	1.37	£6225
Hospitalisation	3.76	£8178	3.76	£8177
Mortality within 5 years of first HK event	0.37	–	0.49	–

Abbreviations: HK, hyperkalaemia; MACE, major adverse cardiac event; SZC, sodium zirconium cyclosilicate.

Table 78. Disaggregated clinical outcomes and costs per patient for chronic setting

	SZC		Standard care	
	Incidents	Cost	Incidents	Cost
Intervention costs	–	[redacted]	–	£0
Adverse events	2.38	£769	0.00	£0
Acute HK event	12.29	£759	22.49	£2033
MACE	1.58	£6980	1.43	£6450
Hospitalisation	4.43	£9120	3.81	£8205

Mortality within 5 years of first HK event	0.37	–	0.45	–

Abbreviations: HK, hyperkalaemia; MACE, major adverse cardiac event; SZC, sodium zirconium cyclosilicate.

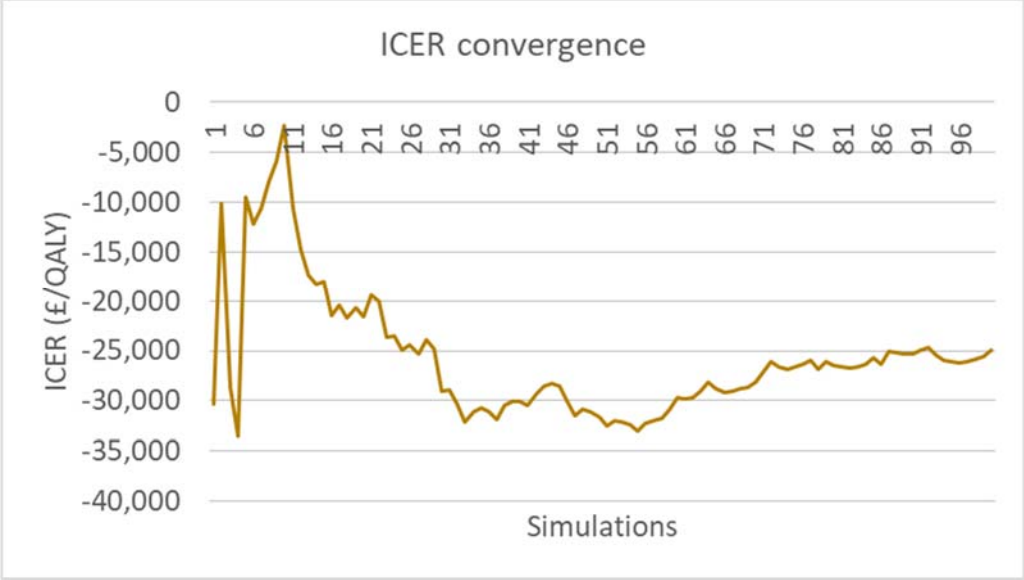
B.3.8 *Sensitivity analysis*

Sensitivity analyses were conducted to explore the level of uncertainty in the model results.

B.3.8.1 *Probabilistic sensitivity analysis*

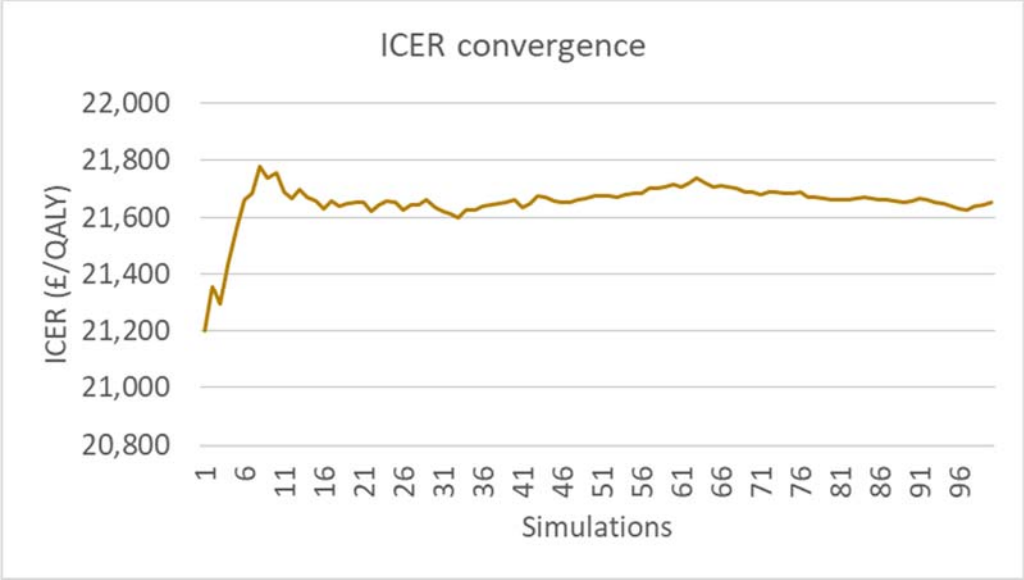
Probabilistic sensitivity analysis (PSA) was performed to explore the uncertainty around key model inputs. In the base case of the model patients are generated probabilistically, but in the PSA all values are drawn from a distribution at the beginning of each simulated cohort in order to vary parameters that would otherwise remain fixed in the deterministic case. One hundred PSA iterations were run in order to obtain a stable estimate of the mean model results. The number of runs was selected based on analysis of the speed and durability of ICER convergence in the chronic and acute settings, which is shown in Figure 22 and Figure 23.

Figure 22. ICER convergence in PSA runs – acute



Abbreviations: ICER, incremental cost-effectivness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

Figure 23. ICER convergence in PSA runs – chronic



Abbreviations: ICER, incremental cost-effectivness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

As shown in Table 69, the following parameters were kept fixed in the PSA: maximum length of initial treatment, maximum length of subsequent treatment, discount rate for costs and benefits, time horizon, S-K thresholds (for treatment, repeat treatment, “Less Severe” HK event, “Severe” HK event) and all transition probabilities derived from CPRD regression equations. Separate PSAs were run for the acute and chronic setting.

Mean incremental results were recorded and illustrated through an incremental cost-effectiveness plane (ICEP). In addition, a cost-effectiveness acceptability curve (CEAC) and cost-effectiveness acceptability frontier (CEAF) were plotted.

PSA results of SZC versus standard care are presented in Table 80 and Table 79. The mean PSA results lie close to the deterministic base-case results (Table 76 and Table 75). The chronic cohort receiving SZC accrued [redacted] QALYs at a cost of [redacted]. Patients receiving standard care accrued [redacted] QALYs at a cost of [redacted]. The acute cohort receiving SZC accrued QALYs at a cost of [redacted]. Patients receiving standard care accrued [redacted] QALYs at a cost of [redacted]. As with the base case analysis, SZC dominates standard care in the acute case, and the ICER of SZC verus standard care in the chronic case was £21,775.

The ICEP showing the PSA results is presented in Figure 25 and Figure 24. The CEAC and CEAF are presented in Figure 27 and Figure 29, and Figure 26 and Figure 28 for chronic and acute scenarios, respectively. The majority of simulations in the chronic cohort were when SZC had higher incremental costs and higher incremental QALYs. The majority of simulations in the acute cohort were when SZC had lower incremental costs and higher incremental QALYs. The CEAF found that there was only a narrow band of uncertainty in the chronic setting where it was unclear whether SZC or standard care was likely to be more cost-effective, and that there was no such uncertainty in the acute setting (that is SZC was cost-effective at all willingness to pay thresholds in the acute setting).

Table 79. PSA results – acute scenario

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Sodium zirconium cyclosilicate	[redacted]	[redacted]	[redacted]			
Standard care	[redacted]	[redacted]	[redacted]	-109	0.05	Dominates

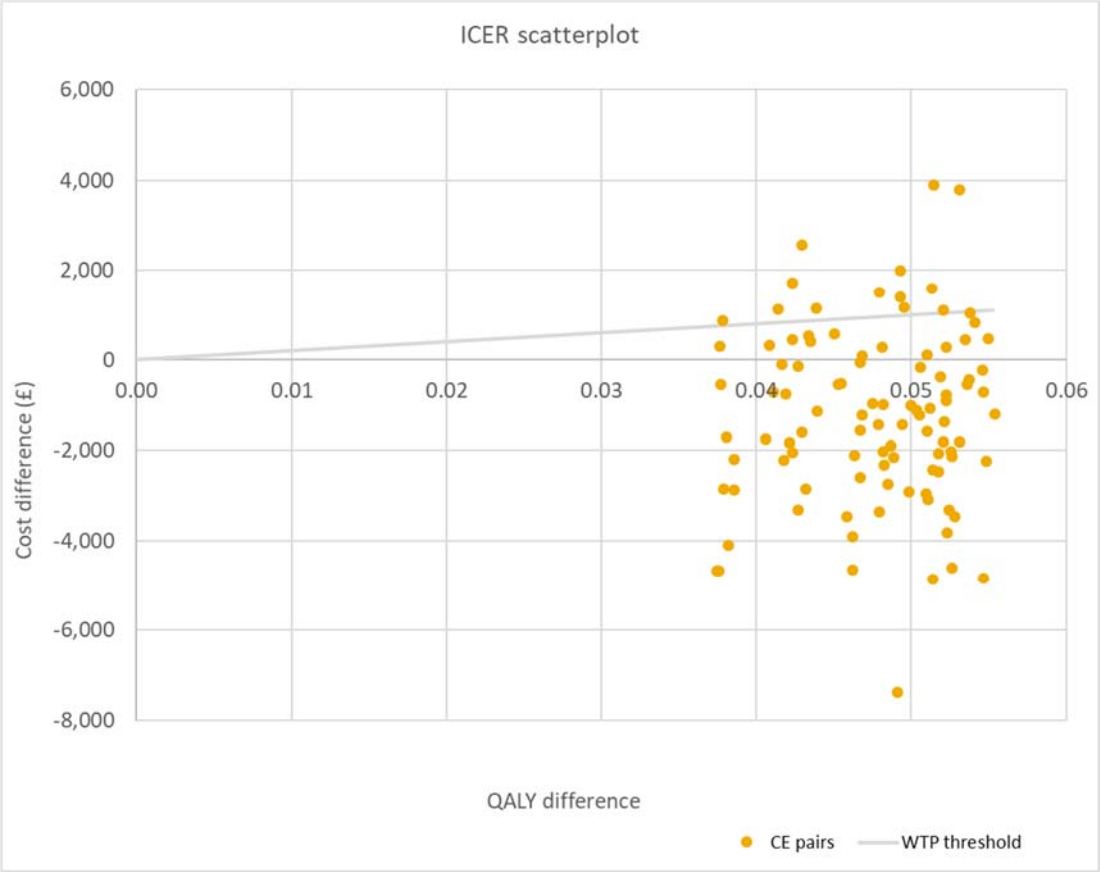
Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensibility analysis; QALYs, quality-adjusted life years.

Table 80. PSA results – chronic scenario

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Sodium zirconium cyclosilicate	[redacted]	[redacted]	[redacted]			
Standard care	[redacted]	[redacted]	[redacted]	16,459	0.76	21,775

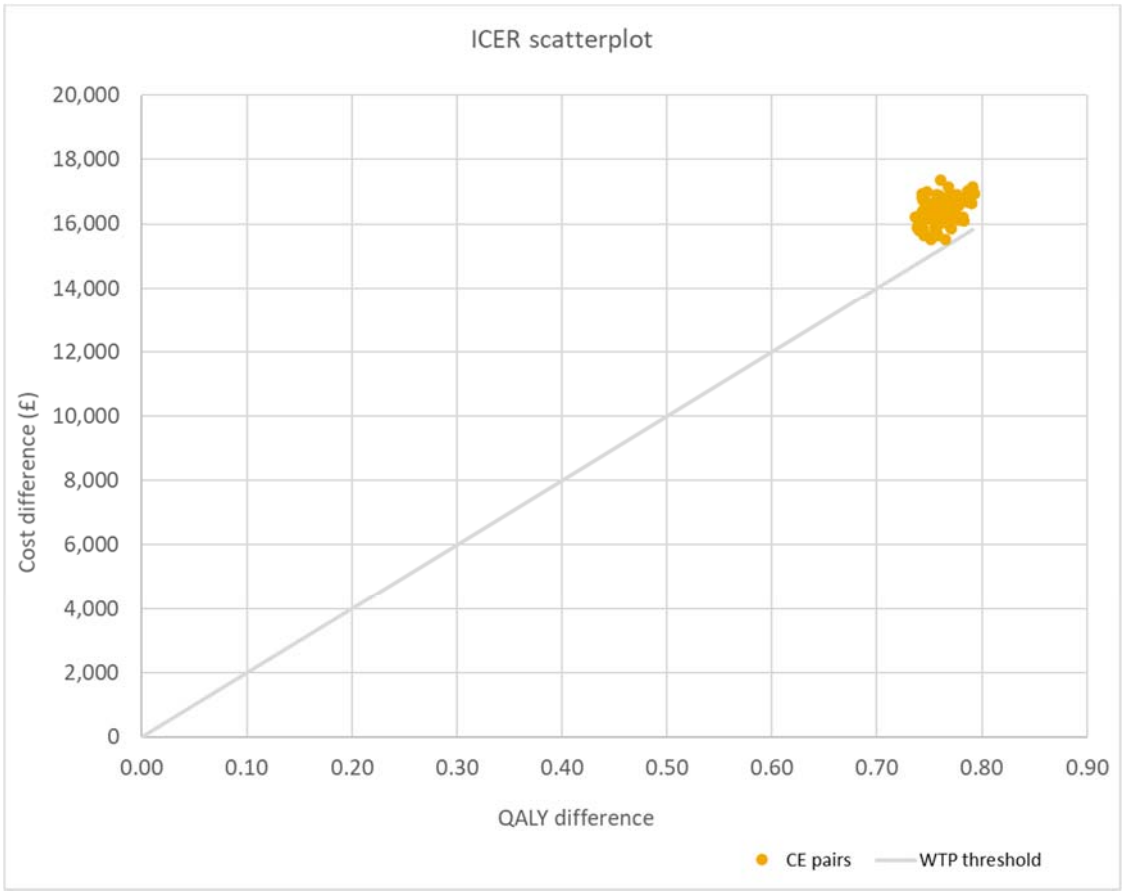
Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensibility analysis; QALYs, quality-adjusted life years.

Figure 24. Incremental cost-effectiveness plane – acute cohort



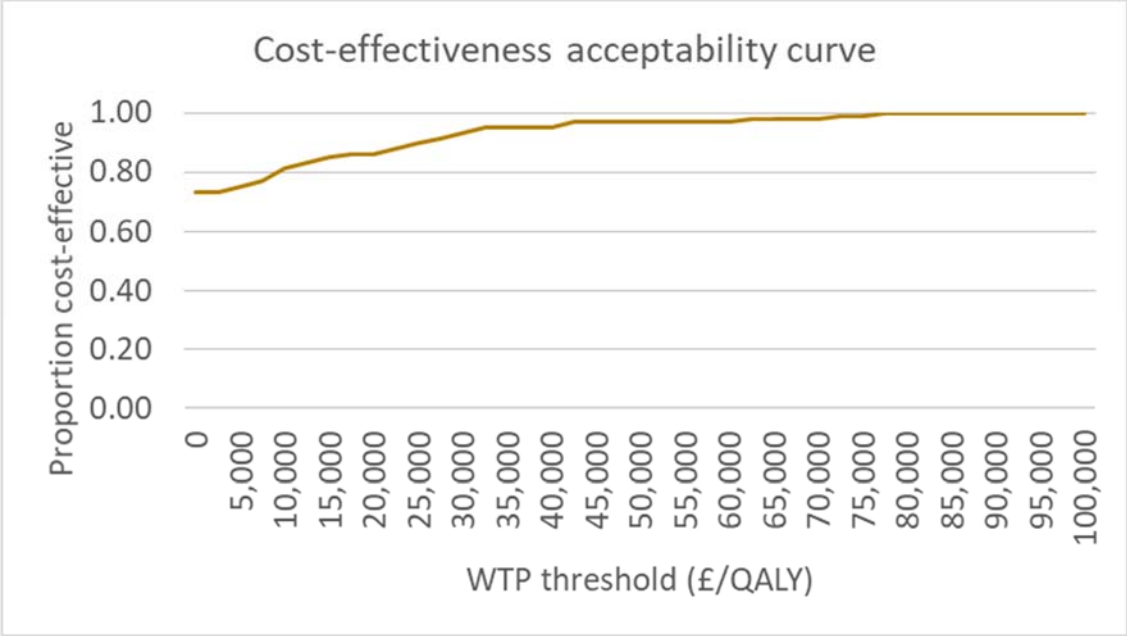
Abbreviations: CE, cost-effect; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; WTP, willingness to pay.

Figure 25. Incremental cost-effectiveness plane – chronic cohort



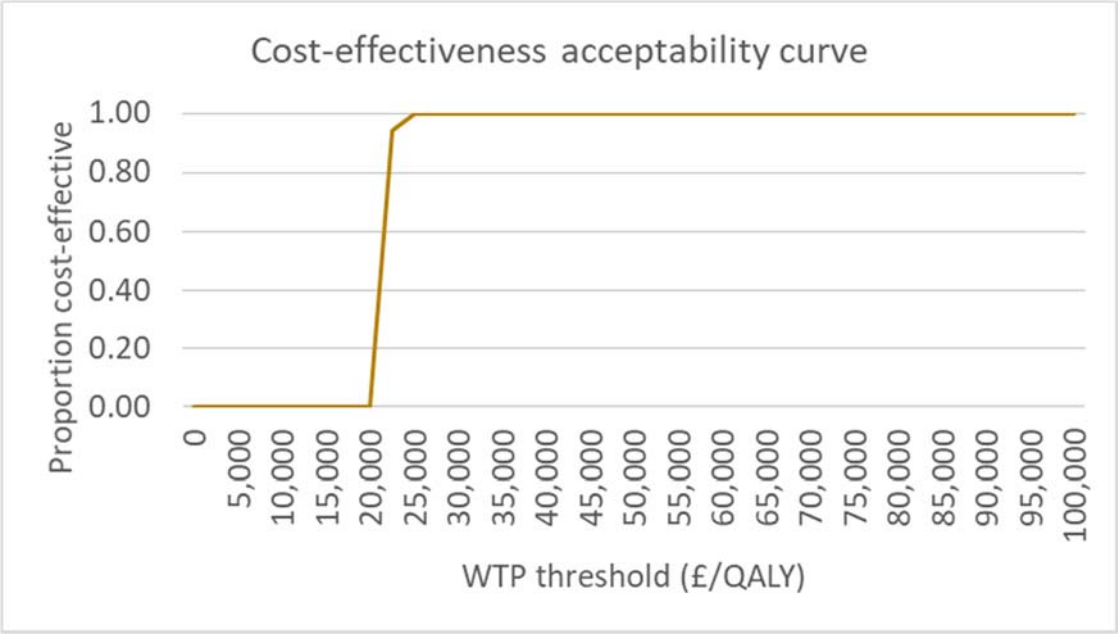
Abbreviations: CE, cost-effect; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; WTP, willingness to pay.

Figure 26. Cost-effectiveness acceptability curve – acute cohort



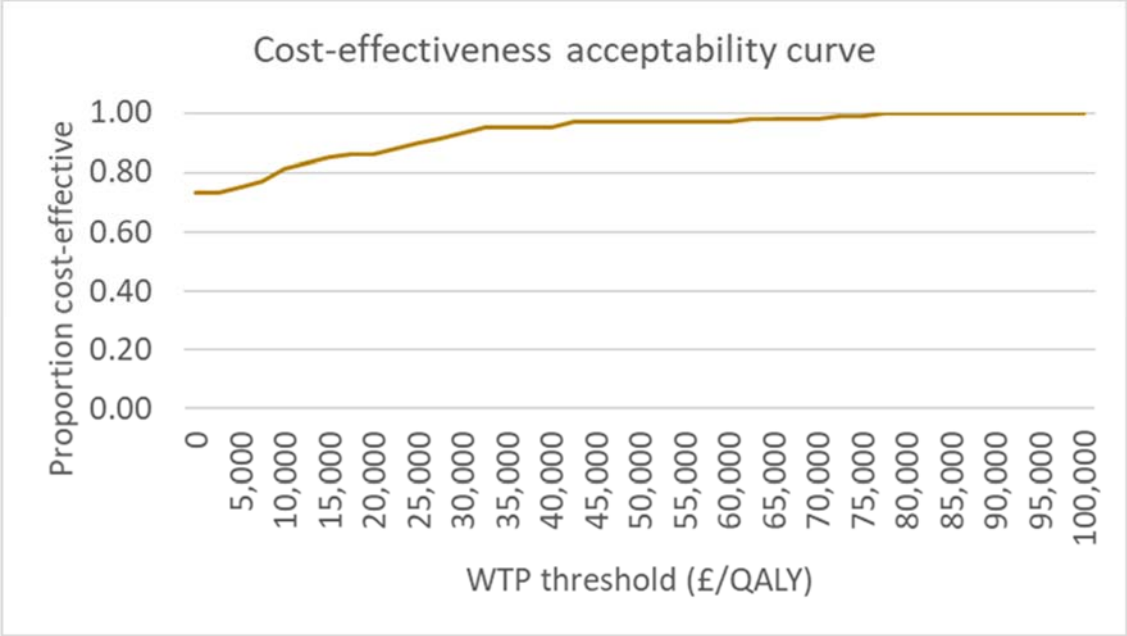
Abbreviations: QALY, quality-adjusted life-year; WTP, willingness to pay.

Figure 27. Cost-effectiveness acceptability curve – chronic cohort



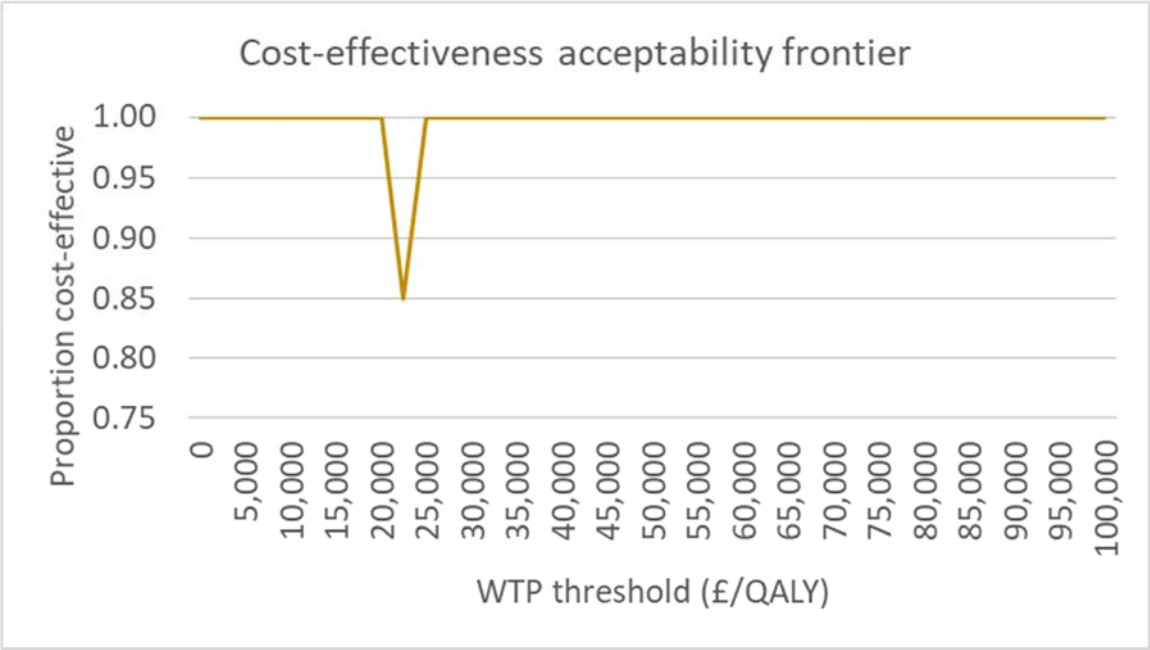
Abbreviations: QALY, quality-adjusted life-year; WTP, willingness to pay.

Figure 28. Cost-effectiveness acceptability frontier – acute cohort



Abbreviations: CE, cost-effect; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; WTP, willingness to pay.

Figure 29. Cost-effectiveness acceptability frontier – chronic cohort



Abbreviations: CE, cost-effect; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; WTP, willingness to pay.

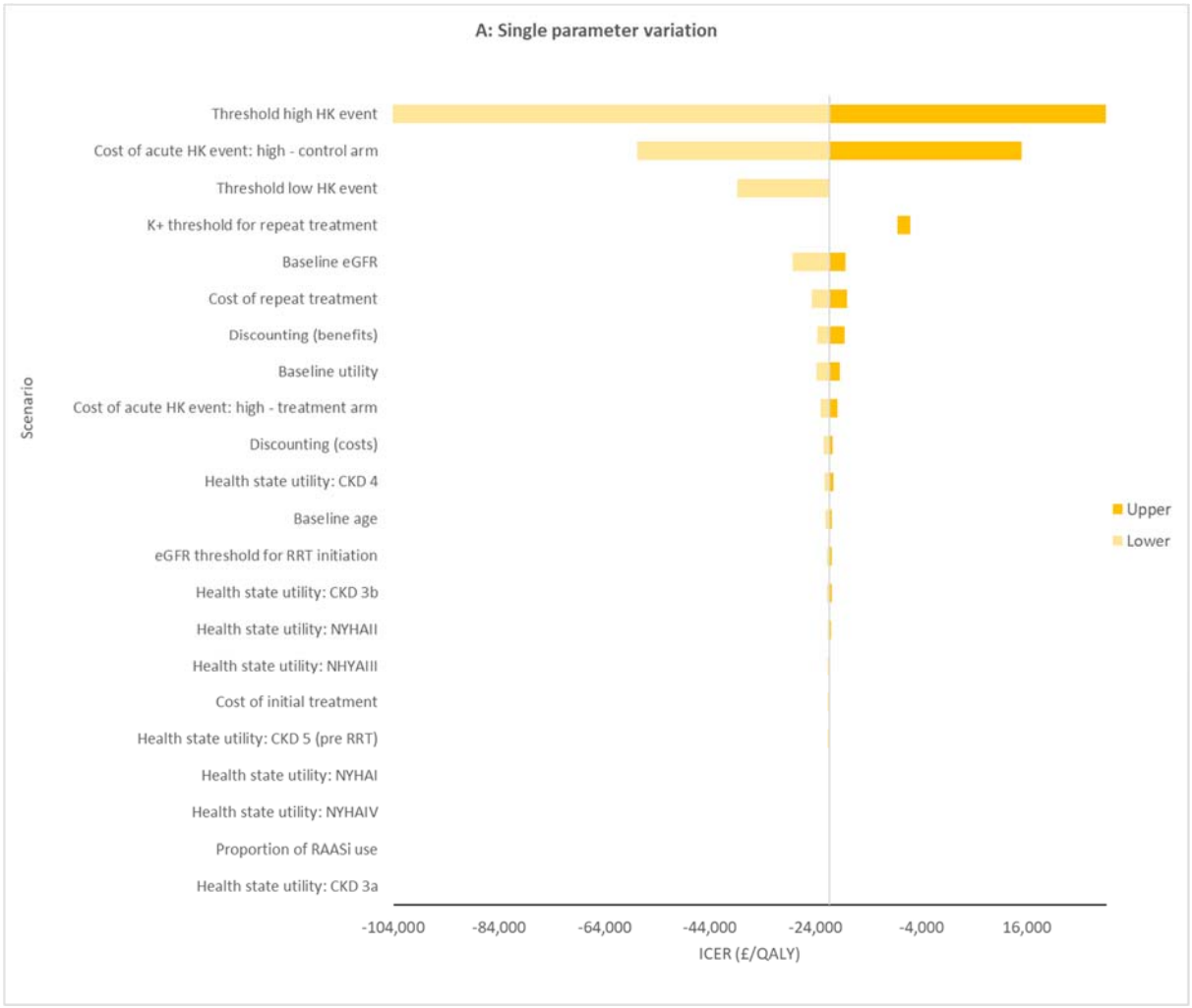
B.3.8.2 *Deterministic sensitivity analysis*

One-way sensitivity analysis (OWSA) was performed to assess the impact of individual parameters on the model results. OWSA considered upper and lower CIs sourced from literature in the first instance or calculated from the pre-specified probabilistic distributions assigned to each parameter as an alternative. Where the standard error was unavailable to calculate upper and lower CIs, this was assumed to be 10% of the mean value. The upper and lower bounds for the parameters included in the OWSA are shown in Table 69.

A tornado diagram is presented in Figure 31 (chronic) and Figure 30 (acute) to illustrate the level of uncertainty over the ICER inherent in each parameter, and varying some parameters as groups to represent correlation between certain groups of parameters (for example, if the annual rate of death is higher than estimated in earlier CKD stages it is likely to be higher in later CKD stages too).

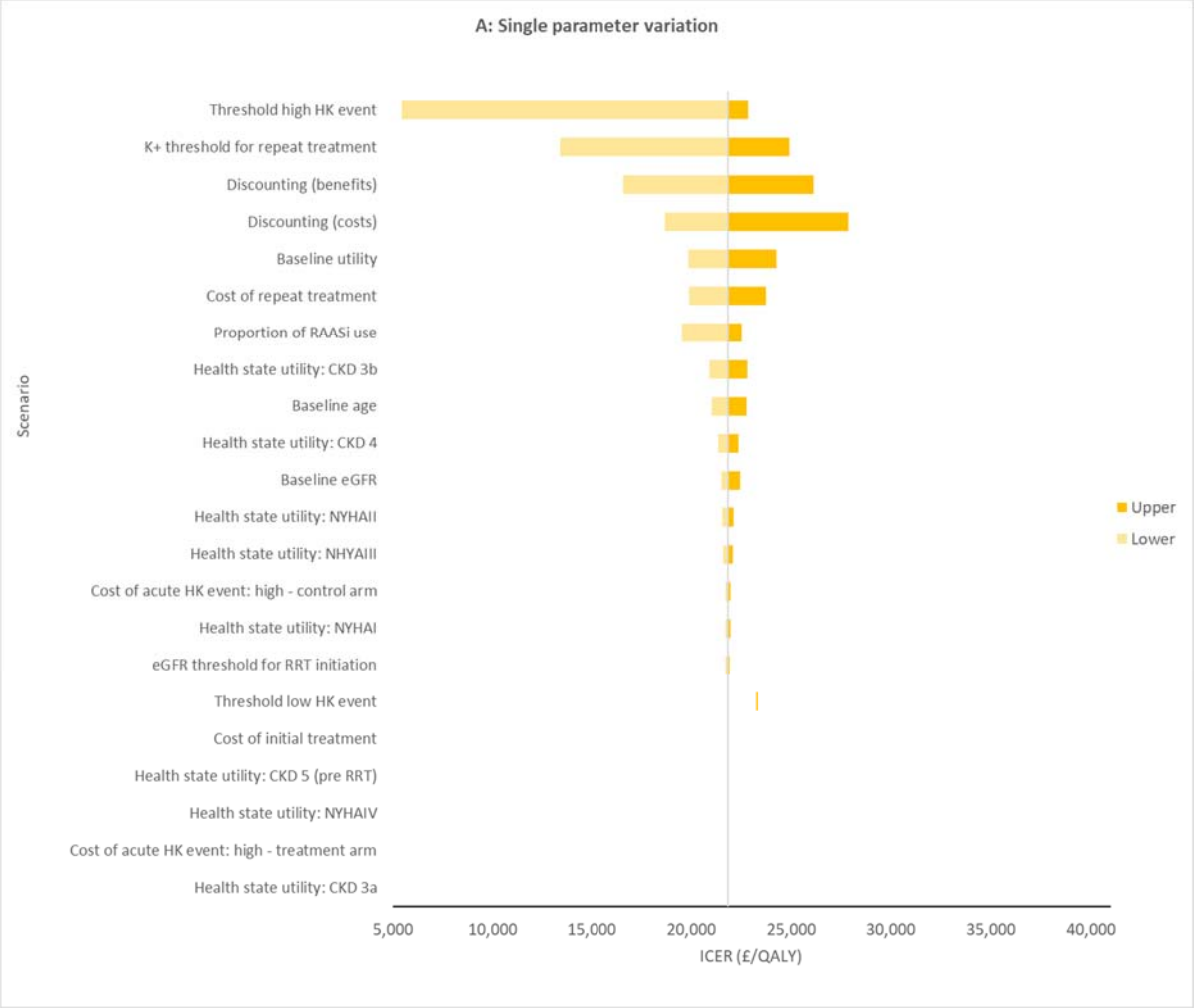
The most sensitive parameters in the chronic setting related to the S-K+ thresholds for treatment – that is, the S-K+ threshold triggering a hospitalisation, and the S-K+ threshold used for retreatment. Discounting, the cost of treatment and baseline utility were also important. The most sensitive parameters in the acute setting also related to the threshold for a high cost HK event, and the cost of an HK event was also significant. After this, the variation of parameters was less significant to overall results, since no variation led to SZC being anything but dominant over standard care.

Figure 30. Tornado diagram of SZC versus standard care – acute setting



Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HK, hyperkalaemia; ICER, incremental cost-effectiveness ratio; NYHA, New York Heart Association; QALY, quality-adjusted life-year; RAASi, renin-angiotensin-aldosterone system inhibitor; RRT, renal replacement therapy; SZC, sodium zirconium cyclosilicate.

Figure 31. Tornado diagram of SZC versus standard care – chronic setting



Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HK, hyperkalaemia; ICER, incremental cost-effectiveness ratio; NYHA, New York Heart Association; QALY, quality-adjusted life-year; RAASi, renin-angiotensin-aldosterone system inhibitor; RRT, renal replacement therapy; SZC, sodium zirconium cyclosilicate.

Table 81. OWSA results of SZC versus standard care – acute scenario

Parameter	ICER		
	Lower bound (£)	Upper bound (£)	Difference (£)
Threshold high HK event	[redacted]	[redacted]	135,645
Cost of acute HK event: high - control arm	[redacted]	[redacted]	72,777
Threshold low HK event	[redacted]	[redacted]	17,405
Baseline eGFR	[redacted]	[redacted]	9,977
Cost of repeat treatment	[redacted]	[redacted]	6,756
Discounting (benefits)	[redacted]	[redacted]	5,210
Baseline utility	[redacted]	[redacted]	4,341
Cost of acute HK event: high - treatment arm	[redacted]	[redacted]	3,118
K+ threshold for repeat treatment	[redacted]	[redacted]	2,552
Discounting (costs)	[redacted]	[redacted]	1,711
Health state utility: CKD 4	[redacted]	[redacted]	1,600
Baseline age	[redacted]	[redacted]	1,341
eGFR threshold for RRT initiation	[redacted]	[redacted]	939
Health state utility: CKD 3b	[redacted]	[redacted]	855
Health state utility: NYHAII	[redacted]	[redacted]	566
Cost of initial treatment	[redacted]	[redacted]	522
Health state utility: NHYAIII	[redacted]	[redacted]	521
Health state utility: CKD 5 (pre RRT)	[redacted]	[redacted]	433
Health state utility: NYHAI	[redacted]	[redacted]	231
Health state utility: NYHAIV	[redacted]	[redacted]	91

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; OWSA, one-way sensitivity analysis; RAASi, renin-angiotensin-aldosterone system inhibitor; RRT, renal replacement therapy; SZC, sodium zirconium cyclosilicate.

Table 82. OWSA results of SZC versus standard care – chronic setting

Parameter	ICER		
	Lower bound (£)	Upper bound (£)	Difference (£)
Threshold high HK event	[redacted]	[redacted]	17,361
K+ threshold for repeat treatment	[redacted]	[redacted]	11,546
Discounting (benefits)	[redacted]	[redacted]	9,578
Discounting (costs)	[redacted]	[redacted]	9,192
Baseline utility	[redacted]	[redacted]	4,411
Cost of repeat treatment	[redacted]	[redacted]	3,846
Proportion of RAASi use	[redacted]	[redacted]	2,993
Health state utility: CKD 3b	[redacted]	[redacted]	1,898
Baseline age	[redacted]	[redacted]	1,725

Parameter	ICER		
	Lower bound (£)	Upper bound (£)	Difference (£)
Health state utility: CKD 4	[redacted]	[redacted]	1,010
Baseline eGFR	[redacted]	[redacted]	936
Health state utility: NYHAII	[redacted]	[redacted]	562
Health state utility: NHYAIII	[redacted]	[redacted]	513
Cost of acute HK event: high - control arm	[redacted]	[redacted]	268
Health state utility: NYHAI	[redacted]	[redacted]	232
eGFR threshold for RRT initiation	[redacted]	[redacted]	194
Threshold low HK event	[redacted]	[redacted]	131
Cost of initial treatment	[redacted]	[redacted]	99
Health state utility: CKD 5 (pre RRT)	[redacted]	[redacted]	95
Health state utility: NYHAIV	[redacted]	[redacted]	62
Cost of acute HK event: high - treatment arm	[redacted]	[redacted]	13

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HK, hyperkalaemia; ICER, incremental cost-effectiveness ratio; NYHA, New York Heart Association; OWSA, one-way sensitivity analysis; RAASi, renin-angiotensin-aldosterone system inhibitor; RRT, renal replacement therapy; SZC, sodium zirconium cyclosilicate.

B.3.8.3 *Scenario analysis*

Scenario analyses were conducted to assess alternate model settings and structural uncertainty of the model as described in Table 73.

As shown in Table 84, base-case results were most sensitive to the fraction of patients who were HF versus CKD, and sensitive to assumptions made about RAASi discontinuation following HK event. In the acute setting, scenario analysis did not typically change the conclusion that SZC dominated standard care.

Table 83. Scenario analysis results – acute

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Base case							
SZC	[redacted]	[redacted]	[redacted]				
Standard care	[redacted]	[redacted]	[redacted]	-1,060	0.08	0.05	Dominates
10.95% HF, 89.05% CKD population (Horne et al.[163])							
SZC	[redacted]	[redacted]	[redacted]				
Standard care	[redacted]	[redacted]	[redacted]	-1,158	0.07	0.04	Dominates
80% RAASi use at initialisation							
SZC	[redacted]	[redacted]	[redacted]				
Standard care	[redacted]	[redacted]	[redacted]	-1,060	0.08	0.05	Dominates
No length of stay difference following HK event							
SZC	[redacted]	[redacted]	[redacted]				
Standard care	[redacted]	[redacted]	[redacted]	-227	0.08	0.05	Dominates
Price of calcium resonium £0.00							
SZC	[redacted]	[redacted]	[redacted]				
Standard care	[redacted]	[redacted]	[redacted]	-989	0.08	0.05	Dominates
RAASi mix taken from trial instead of ESC guidelines							
SZC	[redacted]	[redacted]	[redacted]				
Standard care	[redacted]	[redacted]	[redacted]	-1060	0.08	0.05	Dominates

The following scenarios are not relevant to the acute population, and so are not run: 100% RAASi discontinuation following HK event in standard care arm, 50% RAASi discontinuation, 50% down-titration following HK event in standard care arm, 52 weeks maximum initial treatment length

Abbreviations: CKD, chronic kidney disease; HF, heart failure; ICER, incremental cost-effectiveness ratio; LYG, life-year gained; QALY, quality-adjusted life-year; RAASi, renin-angiotensin-aldosterone system inhibitor.

Table 84. Scenario analysis results – chronic

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Base case							
SZC	[redacted]	[redacted]	[redacted]				
Standard care	[redacted]	[redacted]	[redacted]	16,688	1.25	0.76	21,835
10.95% HF, 89.05% CKD population (Horne et al. [163])							
SZC	[redacted]	[redacted]	[redacted]				
Standard care	[redacted]	[redacted]	[redacted]	15,863	1.03	0.65	24,471
80% RAASi use at initialisation							
SZC	[redacted]	[redacted]	[redacted]				
Standard care	[redacted]	[redacted]	[redacted]	17,340	1.34	0.83	20,987
No length of stay difference following HK event							
SZC	[redacted]	[redacted]	[redacted]				
Standard care	[redacted]	[redacted]	[redacted]	16,892	1.25	0.76	22,101
100% RAASi discontinuation following HK event in standard care arm							
SZC	[redacted]	[redacted]	[redacted]				
Standard care	[redacted]	[redacted]	[redacted]	18,647	1.44	0.89	21,005
50% RAASi discontinuation, 50% down-titration following HK event in standard care arm							
SZC	[redacted]	[redacted]	[redacted]				
Standard care	[redacted]	[redacted]	[redacted]	17,350	1.33	0.82	21,218
52 weeks maximum initial treatment length							
SZC	[redacted]	[redacted]	[redacted]				
Standard care	[redacted]	[redacted]	[redacted]	17,608	1.30	0.79	22,233
RAASi mix taken from trial instead of ESC guidelines							
SZC	[redacted]	[redacted]	[redacted]				
Standard care	[redacted]	[redacted]	[redacted]	16,584	1.25	0.76	21,699

CKD, chronic kidney disease; HF, heart failure; HK, hyperkalaemia; ICER, incremental cost-effectiveness ratio; LYG, life-year gain; QALY, quality-adjusted life-year; RAASi, renin-angiotensin-aldosterone system inhibitor.

B.3.8.4 *Summary of sensitivity analyses results*

All sensitivity analyses conducted resulted in SZC remaining cost-effective at a threshold of £30,000 / QALY, with the exception of the upper boundary for the treatment threshold for HK event in the acute setting, where the ICER was £30,856.

Mean PSA results provided the same conclusion as the deterministic base-case results, such that SZC is likely to be cost-effective at willingness-to-pay thresholds of around £22,000 in the chronic case and likely to be cost-effective at any threshold in the acute case.

B.3.9 *Subgroup analysis*

No subgroup analyses were explored in the cost-effectiveness analysis.

B.3.10 *Validation*

B.3.10.1 *Validation of de novo cost-effectiveness analysis*

The model has undergone thorough internal and external validation, to ensure it is reflective of the natural disease progression and complexities of HK and its management. The model was initially developed by an external health economics consultancy. During the development stage, AstraZeneca sought input from health economists. Professor Ben van Hout, Professor of Health Economics, suggested the underlying structure of natural disease progression in HF and CKD, on top of which S-K and its management is overarching. This structure was considered appropriate to capture the complexity of HK management in patients with CKD or HF, while enabling the modification of RAASi therapies, including down-titration or discontinuation. The use of recognised published literature and risk equations was considered appropriate to model the benefits of SZC. Another external health economics consultancy then reviewed the approach and methodology and provided suggestions for improvement. Clinical trial data underpinning the decision-tree section of the model has been taken directly from the ZS-004[99] and ZS-005[103] trials. Assumptions were ratified by external UK clinical experts with relevant expertise. All feedback obtained by internal and external ratification went into the final model and this written submission.

B.3.11 *Interpretation and conclusions of economic evidence*

Cost-effectiveness of SZC has been assessed for both the acute and chronic settings. In the acute setting, SZC is more effective and less costly than standard care, leading to SZC dominating standard care. In the chronic setting, SZC is more effective and more costly than standard care, which leads to an ICER on the lower end of the range usually considered by NICE to be the threshold for cost-effectiveness (£20,000–30,000). Sensitivity and scenario analyses show that the results are robust to altering parameter values and assumptions underpinning the model. As such, it can be concluded that SZC is a cost-effective use of NHS resources in both the acute and chronic settings.

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B.5. Appendices

Appendix C: Summary of product characteristics or information for use, European public assessment report, scientific discussion or drafts

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality of life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Methodologies for studies ZS-002, ZS003 and ZS-004E

Appendix M: Clinical effectiveness results of studies ZS-002, ZS-003 and ZS-004E

Appendix N: Supplementary data

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Single Technology Appraisal (STA)

Sodium zirconium cyclosilicate for treating hyperkalaemia [ID1293]

Dear Company,

The Evidence Review Group, School of Health and Related Research (ScHARR), and the technical team at NICE have looked at the submission received on 9 July from AstraZeneca. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by the end of **8 August 2018**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Alan Lamb, Technical Lead (Alan.Lamb@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (Jeremy.Powell@nice.org.uk).

Yours sincerely

Melinda Goodall
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Section A: Clarification on effectiveness data

Questions related to the SZC trials.

A1. **Priority question**: Please clarify whether patients in either the study or control arms of trials ZS-004 and ZS-005 had any dietary intervention/modification including concomitant dietary modifications.

A2. **Priority question**: Please confirm whether in the study populations of ZS-004 and ZS-005, patients in the "acute phase" of the included trials are patients with chronic HK who have been treated in the outpatient setting.

A3. **Priority question:** Clarify whether the population in the 'acute phase' would be seen as a distinct population by treating physicians and if so, what characteristics would distinguish them from patients in the chronic phase with an S-K level >6 mmol/L who are hospitalised. Clarify whether in the longer-term acute patients would be treated in an identical manner to chronic patients.

A4. For trial ZS-003, in Table 10 of Appendix D, please provide the number of patients in each arm that did not enter the sub-acute phase due to hypokalaemia and hyperkalaemia separately.

A5. Please provide the number of UK sites and number of UK patients enrolled in ZS-005.

A6. Please clarify the justification for excluding trial ZS-003 from the model given it is described as a pivotal trial in the Summary of Product Characteristics. A stated rationale for not including the trial in the model was that patient numbers were small. However, appendix L (page 3) states the patient numbers randomised to receive treatment in the acute phase were SZC 5 g (n=158), SZC 10 g (n=143) and placebo (n=158). A further stated justification for excluding trial ZS-003 was that 3/4 patients had a baseline S-K level of <5.5 mmol/L. However, a substantial proportion of patients in ZS-004 (46.1%) and ZS-005 (38.2%) had baseline S-K levels <5.5 mmol/L (tables 11 and 12 of CS) and were included in the model.

Literature searching

A7. **Priority question**: The NICE scope specifies that a low-potassium diet is a comparator to SZC as part of standard care. Please clarify why literature searches for the clinical review did not include terms to retrieve trials on the effect of treating hyperkalaemia with dietary modifications.

A8. Company submission Section B.2.9 (page 68) states that since "ZS-004 has a valid comparator, an indirect comparison was not deemed necessary". Please confirm why a systematic review was not conducted to check for other evidence relating to relevant comparators in the maintenance phase.

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A9. Company submission appendix D (page 2) states that the review question for the clinical SLR is "What randomised controlled trials have been conducted in HK?". However, the search strategy used for Medline, EMBASE and Cochrane for the period since 2017 would retrieve only those studies mentioning at least one of the named intervention/comparator terms given in line 2. It is also noted that this list is incomplete since “zirconium silicate”, used in some trials, is not included as a search term. Please comment on the mismatch between the stated review question and search approach, and the implications of omitting intervention terms.

A10. The clinical effectiveness searches presented in Appendix D only cover the period from April 2017-2018, with evidence prior to this date being drawn from a published review (Palaka et al 2018) based on a narrower search strategy and inclusion criteria. Please clarify what steps were taken to avoid missing pre-2017 studies within the scope of the company submission but excluded by the previous review?

A11. Given that the Medline and EMBASE searches were conducted in a “multi-file” (cross-database) search on the EMBASE.com platform, please describe how the company addressed the challenges of searching two different controlled vocabularies simultaneously in order to ensure that the strategy was optimised for each database?

A12. Please provide the sources of the economic and quality-of-life filters used in the Medline/EMBASE searches for cost-effectiveness data and confirm that these have been validated for use in a multi-file (cross-database) context.

Systematic review

A13. Please clarify why only 4 trials are described in detail in the main submission when Appendix D states that 73 references are included and quality assessment is performed on 13 RCTs. Specifically, please clarify:

a) Which of the 13 trials that are subjected to quality appraisal in Appendix D are relevant to the decision problem in terms of:
    - Population
    - Licensed dose of SZC
    - Standard care
    - Preferably please clarify the corresponding trial (using NCT number) for each citation
b) If any of the 13 trials are deemed relevant, provide an evidence network with these trials included.
c) If the 73 citations corresponding to 13 RCTs described as “included” in Appendix D are not relevant to the decision problem, please provide reasons for exclusion for each trial.

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Statistical methodology and reporting

A15. **Priority question**: Company submission Section B.2.4.1.5 page 45 states that the primary efficacy endpoint for the maintenance phase of ZS-004 was analysed with a longitudinal model (SAS PROC MIXED):

- Please provide the written mathematical equation of the full model that was fitted.
- An unstructured variance-covariance matrix was used. Please confirm how the most appropriate variance structure was identified (not a priority).
- Please provide the full results of the fitted model, with parameter estimates, CIs and p-values for all fitted variables (random patient effect, variance-covariance parameters, all fixed effects including baseline S-K, age, RAASi use, CKD, HF, diabetes mellitus).

A16. **Priority question**: Company submission Section B.2.4.1.5 page 45 states that the exponential rate of change in S-K values in the acute phase of ZS-004 were derived from a mixed effect model with several covariates:

- Please provide the written mathematical equation of the full model.
- Selected results from this model are summarised in Table 13. Please provide the full results of the fitted model, with parameter estimates, CIs and p-values for all fitted variables (log time, baseline eGFR, CKD status, HF status, RAASi use, diabetes status, age).

A17. **Priority question**: Company submission Section B.2.4.1.5 page 45 states that S-K measurements for the extended phase of ZS-005 were analysed using logistic regression and longitudinal model.

- Please provide the written mathematical equation of the full model longitudinal model that was fitted.
- Please provide the full results of the fitted model, with parameter estimates, CIs and p-values for all fitted variables.

A18. **Priority question**: Company submission appendix E page 3 states that full results of pre-planned subgroup analyses for the maintenance phase of ZS-004 “are not available from the ZS-004 Clinical Study Report, so are not presented here.” Please provide analyses for the remaining subgroups or clarify why these data are not available.

A19. **Priority question**: Company submission page 101 states “Pooled data was used as patients in ZS-005[103] received the same treatment as those in ZS-004[99] for the first 28 days, therefore the first 28 days could be pooled across both trials patients included in the analysis received the same as per protocol dose of SZC in the acute phase (i.e. 10 g TID for 1–3 days: 2 days in ZS-004[99] and 1–3 days in ZS-005[103]) and in the maintenance phase (5 g or 10 g OD for 28 days in ZS-004[99] and 5 g once every other day, OD or 10 g OD for up to 12 months).” However, Section B.2.8, page 67 states that “the ZS-004 and ZS-005 studies cannot be deemed comparable to meta-analyse” due to the following treatment differences i)

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the duration of treatment in the acute phase (before randomisation) and ii) titration was allowed in the maintenance phase of ZS-005. This appears to be inconsistent, please clarify.

A20. **Priority question**: Company submission page 100 states "trial-, treatment- and patient-specific S-K profiles are simulated using mixed effects regression models"

- Please provide the mathematical equation of the model that was fitted.
- Also, please provide examples of how the values in Tables 30 and 31 relate to the parameters within the potassium worksheet.
- If this model is different to the model used for the clinical-effectiveness analysis then please state the justification for this, and the anticipated effect on the data simulated in the model (e.g. is all heterogeneity accurately represented).
- Please provide the full results of the fitted model including parameter estimates, CIs and p-values for all fitted variables, or clarify the results provided in Table 30/31, including the points below:
- Please clarify what components of the heterogeneity are captured by the observation component (Table 30) and measurement component (Table 31). Does this account for variation in the measurement process (repeated tests on the same sample may yield different results) as well as other sources of uncorrelated error in the data (for example, patient fluctuations in S-K levels)?
- Please clarify the values presented under patient component (SD) and observation observation/measurement component (SD). Do these numbers relate to different parameters used in the acute and maintenance phase? Were they estimated from fitting separate models to both phases, or in a combined model of both phases?
- Please provide all the results for (1) the entire population and (2) only in those who meet the criteria eligible for treatment (S-K >5.5 at baseline).

A21. CS Section B.2.8 page 67.

- The CS states that the ZS-003 trial population is not consistent and generalisable to UK clinical management of patients with HK and CKD or HF due to approximately three-quarters of patients having a baseline S-K level < 5.5 mmol/L. However, ZS-004 also had a considerable proportion of patients with baseline S-K <5.5%. Perform a meta-analysis using data at 28 days (or close to it) from randomisation to the maintenance phase of ZS-005, ZS-003 and ZS-004 using just the subgroup of patients with S-K level >5.5% mmol/L.

Section B: Clarification on cost-effectiveness data

B1. **Priority question**: As stated on p26 of the company submission NICE Guidelines for CKD state that RAASi should be stopped if the S-K level increases to ≥6.0 mmol/L. The model assumes in the chronic phase that NICE guidance is not followed for patients treated with SZC as all remain on RAASi treatment. Please provide a scenario analysis where patients on SZC treatment with an S-K level ≥6.0 mmol/L have RAASi treatment

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discontinued. For both the SZC and the control arm, provide analyses where RAASi treatment would be withheld for a short period of time in patients with an S-K level ≥6.0 mmol/L, with resumption if the S-K level of a patient fell below 6.0 mmol/L and discontinuation otherwise. If the model is amended provide full details of the changes.

B2. **Priority question**: Please provide a scenario analysis where SZC treatment is only initiated in patients with an S-K level of ≥6.0 mmol/L. Within these analyses allow RAASi treatment to be withheld in patients with an S-K level ≥6.0 mmol/L for a short period of time with resumption if the S-K level fell below 6.0 mmol/L and discontinuation otherwise.

B3. **Priority question**: Provide an analyses for the 'acute population' where the time horizon is 28 days. If possible, incorporate the longer-term consequences of differential mortality rates within the 28-day period via the use of additional estimated QALY gains and costs so that SZC is not disadvantaged. Please provide details of how this analysis is performed.

B4. **Priority question**: Please clarify why the values reported in Table 30 of the company submission for SZC treatment do not match those in the model (Potassium worksheet [cells D9:G9]). If the model is incorrect, please amend. If Table 30 is incorrect please provide a scenario analysis where the value for treatment at Day 29+ is 4.753, rather than 4.669. Comment on the clinical plausibility of the change from 4.753 to 4.669 after day 29 compared with the probability that this is an artefact due to changes in the data sets being used to estimate the values.

B5. **Priority question**: Clarify whether the model assumes that all of the observational/measurement component (Tables 30 and 31) is patient fluctuation and that there is no measurement error. Clinical advice suggests that tests (bloods and ECG) are undertaken in hospitals to verify the community test result, due to measurement error. Please discuss the likely biases in the ICER that would be caused by assuming no measurement error.

B6. **Priority question**: Clarify the clinical plausibility that the costs associated with unused doses of SZC can be recouped. Please provide sensitivity analyses where these costs are not recouped and drug wastage is assumed.

B7. **Priority question**: Please clarify whether there is a coding error in the common parameters subroutine. It is believed that:

```
For i = 1 To 5
        dbl_arrAnnRate_CKD_CVDbyEGFR(i) = vnt_arrRiskParams(i + 15, 1)
```

Should be

```
        For i = 1 To 5
         dbl_arrAnnRate_CKD_CVDbyEGFR(i) = vnt_arrRiskParams(i + 13, 1)
```

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B8. **Priority question**: Please clarify whether in the EvaluteKThresholds subroutine the costs being incremented by 1 is a coding error

For example, why is the code:

dbl_arrCostAcuteHK(cycle) = dbl_arrCostAcuteHK(cycle) + dbl_cAcuteHKHigh **+ 1**?

B9. **Priority question**: Please clarify whether in the fnc_cycleProbACdeath Function cycle weeks being passed as a long rather than a double is a coding error.

B10. **Priority question**: Please clarify whether the modelled patients can have both HF and CKD. If not, provide all results separately for the two populations.

B11 Please provide an analysis where the maximum dose of RAASi is continued in patients with S-K levels <6.0 mmol/L who are treated with standard of care. That is, the proportion of patients who down-titrate or discontinue are both zero.

B12. Clarify the rationale for setting the value for the hazard ratio for survival in HF to 1.0 in the model (AA114 in 'Inputs 2') rather than using the value of 1.1 from Table 46 in the company submission. The approach is inconsistent with that taken elsewhere in the modelling, for example in AA122 where a value of 1.01 (Table 44) is used. Please provide sensitivity analyses using a value of 1.1 for AA114.

B13. Clarify the rationale for why there are many variables within the model (for example, all of those contained within the 'Inputs 2' sheet) that appear not to be included in the probabilistic sensitivity analysis (PSA). Please provide a table showing which variables are included in and excluded from the PSA.

B14. Please clarify how the one-way sensitivity analysis for proportions in NYHA groups (company submission, Table 70) is implemented as the current text is not clear.

B15. Please clarify why patients cannot have multiple experiences of the same adverse event. Provide further detail of why there are 13 cycles for intervention and only 1 for standard of care. For both parts provide additional text to that in Table 74 and page 95. We note that the cycle lengths are the same for SZC treatment and standard of care.

B16. Clarify whether the results in company submission Table 81 when adjusting the 'K+ threshold for treatment' are correct - currently both the upper and lower value are the same side of the deterministic ICER. If this is correct please provide the explanation for these results.

B17. Please clarify why, within an individual patient model, the age and eGFR values are assumed equal for all patients.

B18. Please clarify whether the results are sensitive to time with CKD, or time since MACE event?

B19. Clarify further how the values in Table 66 of the company submission were derived. Do these use the most recent HRG costs? If possible, please provide an example of how

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weighting was performed to calculate mean and standard error. Are there typographical errors (for example, the source for nausea appears to be the same as for diarrhoea)?

B20. Please evaluate the sensitivity of the model to changes in the costs assumed for each NYHA state. It is unlikely the costs are zero.

B21. Provide a scenario analysis where patients remain in CKD5 at a fixed eGFR score rather than receiving renal replacement therapy and exiting the model. Please highlight the changes made in the VBA to enable this change.

B22. Please clarify whether the utilities for NYHA categories and CKD categories are absolute values from the source reference or are multipliers as they have been used within the model.

B23. Please provide the supplementary tables associated with Sullivan et al 2011 and confirm that these contain the disutility values for the conditions incorporated in the model.

B24. Clarify why the number of weeks in the year is set to 52 rather than a more accurate value. If producing new analyses based on the potential coding errors/changed assumptions then please change this value.

B25. Please perform analyses that consider all of the requested amendments simultaneously.

Section C: Textual clarifications and additional points

C1. Please clarify whether there is a typo in Table 80. If so, what should the life year gained value for standard care be?

C2. Please clarify the apparent contradiction within Table 11. Table 11 reports baseline SK in the randomised phase as approximately 4.5 in each arm although the acute phase values in the rows below appear to give an average higher than 4.5 (for example in the SZC 10 g dose 63% of patients have values greater than, or equal, to 5.5). Clarify what is meant by acute phase S-K in Table 11.

C3. Please clarify whether in the model ‘lng_ageCatIndirect’ is an orphan variable.

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Single Technology Appraisal (STA)

Sodium zirconium cyclosilicate for treating hyperkalaemia [ID1293]

Dear Company,

The Evidence Review Group, School of Health and Related Research (ScHARR), and the technical team at NICE have looked at the submission received on 9 July from AstraZeneca. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by the end of **8 August 2018**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as [redacted] in turquoise, and all information submitted as [redacted] in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Alan Lamb, Technical Lead (Alan.Lamb@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (Jeremy.Powell@nice.org.uk).

Yours sincerely

Melinda Goodall
Associate Director – Appraisals
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Section A: Clarification on effectiveness data

Questions related to the SZC trials.

A1. **Priority question**: Please clarify whether patients in either the study or control arms of trials ZS-004 and ZS-005 had any dietary intervention/modification including concomitant dietary modifications.

Subjects in study ZS-004 or ZS-005 were not under any protocol-mandated dietary restrictions. Thus, the populations evaluated are representative of patients who would receive the drug in clinical practice.

A2. **Priority question**: Please confirm whether in the study populations of ZS-004 and ZS-005, patients in the "acute phase" of the included trials are patients with chronic HK who have been treated in the outpatient setting.

All patients enrolled in studies ZS-004 and ZS-005 are enrolled in an outpatient setting. Given the comorbidities, with approximately one-third having heart failure (HF), and two-thirds with chronic kidney disease (CKD), the patient population reflects those who will be seen in UK clinical practice. Therefore, given the progressive and complex nature of their underlying disease, and that the majority of patients receive treatment with RAASi therapy, these patients represent a cohort with chronic HK. Irrespective of the setting, all patients would initially receive a corrective phase, followed by a maintenance phase of SZC treatment in line with the Summary or Product Characteristics (SmPC).[1]

A3. **Priority question:** Clarify whether the population in the 'acute phase' would be seen as a distinct population by treating physicians and if so, what characteristics would distinguish them from patients in the chronic phase with an S-K level >6 [redacted]/L who are hospitalised. Clarify whether in the longer-term acute patients would be treated in an identical manner to chronic patients.

Patients with hyperkalaemia may be managed in an acute setting (i.e. in A&E), or in the chronic setting as part of ongoing management of their underlying disease (i.e. HF or CKD) through routine cardiology/nephrology appointments.

In general, patients who are identified in an acute setting (i.e. in A&E) generally attend A&E due to an acute medical problem, such as sepsis, dehydration/acute kidney injury, or pneumonia. As a result of these acute conditions, patients are likely to suffer from hyperkalaemia, and are therefore managed in line with local acute-care protocols and the Renal Association guidelines for the emergency management of hyperkalaemia in adults.[2-10] These guidelines, supported by expert clinical opinion from A&E consultants, nephrologists, and cardiologists, support the treatment pathway modelled in the acute setting and confirm that patients with a S-K ≥6 mmol/L are treated with IV insulin-glucose.[11]

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In contrast, patients in the chronic setting are regularly monitored through routine nephrology/cardiology appointments. In the chronic setting, there is a lack of pharmacological interventions, and management of hyperkalaemia is predominately limited to down-titration/discontinuation of RAASi therapy. Clinical feedback also indicated that a low-potassium diet may also be implemented, but adherence is usually low and it is considered to be unhealthy.[11] Clinicians reported that NICE and other guidelines, such as KDOQI and the European Society of Cardiology Heart Failure guidelines are generally followed, and that modifications to RAASi therapies are generally initiated at S-K ≥5.5 mmol/L.[11-13] However, if a patient's S-K increases to ≥6.5 mmol/L, clinicians in the chronic setting would manage patients in a manner mirroring the acute treatment pathway (i.e. hospital admission and administration of intravenous insulin and glucose). The higher S-K threshold for emergency treatment used in the chronic setting (S-K ≥6.5 mmol/L) compared to the acute setting (S-K ≥6 mmol/L), is driven by the availability of historical patient clinical information to the treating clinician, particularly past S-K measurements, and by the expertise of cardiologists/nephrologists in the management of chronic hyperkalaemia. It is important to consider that patients in the chronic setting will have a history of persistently elevated potassium that is available to the treating clinician, and that clinicians with experience in the management of chronic hyperkalaemia (i.e. cardiologists or nephrologists) use a higher threshold for initiating emergency management (i.e. vs the acute cohort approach). This chronic management protocol was supported by expert clinical opinion.[11]

These two distinct approaches in the acute versus the chronic settings are based on detailed discussions with UK experts in the management of acute and chronic hyperkalaemia.[11] The model was developed to reflect UK clinical practice, based on the recommendations by European, national, and local guidelines, and the modelled treatment pathways are supported by expert clinical opinion from across the care pathway.

A4. For trial ZS-003, in Table 10 of Appendix D, please provide the number of patients in each arm that did not enter the sub-acute phase due to hypokalaemia and hyperkalaemia separately.

Among subjects in the SZC 10 g TID group who did not enter the Subacute Phase, 2 had S-K values <3.5 mmol/L (range: 3.2 and 3.3 mmol/L). One of these subjects had a normal S-K value, based on central laboratory measurements, at the Study Day 3 pre-dose time point (3.7 mmol/L, respectively), whereas the other subject's S-K value was 3.4 mmol/L. All other subjects (n=13) who did not enter the Subacute Phase due to not achieving normokalemia had potassium values ≥5.0 mmol/L and did not qualify for the Subacute Phase. A summary of the number of patients defined as hypokalaemic or hyperkalaemic at the end of the acute (i.e. corrective) phase are summarised below.

Reason	Placebo (N=158)	ZS 1.25g TID (N=154)	ZS 2.5 g TID (N = 141)	ZS 5 g TID (N = 158)	ZS 10 g TID (N = 143)
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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A5. Please provide the number of UK sites and number of UK patients enrolled in ZS-005.

In total, 10 patients from 1 UK site were enrolled in study ZS-005.

A6. Please clarify the justification for excluding trial ZS-003 from the model given it is described as a pivotal trial in the Summary of Product Characteristics. A stated rationale for not including the trial in the model was that patient numbers were small. However, appendix L (page 3) states the patient numbers randomised to receive treatment in the acute phase were SZC 5 g (n=158), SZC 10 g (n=143) and placebo (n=158). A further stated justification for excluding trial ZS-003 was that 3/4 patients had a baseline S-K level of <5.5 mmol/L. However, a substantial proportion of patients in ZS-004 (46.1%) and ZS-005 (38.2%) had baseline S-K levels <5.5 mmol/L (tables 11 and 12 of CS) and were included in the model.

Study ZS-003 was a two-part, double-blind, randomised, placebo-controlled, dose-titration study. As such, patients were randomised to receive SZC 1.25 g (n=154), 2.5 g (n=141), 5 g (n=158), 10 g (n=143) three times daily or placebo (n=158) in the 48-hour correction phase (part 1 of study). Patients who achieved normokalaemia at the end of the correction phase within each of the SCZ-treated groups were randomly assigned to placebo or 1.25 g (n=49), 2.5 g (n=54), 5 g (n=65) or 10 g (n=63) daily, respectively, during the maintenance phase (days 3 to 14, part 2 of study). Patients randomised to placebo in the correction phase who achieved normokalaemia after 48-hours were randomised to SZC 1.25 g (n=45) or 2.5 (n=50) in the maintenance phase.[14]

AstraZeneca do not consider study ZS-003 to be relevant for inclusion in the cost-effectiveness model due to the following reasons:

- **Only a small number of patients were treated in line with the licenced dose[1]**

  As per the summary of product characteristics (SmPC), the licenced dose of SZC is 10 g administered three times a day during the 1–3 day correction phase.[1] As such, only the 63 patients who were initially randomised to receive 10 g SZC three times daily in the correction phase of ZS-003 and who subsequently were randomised to continue receiving 10 g daily would be relevant for the current decision problem. Furthermore, whilst 65 patients were randomised to receive 5 g once daily during the sub-acute phase of the study, it is important to consider that these patients were not previously exposed to the licensed dose during the corrective/acute phase of the study. That is, patients received treatment with 5 g SZC three times daily during this period. Therefore, the full treatment regimen for these patients is not in line with the European license, and it would be considered inappropriate to include the patient population for further analyses.

- **Only 15.4% of patients who received 10 g three times daily during the correction phase had a baseline S-K level >5.5 mmol/L)[14]**

  Only 22 (15.4%) of the 143 patients who were randomised to receive SZC 10g three time daily had a baseline S-K level >5.5 mmol/L. Therefore, it is estimated that a

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minority of patients (approx. 9–10 patients) treated with 10 g SZC in the sub-acute phase would be of clinical relevance in the UK.

As such, the majority of patients in ZS-003 are not relevant to the current decision problem, and the outcomes from ZS-003 may not be representative of the population of interest.

Furthermore, during assessment by the EMA, ZS-003 was considered a pivotal trial. However, the study duration was only 14 days and is further limited in terms of relevance to UK clinical practice by the points highlighted above. In addition, study ZS-003 has been superseded by studies ZS-004 and ZS-005 due to the following reasons:

- Both have longer study durations (28 days and 12 months, respectively).
- The dosing schedule in the correction phase of ZS-004 and ZS-005 are more representative of clinical practice (as per the SmPC)[1] and the patients within these studies are more representative of the target population, with the majority of patients having a baseline S-K level of >5.5 mmol/L (53.9% and 61.8%, respectively).

Literature searching

A7. **Priority question**: The NICE scope specifies that a low-potassium diet is a comparator to SZC as part of standard care. Please clarify why literature searches for the clinical review did not include terms to retrieve trials on the effect of treating hyperkalaemia with dietary modifications.

The clinical search strategy for Embase was updated with the term "('potassium' NEAR/3 ('diet*' OR 'intak*' OR 'consum*')):ti,ab" adding another 19 hits. The Cochrane search strategy was also updated by adding the term "('potassium' NEAR/3 ('diet*' OR 'intak*' OR 'consum*')):ti,ab,kw", giving an additional 7 hits.

Of the 26 additional hits, 2 were duplicates and so were removed before the first pass. Of the remaining 24 papers listed in Table 1, all 24 were rejected at the first pass meaning that no papers were added to the SLR. Of the 24 papers rejected, 2 papers had already been included in the SLR (Arnold, 2017 and Lambert, 2017), and the other 22 were not relevant to the review question.

Table 1: List of additional studies identified in the updated search strategy and rejected at the first pass

Author, Year	Title	Publication	Reason for exclusion
Arnold R, 2017	Randomized, controlled trial of the effect of dietary potassium restriction on nerve function in CKD	Clinical Journal of the American Society of Nephrology	It was a study to determine whether dietary restriction of potassium intake may be a neuroprotective factor in CKD.

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Author, Year	Title	Publication	Reason for exclusion
			SPS is not commonly used in UK clinical practice
Boyd-Shiwarski C, 2017	KS-WNK1 expands the dynamic range of NCC regulation by dietary potassium	FASEB Journal	It was an animal study
Chatterjee R, 2017	Serum potassium is a predictor of incident diabetes in African Americans with normal aldosterone: the Jackson Heart Study	American journal of clinical nutrition	The study only included diabetes patients and incidence of diabetes as an outcome; population and outcomes of interest were therefore not included. Also, the study was not an RCT
Chu L, 2018	Late-stage development and patient population applications of a quantitative systems pharmacology model of potassium homeostasis for sodium zirconium cyclosilicate	Clinical Pharmacology and Therapeutics	Study was a Quantitative Systems Pharmacology model, not an RCT
Clegg D, 2017	Challenges in Treating Cardiovascular Disease: Restricting Sodium and Managing Hyperkalemia	Mayo Clinic Proceedings	Study was a literature review, not an RCT
Farapti, 2017	Plasma Potassium Levels in Healthy Prehypertension Subjects and the Role of A High Potassium Drink	Current hypertension reviews	The study doesn't mention hyperkalaemia and was looking at increasing potassium rather than reducing it
Gritter M, 2018	Rationale and Design of a Randomized Placebo-Controlled Clinical Trial Assessing the Reno-protective Effects of Potassium Supplementation in Chronic Kidney Disease	Nephron	The study assessed the benefits of a dietary potassium (K+) diet in subjects with CKD. Patients with hyperkalaemia were excluded.
Lambert K, 2017	Preliminary results of an economic evaluation of resonium use in adults with chronic hyperkalemia	Nephrology	Study already included in SLR
McDonnell T, 2017	Alport's syndrome with type 4 renal tubular acidosis	BMJ Case Reports	This was a case report, not an RCT
NCT03059680, 2017	Effects of Implementing a High Potassium Diet in Heart Failure Patients	Https://clinicaltrials.gov/show/nct03059680	The intervention was increasing dietary potassium intake
NCT03253172, 2017	Potassium Supplementation in CKD	Https://clinicaltrials.gov/show/nct03253172	Intervention in the study was potassium supplementation.

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Author, Year	Title	Publication	Reason for exclusion
			Also, it was not an RCT
Nizar J, 2018	Chronic high potassium diet decreases thiazide-sensitive sodium excretion in high fat-fed mice	FASEB Journal	This was an animal study
Okuyama Y, 2017	Repeated measurement of casual urine NA/K ratio may provide useful information to screen early stage chronic kidney disease patients with higher sodium and lower potassium intake	Hypertension	This was not an RCT and was focus on lowering sodium to potassium ratio
Palma-Duran S, 2017	Dietary intake of polyphenol and potassium in the management of Type 2 Diabetes Mellitus Subjects with Chronic Kidney Disease	Proceedings of the Nutrition Society	This was a cross-sectional study (not RCT) conducted in CKD patients
Palmer B, 2017	Treatment of Abnormalities of Potassium Homeostasis in CKD	Advances in Chronic Kidney Disease	This was not an RCT
Penton Ribas D, 2016	Dietary potassium and the renal control of salt balance and blood pressure	Acta Physiologica	The intervention was high potassium diet
Rhee M, 2018	Isolated nocturnal hypertension had higher 24-hour urine sodium/potassium ratio than normotension	Journal of Hypertension	The intervention was high ratio of sodium/potassium intake and tis association with nocturnal blood pressure; also, it was not an RCT
Rhee M, 2017	High sodium intake and high ratio of sodium/potassium intake has a stronger association with night time blood pressure in the elderly	European Heart Journal	Intervention included was high sodium intake and it was not an RCT
Rhee M, 2017	Reduction of dietary sodium/potassium ratio is more effective in lowering of night time blood pressure	European heart journal. Conference: European Society of Cardiology, ESC congress 2017.Spain	Intervention included was high sodium intake and it was not an RCT
Rossignol P, 2018	The dilemma of recurrent hyperkalaemia management and use of renin-angiotensin-aldosterone system inhibitors: A European multinational targeted chart review	Nephrology Dialysis Transplantation	This was a retrospective study (not RCT); also, it did not include intervention of interest

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Author, Year	Title	Publication	Reason for exclusion
Rossignol P, 2018	The dilemma of recurrent hyperkalaemia and use of renin-angiotensin-aldosterone system inhibitors in heart failure with reduced ejection fraction: A European multi-national targeted chart review	European Journal of Heart Failure	This was a retrospective study (not RCT); also, it did not include intervention of interest
St-Jules D, 2016	Nutrient Non-equivalence: Does Restricting High-Potassium Plant Foods Help to Prevent Hyperkalemia in Hemodialysis Patients?	Journal of renal nutrition: the official journal of the Council on Renal Nutrition of the National Kidney Foundation	This was not an RCT
Wang X, 2017	Effect of long-term enriched potassium salt intake on salt reduction in Chinese living in nursing houses	Journal of hypertension. Conference: 27th European meeting on hypertension and cardiovascular protection, ESH 2017.Italy	The study included enriched potassium salt intake as the intervention
Žarak M, 2018	The role of medical biochemist in the diagnosis of pseudohyperkalemia - A case report	Biochemia Medica	This was a case report, not an RCT

A8. Company submission Section B.2.9 (page 68) states that since “ZS-004 has a valid comparator, an indirect comparison was not deemed necessary”. Please confirm why a systematic review was not conducted to check for other evidence relating to relevant comparators in the maintenance phase.

Clinical expert opinion confirms that no pharmacological therapy is administered as part of current standard of care treatment for hyperkalaemia following the correction phase (i.e. in the “maintenance” phase). At most, patients are managed by low potassium diets for the maintenance of S-K levels. As patients managed by low potassium diets were not excluded from ZS-004, the results from the placebo arm is likely to capture any effects associated with low potassium diets. As per the response to A7, no publications of low potassium diets were identified in the SLR.

In addition, withdrawal of RAASi treatment should not be considered a relevant comparator for indirect comparison, since RAASi treatment titration depends on the S-K levels of individual patients, rather the on the administration of SZC versus standard care. As such, RAASi down-titration and/or discontinuation is possible in both the intervention arm, and the control arm.

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A9. Company submission appendix D (page 2) states that the review question for the clinical SLR is "What randomised controlled trials have been conducted in HK?". However, the search strategy used for Medline, EMBASE and Cochrane for the period since 2017 would retrieve only those studies mentioning at least one of the named intervention/comparator terms given in line 2. It is also noted that this list is incomplete since “zirconium silicate”, used in some trials, is not included as a search term. Please comment on the mismatch between the stated review question and search approach, and the implications of omitting intervention terms.

The review question of the clinical SLR should be updated to reflect the intervention and comparators specified in the final scope, i.e. SZC and standard care.

To address the ERG’s question in full, the SLR was re-run with “zirconium silicate” added to the search strategy. No additional search results were identified, and as such the omission of this search term did not have any implications on the SLR results.

A10. The clinical effectiveness searches presented in Appendix D only cover the period from April 2017-2018, with evidence prior to this date being drawn from a published review (Palaka et al 2018) based on a narrower search strategy and inclusion criteria. Please clarify what steps were taken to avoid missing pre-2017 studies within the scope of the company submission but excluded by the previous review?

Overall, a wider search strategy and inclusion criteria were used in the SLR by Palaka et al, 2018.

Inclusion and exclusion criteria for both the Palaka et al 2018 and the updated SLR are presented in Table 2 and Table 3 respectively, followed by an overview of the differences in the search strategies.

The same inclusion criteria were used in both SLRs with the exception of the following criteria, marked in red in Table 2:

- A wider inclusion criteria for the population was used in Palaka et al, 2018 (S-K ≥ 4.9 mEq/L) versus the updated SLR (S-K ≥ 5.0 mEq/L)
- Outcomes:
    - The SLR by Palaka et al 2018 included studies looking at quality of life while the updated SLR did not.
    - The updated SLR could appear to have a wider strategy with regard to how the efficacy data for S-K was recorded. There are indeed 5 additional terms included in the updated SLR however, 4 of them can be grouped into the criteria used in the SLR by Palaka et al. 2018:
        - Exponential rate of change = change from baseline
        - Percentage and mean change from baseline = change from baseline

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  - Time to relapse in serum potassium levels = time to hyperkalaemia recurrence in withdrawal phase
  - Change during extended dosing/maintenance phase vs acute/corrective phase = change from baseline

The criteria 'Proportion who remained normokalaemic' was not included in the SLR by Palaka et al, 2018 and as such the updated SLR would have a wider scope than the initial SLR. No step was taken to verify whether studies were missed prior to April 2017 for this criteria however, it can be anticipated that any studies relevant to the decision problem would have reported other S-K related outcomes in addition to the 'Proportion who remained normokalaemic'.

- A wider inclusion criteria for the study type was used in Palaka et al, 2018 (non-RCT were included in addition to RCTs) while only RCTs were included in the updated SLR.

The same exclusion criteria were used in both SLRs with the exception of the following criteria marked in red in Table 3:

- Non-RCTs were excluded from the updated SLR while they were included in the SLR by Palaka et al, 2018

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Table 2: Comparison of the inclusion criteria in the updated SLR and the SLR by Palaka et al 2018

Selection criteria	Updated SLR (April 2017-2018)	SLR by Palaka et al, 2018
Population	• Patients with hyperkalaemia, with "hyperkalaemia" defined as a serum potassium level of ≥5.0 mEq/L. • Studies including mixed populations (i.e. a mixture of relevant and irrelevant patients for the purposes of this SLR) will be included if outcomes are reported separately for the population of interest. Studies that do not report separate outcomes for the population of interest, but where the majority of patients meet these eligibility criteria (and a small proportion do not), will be reviewed on a case-by-case basis to determine their relevance to the SLR. • Studies where patients have normokalemia at baseline but where the aim is specifically to prevent the development of hyperkalemia will also be included. • Any cause of hyperkalaemia, apart from pseudohyperkalaemia (artificially high potassium concentration readings due to blood test methods), will be considered relevant. Relevant causes include (but are not limited to) chronic kidney disease (CKD), diabetes, or use of renin-angiotensin-aldosterone system inhibitor (RAASi).	• Patients with hyperkalemia, with "hyperkalemia" defined as a serum potassium level of ≥4.9 mEq/L. • Studies including mixed populations (i.e. a mixture of relevant and irrelevant patients for the purposes of this SLR) were included if outcomes were reported separately for the population of interest. Studies that did not report separate outcomes for the population of interest, but where the majority of patients met these eligibility criteria (and a small proportion did not), were reviewed on a case-by-case basis to determine their relevance to the SLR. • Studies where patients had normokalemia at baseline but where the aim was specifically to prevent the development of hyperkalemia were also included. • Any cause of hyperkalemia, apart from pseudohyperkalemia (artificially high potassium concentration readings due to blood test methods), was considered relevant. Relevant causes included (but were not limited to) chronic kidney disease, diabetes, or use of RAASi.
Intervention	• Any pharmacological or non-pharmacological therapies used in the management (treatment or prevention) of hyperkalaemia. These include interventions to reduce serum potassium and those to prevent arrhythmias. Relevant interventions include (but are not limited to): o Sodium zirconium cyclosilicate (SZC – previously ZS9) o Patiromer	• Any pharmacological or non-pharmacological therapies used in the management (treatment or prevention) of hyperkalemia, including interventions to reduce serum potassium and those to prevent arrhythmias. Relevant interventions included (but were not limited to): o ZS o Patiromer o Sodium polystyrene sulfonate

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	○ Sodium polystyrene sulfonate ○ Calcium polystyrene sulfonate/Calcium resonium ○ Salbutamol ○ Sodium bicarbonate ○ Insulin-dextrose ○ Aminophylline ○ Down-titration or discontinuation of RAASi agents ○ Dialysis/hemofiltration ○ Low potassium diets • Studies investigating any therapy as either monotherapy or combination therapy will be considered relevant.	○ Calcium polystyrene sulfonate ○ Salbutamol ○ Sodium bicarbonate ○ Insulin-dextrose ○ Aminophylline ○ Down-titration or discontinuation of RAASi agents ○ Dialysis ○ Low potassium diets • Studies investigating any therapy as either monotherapy or combination therapy were considered relevant.
Comparator	• Any pharmacological or non-pharmacological therapies used in the management (treatment or prevention) of hyperkalaemia. These include interventions to reduce serum potassium and those to prevent arrhythmias. Relevant interventions include (but are not limited to): ○ Sodium zirconium cyclosilicate (SZC – previously ZS9) ○ Patiromer ○ Sodium polystyrene sulfonate ○ Calcium polystyrene sulfonate/Calcium resonium ○ Salbutamol ○ Sodium bicarbonate ○ Insulin-dextrose ○ Aminophylline ○ Down-titration or discontinuation of RAASi agents ○ Dialysis/hemofiltration ○ Low potassium diets • Placebo	RCTs: • Any pharmacological or non-pharmacological therapy, as specified for "Interventions" above • •Placebo Non-RCTs: • As specified for RCTs above • No comparator
Outcomes	Efficacy data: • Serum potassium concentration, expressed as:	Articles had to report at least one of the following outcomes: • Efficacy data, such as:

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	o Change from baseline o Absolute value at study endpoints o Time to decrease of 0.5 mEq/L o Time to normokalaemia o Proportion of subjects achieving normokalaemia o Time to hyperkalaemia recurrence in withdrawal phase o Absolute value or change from minimum value after withdrawal of treatment o Exponential rate of change o Percentage and mean change from baseline o Time to relapse in serum potassium levels o Proportion who remained normokalaemic o Change during extended dosing/maintenance phase vs acute/corrective phase • Electrocardiogram (ECG) changes • Prevention of: Arrhythmias o Mortality o Dialysis o Hospitalisations o Emergency room admissions o Need for outpatient care • Safety data: o Overall adverse events o Overall treatment-related adverse events o Overall serious adverse events o Overall grade 3/4 adverse events o Specific adverse events of key importance: ▪ Abdominal pain ▪ Anaemia ▪ Aspartate aminotransferase increased ▪ Cardiac disorder	• Serum potassium concentration, expressed as: o Change from baseline o Absolute value at study endpoints o Time to decrease of 0.5 mEq/L o Time to normokalemia o Proportion of subjects achieving normokalemia o Time to hyperkalemia recurrence in withdrawal phase o Absolute value or change from minimum value after withdrawal of treatment • ECG changes • Prevention of: o Arrhythmias o Mortality o Dialysis o Hospitalisations o Emergency room admissions o Need for outpatient care • Safety data o Overall adverse events o Overall treatment-related adverse events o Overall serious adverse events o Overall grade 3/4 adverse events o Specific adverse events of key importance: ▪ Abdominal pain ▪ Anaemia ▪ Aspartate aminotransferase increased ▪ Cardiac disorder ▪ Cardiac failure ▪ Cellulitis ▪ CKD (worsening of) ▪ Constipation ▪ Diarrhoea ▪ Dyspepsia ▪ Emesis (vomiting)

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	▪ Cardiac failure ▪ Cellulitis ▪ CKD (worsening of) ▪ Constipation ▪ Diarrhoea ▪ Dyspepsia ▪ Emesis (vomiting) ▪ Gastrointestinal disorder ▪ Headache ▪ Heartburn ▪ Hepatotoxicity ▪ Hypertension (worsening of) ▪ Hypoglycaemia ▪ Hypokalaemia ▪ Hypomagnesaemia ▪ Hypermagnesaemia ▪ Myocardial infarction ▪ Nasopharyngitis ▪ Nausea ▪ Oedema /Edema (US) ▪ Pneumonia ▪ Respiratory tract infection, upper swelling ▪ Urinary tract infection	▪ Gastrointestinal disorder ▪ Headache ▪ Heartburn ▪ Hepatotoxicity ▪ Hypertension (worsening of) ▪ Hypoglycaemia ▪ Hypokalemia ▪ Hypomagnesaemia ▪ Hypermagnesaemia ▪ Myocardial infarction ▪ Nasopharyngitis ▪ Nausea ▪ Oedema ▪ Pneumonia ▪ Respiratory tract infection, upper ▪ Swelling ▪ Urinary tract infection • Quality of life data, including (but not limited to): o SF-36 o EQ-5D o HAQ o Disease-specific QoL measures, such as: o Kidney Disease QoL instrument (KDQOL) o Quality of Life index (QLI), eg. o Generic version o Dialysis version o Cardiac version
Study type	• RCTs	• RCTs • Non-RCTs, including: • Experimental studies (eg. single-arm studies, multi-arm studies without randomisation) • Observational studies (prospective, retrospective and cross-sectional)
Language	Article or abstract available in English	English

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Table 3: Comparison of the exclusion criteria in the updated SLR and the SLR by Palaka et al 2018

Selection criteria	Updated SLR (April 2017-2018)	SLR by Palaka et al, 2018
Population	• Studies that do not include patients of interest to the SLR • Studies with a mixed patient population that do not present outcomes separately for patients of interest and patients not of interest, with only a minority of patients being of interest • Studies including only patients with pseudohyperkalaemia • Animal studies or in vitro studies	• Studies that did not include patients of interest to the SLR • Studies with a mixed patient population that did not present outcomes separately for patients of interest and patients not of interest, with only a minority of patients being of interest • Studies including only patients with pseudohyperkalemia • Animal studies or in vitro studies
Intervention	None	None
Comparator	None	None
Outcomes	Any articles not reporting an outcome of interest to the SLR	Any articles not reporting an outcome of interest to the SLR
Study type	• Any study design not specified as being of interest in the SLR, including: o Non-RCTs o Non-systematic or narrative reviews o Case reports o Comments and editorials o Animal studies or in vitro studies	• Any study design not specified as being of interest in the SLR, including: o Non-systematic or narrative reviews o Case reports o Comments and editorials o Animal studies or in vitro studies
Language	Non-English language articles (no abstract available in English)	Any other language

Search strategy

The differences in the search strategies across both SLR are as follows:

- The same filter for population was used in both SLR with one exception. In the SLR by Palaka et al, 2018, abstracts were searched for ≥2 occurrences of the population terms using the term 'freq/2', whereas in the updated SLR, the population filter searched for at least one occurrence. It is considered that the number of relevant trials that could have been missed are minimal.

- The updated SLR included a filter for intervention/comparator, whereas the SLR by Palaka et al, 2018 did not, making their search strategy wider therefore, any intervention/comparator would have been recorded.

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Overall, a wider search strategy and inclusion criteria were used in the SLR by Palaka et al, 2018. It is unlikely that pre-2017 studies would have been missed within the scope of the company submission.

A11. Given that the Medline and EMBASE searches were conducted in a "multi-file" (cross-database) search on the EMBASE.com platform, please describe how the company addressed the challenges of searching two different controlled vocabularies simultaneously in order to ensure that the strategy was optimised for each database?

All journals covered by Embase and MEDLINE in the Embase library are indexed by Embase using Emtree. Journals unique to MEDLINE are not indexed by Embase using Emtree but are indexed using the MEDLINE thesaurus MeSH. These unique MEDLINE records are not re-indexed by Elsevier when added to the Embase library, however their indexing is mapped to Emtree terms used in Embase to ensure that Emtree terminology can be used to search all Embase records, including those originally derived from MEDLINE.[15] Therefore, both databases can be searched on the Embase platform. As such, only one search vocabulary was required.

A12. Please provide the sources of the economic and quality-of-life filters used in the Medline/EMBASE searches for cost-effectiveness data and confirm that these have been validated for use in a multi-file (cross-database) context.

As NICE do not recommend a search filter, we sourced our search filters from SIGN. The filters meet SIGN information needs. These filters sourced from SIGN were devised and tested to run in both the MEDLINE and Embase databases using index terms and free text.[16] The index terms used were those of Embase and as presented in response to question A11, journals covered by both Embase and MEDLINE are indexed using Emtree whilst the indexing of unique MEDLINE journals are mapped to Emtree terms. Therefore filters based on Emtree terminology/indexing can be used to search all Embase records, including those originally derived from MEDLINE.[15]

Systematic review

A13. Please clarify why only 4 trials are described in detail in the main submission when Appendix D states that 73 references are included and quality assessment is performed on 13 RCTs. Specifically, please clarify:

a) Which of the 13 trials that are subjected to quality appraisal in Appendix D are relevant to the decision problem in terms of:
   - Population
   - Licensed dose of SZC
   - Standard care
   - Preferably please clarify the corresponding trial (using NCT number) for each citation

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Out of the 13 trials that are subjected to quality appraisal in Appendix D, only 3 are relevant to the decision problem. These are the trials by Ash 2015 (ZS-002), Packham 2015 (ZS-003), and Kosiborod 2014 (ZS-004) and were presented in Tables 4, 5 and 6 of the NICE submission. Relevant information is summarised in Table 4 below.

Table 4: Overview of ZS-002, ZS-003 and ZS-003 as trials relevant to the decision problem

	Population	Licensed dose of SZC	Comparator / Standard care
Ash 2015 (ZS-002, NCT01493024)[17]	Patients aged >18 years with stable Stage 3 CKD, an estimated glomerular filtration rate of 30–60 ml/min per 1.73 m^2 estimated by CKD Epidemiology Collaboration (CKD-EPI) equation, serum potassium levels between 5.0 and 6.0 mEq/L and with the ability to have repeated blood draws or effective venous catheterisation	SZC 10g (doses of 0.3g and 3g are not licensed)	Comparator was placebo
Packham 2015 (ZS-003, NCT01737697)[14]	Patients aged >18 years of age with an i-STAT potassium value between 5.0 and 6.5 mmol/L at screening and the ability to have repeated blood draws or effective venous catheterisation	SZC 5g and 10g (doses of 1.25g and 2.5g are not licensed)	Comparator was placebo
Kosiborod 2014 (ZS-004 - HARMONIZE, NCT02088073) [18 18 18 18 18 1818]	Adult patients aged >18 years of age with an i-STAT potassium value ≥5.1 mmol/L	SZC 5g and 10g (dose of 15g is not licensed)	Comparator was placebo

b) If any of the 13 trials are deemed relevant, provide an evidence network with these trials included.

All 3 relevant trials included licensed doses of SZC (5g and 10g) and placebo, there is no additional evidence that can contribute to an evidence network.

c) If the 73 citations corresponding to 13 RCTs described as “included” in Appendix D are not relevant to the decision problem, please provide reasons for exclusion for each trial.

Trial	Population	Comparator, dose, duration	Reason for exclusion
Nakayama, 2018	20 pre-dialysis CKD 4–5 outpatients with hyperkalaemia (S-K>5 mmol/l) not treated with	CPS, 5g powder after each meal, 4 weeks SPS, 5g powder after each meal, 4 weeks	The dose of CPS used in UK clinical practice is 15g, 3 or 4 times a day

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Trial	Population	Comparator, dose, duration	Reason for exclusion
	polystyrene sulfonate	After 4 weeks, the patients swapped cohort without a washout period so 8 weeks total	SPS is not used in UK clinical practice
Arnold, 2017	47 patients with CKD 3-4	Dietary potassium restriction group: low potassium diet, 60-75 mmol/d potassium intake for 24 months. If S-K>4.5mmol/L for 2 consecutive readings, a 15g-30g daily dose of SPS was given until S-K levels <4.5mmol/L Control group: N/A, 24 month-duration. SPS administered if S-K>6.0	It was a study to determine whether dietary restriction of potassium intake may be a neuroprotective factor in CKD. SPS is not commonly used in UK clinical practice
Allon 1989	Patients on haemodialysis with S-K>5.0 mmol/L	Albuterol, 20 mg, Albuterol, 10 mg, placebo	Albuterol (also known as salbutamol) is an adjuvant therapy given alongside temporising agents. As such it is not a relevant comparator as it is administered earlier in the treatment pathway to shift potassium into the cells.
Allon 1990	Patients on haemodialysis with S-K>5.0 mmol/L	Albuterol, 20 mg, Insulin 10U + glucose 50 ml, 50%	Temporising agents such as insulin + glucose and adjuvant therapy such as albuterol are not relevant comparators as they are administered earlier in the treatment pathway to shift potassium into the cells
Chothia 2014	Patients on haemodialysis with S-K>5.0 mmol/L	Glucose 100 ml 50%, Insulin 10U + glucose 100 ml 50%	Temporising agents such as insulin + glucose are not relevant comparators as they are administered earlier in the treatment pathway to shift potassium into the cells
Gruy-Kapral 1998	Patients with chronic renal failure maintained on haemodialysis	SPS, 30g, 12 hours Phenolphtalein-docusate, 8 tablets, 12 hours Phenolphtalein-docusate 8 tablets + 30g SPS, 12 hours	SPS is not commonly used in UK clinical practice Only 6 patients were included in the study

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Trial	Population	Comparator, dose, duration	Reason for exclusion
		Sorbitol + 30g SPS, 12 hours Placebo, 12 hours	
Lepage 2015 (SKIP)	Patients with CKD and S-K 5.0-5.9 mmol/L	Sodium polystyrene sulfonate 30 g QD, 7 days Placebo QD, 7 days	SPS is not commonly used in UK clinical practice
Mandelberg 1999	Patients with severe renal failure and S-K>5.0 mmol/L	Salbutamol, 1.2 mg, Placebo	Salbutamol is not a relevant comparator as it is administered as an adjuvant therapy earlier in the treatment pathway to shift potassium into the cells
Nasir 2014	Patients with CKD and hyperkalemia (S-K>5.2 mmol/L)	SPS, 5g TID, 3 days CPS, 5g TID, 3 days	The dose of CPS used in clinical practice is 15g, 3 or 4 times a day SPS is not commonly used in UK clinical practice
Ngugi 1997	Patients with acute or chronic renal failure with S-K>5.0 mmol/L	Insulin 10U + glucose 50 ml 50%, Salbutamol 0.5 mg, 8.4% sodium bicarbonate	Temporising agents such as insulin + glucose and adjuvant therapy such as albuterol are not relevant comparators as they are administered earlier in the treatment pathway to shift potassium into the cells

Abbreviations: CKD, chronic kidney disease; CPS, calcium polystyrene sulfonate; S-K, serum potassium; QD, once daily; TID, three times daily

Statistical methodology and reporting

A15. **Priority question**: Company submission Section B.2.4.1.5 page 45 states that the primary efficacy endpoint for the maintenance phase of ZS-004 was analysed with a longitudinal model (SAS PROC MIXED):

- Please provide the written mathematical equation of the full model that was fitted.

The mathematical model below was used to conduct the analyses for studies ZS-004 and ZS-005, and is therefore relevant to questions A15–17. The mathematical equation of the full model is:

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[redacted]

The fixed and random effects for ZS-004 maintenance phase model are reported in the table below.

Table 5: ZS-004 maintenance phase: fixed and random effects

Fixed Effects	Random Effects
treatment groups (ZS 15 g, ZS 10g qd, ZS 5g qd and placebo) acute phase baseline S-K maintenance phase baseline S-K baseline eGFR age category (<55, 55-64, ≥65 years) baseline RAAS inhibitor use, indicator variable for yes/no baseline chronic kidney disease status (CKD), indicator variable for yes/no baseline congestive heart failure status (CHF), indicator variable for yes/no baseline diabetes mellitus status (DM), indicator variable for yes/no	Patient

- An unstructured variance-covariance matrix was used. Please confirm how the most appropriate variance structure was identified (not a priority).

An unstructured variance-covariance matrix was used due to lack of prior data providing information on suitable structured matrices.

- Please provide the full results of the fitted model, with parameter estimates, CIs and p-values for all fitted variables (random patient effect, variance-covariance parameters, all fixed effects including baseline S-K, age, RAASi use, CKD, HF, diabetes mellitus).

Table 6: Fixed model results for the maintenance phase of study ZS-004

Effect	Estimate	Standard Error	95% CI	Two-sided p-value
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance Phase Treatment Group (Referent: Placebo)				
5 g ZS	[redacted]	[redacted]	[redacted]	[redacted]
10 g ZS	[redacted]	[redacted]	[redacted]	[redacted]
15 g ZS	[redacted]	[redacted]	[redacted]	[redacted]

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Effect	Estimate	Standard Error	95% CI	Two-sided p-value
Acute Phase Baseline eGFR	[redacted]	[redacted]	[redacted]	[redacted]
Acute Phase Baseline S-K	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance Phase Baseline S-K	[redacted]	[redacted]	[redacted]	[redacted]
Age (Referent: <55)				
55-64	[redacted]	[redacted]	[redacted]	[redacted]
>=65	[redacted]	[redacted]	[redacted]	[redacted]
RAASi Use (Referent: No)	[redacted]	[redacted]	[redacted]	[redacted]
CKD (Referent: No)	[redacted]	[redacted]	[redacted]	[redacted]
CHF (Referent: No)	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes (Referent: No)	[redacted]	[redacted]	[redacted]	[redacted]

A16. **Priority question**: Company submission Section B.2.4.1.5 page 45 states that the exponential rate of change in S-K values in the acute phase of ZS-004 were derived from a mixed effect model with several covariates:

- Please provide the written mathematical equation of the full model.

Please see response to Question A15 for the full mathematical model used. The fixed and random effects for ZS-004 acute phase model are reported in the table below.

Table 7: ZS-004 acute phase: fixed and random effects

Fixed Effects	Random Effects
time baseline eGFR age category (<55, 55-64, ≥65 years) baseline RAAS inhibitor use, indicator variable for yes/no baseline chronic kidney disease status (CKD), indicator variable for yes/no baseline congestive heart failure status (CHF), indicator variable for yes/no baseline diabetes mellitus status (DM), indicator variable for yes/no	Patient

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- Selected results from this model are summarised in Table 13. Please provide the full results of the fitted model, with parameter estimates, CIs and p-values for all fitted variables (log time, baseline eGFR, CKD status, HF status, RAASi use, diabetes status, age).

Results for the first 24 and 48 hours of the acute phase of study ZS-004 are presented in Table 8 and Table 9, respectively.

Table 8: Model results for the first 24 hours

Effect	Estimate	Standard Error	95% CI	Two-sided p-value
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
TIMEPNT	[redacted]	[redacted]	[redacted]	[redacted]
Age (Referent: <55)				
55-64	[redacted]	[redacted]	[redacted]	[redacted]
>=65	[redacted]	[redacted]	[redacted]	[redacted]
RAASi Use (Referent: No)	[redacted]	[redacted]	[redacted]	[redacted]
CHF (Referent: No)	[redacted]	[redacted]	[redacted]	[redacted]
CKD (Referent: No)	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes (Referent: No)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline eGFR	[redacted]	[redacted]	[redacted]	[redacted]

Table 9: Model results for 48 hours

Effect	Estimate	Standard Error	95% CI	Two-sided p-value
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
TIMEPNT	[redacted]	[redacted]	[redacted]	[redacted]
Age (Referent: <55)				
55-64	[redacted]	[redacted]	[redacted]	[redacted]
>=65	[redacted]	[redacted]	[redacted]	[redacted]

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Effect	Estimate	Standard Error	95% CI	Two-sided p-value
RAASi Use (Referent: No)	[redacted]	[redacted]	[redacted]	[redacted]
CHF (Referent: No)	[redacted]	[redacted]	[redacted]	[redacted]
CKD (Referent: No)	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes (Referent: No)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline eGFR	[redacted]	[redacted]	[redacted]	[redacted]

A17. **Priority question**: Company submission Section B.2.4.1.5 page 45 states that S-K measurements for the extended phase of ZS-005 were analysed using logistic regression and longitudinal model.

- Please provide the written mathematical equation of the full model longitudinal model that was fitted.

Please see response to Question A15 for the full mathematical model used. The fixed and random effects for the extended phase of ZS-005 are reported in the table below.

Table 10: ZS-005 extended phase: fixed and random effects

Fixed Effects	Random Effects
acute phase baseline S-K extended phase baseline S-K baseline eGFR age category (<55, 55-64, ≥65 years) baseline RAAS inhibitor use, indicator variable for yes/no baseline chronic kidney disease status (CKD), indicator variable for yes/no baseline congestive heart failure status (CHF), indicator variable for yes/no baseline diabetes mellitus status (DM), indicator variable for yes/no	Patient

- Please provide the full results of the fitted model, with parameter estimates, CIs and p-values for all fitted variables.

Table 11: Fixed model results for the extended phase of study ZS-005

Effect	Estimate	Standard Error	95% CI	Two-sided p-value
Intercept	[redacted]	[redacted]	[redacted]	[redacted]

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Effect	Estimate	Standard Error	95% CI	Two-sided p-value
Acute Phase Baseline eGFR	[redacted]	[redacted]	[redacted]	[redacted]
Acute Phase Baseline S-K	[redacted]	[redacted]	[redacted]	[redacted]
Extended Dosing Phase Baseline S-K	[redacted]	[redacted]	[redacted]	[redacted]
Age (Referent: <55)				
55-64	[redacted]	[redacted]	[redacted]	[redacted]
>=65	[redacted]	[redacted]	[redacted]	[redacted]
RAASi Use (Referent: No)	[redacted]	[redacted]	[redacted]	[redacted]
CKD (Referent: No)	[redacted]	[redacted]	[redacted]	[redacted]
CHF (Referent: No)	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes (Referent: No)	[redacted]	[redacted]	[redacted]	[redacted]

A18. **Priority question**: Company submission appendix E page 3 states that full results of pre-planned subgroup analyses for the maintenance phase of ZS-004 “are not available from the ZS-004 Clinical Study Report, so are not presented here.” Please provide analyses for the remaining subgroups or clarify why these data are not available.

Subgroup analyses for the clinically important subgroups (subpopulation using RAASi, or having CKD, HF or diabetes) were presented as treatment group differences for the acute and maintenance phases in Appendix E for ZS-004.

Additional subgroups analyses conducted for patients with baseline eGFR <60 mL/min and acute phase baseline S-K <5.5, 5.5-<6.0, and ≥6.0 mmol/L in the maintenance phase are presented in Table 12 below. The same analyses are also presented for the 4 clinically important subgroups (subpopulation using RAASi, or having CKD, HF or diabetes) so that

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the same analyses are presented across all subgroups. All these analyses are based on small patient numbers, less than 40, in both SZC groups. No statistical tests were reported.

Table 12: ZS-004 - Additional subgroups analyses[19]

Acute Phase Baseline eGFR<60	**Placebo (N=51)**	**SZC 5 g (N=31)**	**SZC 10g (N=38)**
MP baseline mean (SD)	[redacted]	[redacted]	[redacted]
MP Day 8 mean (SD)	[redacted]	[redacted]	[redacted]
MP Day 29 mean (SD)	[redacted]	[redacted]	[redacted]
Change from MP baseline	[redacted]	[redacted]	[redacted]
Percent change from MP baseline	[redacted]	[redacted]	[redacted]
Acute phase baseline S-K < 5.5	**Placebo (N=40)**	**SZC 5 g (N=23)**	**SZC 10g (N=18)**
MP baseline mean (SD)	[redacted]	[redacted]	[redacted]
MP Day 8	[redacted]	[redacted]	[redacted]
MP Day 29	[redacted]	[redacted]	[redacted]
Change from MP baseline	[redacted]	[redacted]	[redacted]
Percent change from MP baseline	[redacted]	[redacted]	[redacted]
Acute phase baseline S-K 5.5-<6.0 mmol/L	**Placebo (N=30)**	**SZC 5 g (N=17)**	**SZC 10g (N=23)**
MP baseline mean (SD)	[redacted]	[redacted]	[redacted]
MP Day 8	[redacted]	[redacted]	[redacted]
MP Day 29	[redacted]	[redacted]	[redacted]
Change from MP baseline	[redacted]	[redacted]	[redacted]
Percent change from MP baseline	[redacted]	[redacted]	[redacted]
Acute phase baseline S-K ≥6.0 mmol/L	**Placebo (N=12)**	**SZC 5 g (N=5)**	**SZC 10g (N=9)**
MP baseline mean (SD)	[redacted]	[redacted]	[redacted]
MP Day 8	[redacted]	[redacted]	[redacted]
MP Day 29	[redacted]	[redacted]	[redacted]
Change from MP baseline	[redacted]	[redacted]	[redacted]
Percent change from MP baseline	[redacted]	[redacted]	[redacted]
Patients using RAASi	**Placebo (N=59)**	**SZC 5 g (N=33)**	**SZC 10g (N=35)**
MP baseline mean (SD)	[redacted]	[redacted]	[redacted]
MP Day 8 mean (SD)	[redacted]	[redacted]	[redacted]
MP Day 29 mean (SD)	[redacted]	[redacted]	[redacted]

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Change from MP baseline	[redacted]	[redacted]	[redacted]
Percent change from MP baseline	[redacted]	[redacted]	[redacted]
CKD	**Placebo (N=49)**	**SZC 5 g (N=29)**	**SZC 10g (N=36)**
MP baseline mean (SD)	[redacted]	[redacted]	[redacted]
MP Day 8 mean (SD)	[redacted]	[redacted]	[redacted]
MP Day 29 mean (SD)	[redacted]	[redacted]	[redacted]
Change from MP baseline	[redacted]	[redacted]	[redacted]
Percent change from MP baseline	[redacted]	[redacted]	[redacted]
HF	**Placebo (N=25)**	**SZC 5 g (N=18)**	**SZC 10g (N=18)**
MP baseline mean (SD)	[redacted]	[redacted]	[redacted]
MP Day 8 mean (SD)	[redacted]	[redacted]	[redacted]
MP Day 29 mean (SD)	[redacted]	[redacted]	[redacted]
Change from MP baseline	[redacted]	[redacted]	[redacted]
Percent change from MP baseline	[redacted]	[redacted]	[redacted]
Diabetes Mellitus	**Placebo (N=51)**	**SZC 5 g (N=26)**	**SZC 10g (N=37)**
MP baseline mean (SD)	[redacted]	[redacted]	[redacted]
MP Day 8 mean (SD)	[redacted]	[redacted]	[redacted]
MP Day 29 mean (SD)	[redacted]	[redacted]	[redacted]
Change from MP baseline	[redacted]	[redacted]	[redacted]
Percent change from MP baseline	[redacted]	[redacted]	[redacted]

Abbreviations: eGFR, estimated glomerular filtration rate; MP, maintenance phase; RAASi, renin-angiotensin-aldosterone system inhibitor; SD, Standard Deviation; S-K, Serum Potassium; SZC, Sodium Zirconium Cyclosilicate

A19. **Priority question**: Company submission page 101 states "Pooled data was used as patients in ZS-005[103] received the same treatment as those in ZS-004[99] for the first 28 days, therefore the first 28 days could be pooled across both trials patients included in the analysis received the same as per protocol dose of SZC in the acute phase (i.e. 10 g TID for 1–3 days: 2 days in ZS-004[99] and 1–3 days in ZS-005[103]) and in the maintenance phase (5 g or 10 g OD for 28 days in ZS-004[99] and 5 g once every other day, OD or 10 g OD for up to 12 months)." However, Section B.2.8, page 67 states that "the ZS-004 and ZS-005 studies cannot be deemed comparable to meta-analyse" due to the following treatment differences i) the duration of treatment in the acute phase (before randomisation) and ii) titration was allowed in the maintenance phase of ZS-005. This appears to be inconsistent, please clarify.

Given that both ZS-004 and ZS-005 trials generated data on SZC in the acute phase and in the maintenance phase up to 28 days, data was pooled and used as part of the cost

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effectiveness analysis to estimate individual patient serum potassium trajectories to increase sample size and provide more robust estimates.

A formal meta-analysis between the clinical effectiveness study endpoints of ZS-004 and ZS-005 trials was not undertaken for the reasons stated in Section B.2.8 (page 67). ZS-004 was a placebo controlled trial from entry into the maintenance phase (upon achievement of normokalaemia) and up to 28 days, where patients were then randomised to receive treatment with 5 g, 10 g, or 15 g SZC or placebo once daily, whereas ZS-005 was an open label, long term, titration study up to 52 weeks without a placebo arm. Therefore, patients in the ZS-005 group were not randomised to receive a specific dose of SZC following achievement of normokalaemia, but were all administered 5 g once daily and titrated to 10 g daily or 5 g every other day depending on S-K levels. Therefore, a meta-analysis of the data up to 28 days from these two studies was not deemed feasible due to the differences in dosing regimens (ZS-005 being a dose titration study) and due to the lack of common anchor/control arm between the two studies (ZS-005 being an open label long term safety and efficacy study).

A20. **Priority question**: Company submission page 100 states “trial-, treatment- and patient-specific S-K profiles are simulated using mixed effects regression models”

Corrections have been made to Tables 30 and 31 as depicted in Table 13 and Table 14 below, with amends highlighted in red text. All responses to ERG question A20 relate to these amended tables.

Table 13: Pre-defined S-K profile for SZC: mixed-effects model parameters

	Fixed component	Time-dependent component	Patient component ~~(SD)~~	Observation component ~~(SD)~~	Source
Day 0–3	[redacted]	[redacted]	[redacted]	[redacted]	Pooled data from ZS-004[18] and ZS-005[20]
Day 4–14	[redacted]	[redacted]	[redacted]	[redacted]	
Day 15–28	[redacted]	[redacted]	[redacted]	[redacted]	
Day >28	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: N/A, not applicable; SD, standard deviation; S-K, serum potassium; SZC, sodium zirconium cyclosilicate.

Table 14: Pre-defined S-K profile for standard care: mixed effects model parameters

	Fixed component	Time-dependent component	Patient component ~~(SD)~~	Measurement component ~~(SD)~~	Source
Day 0–3	[redacted]	[redacted]	[redacted]	[redacted]	Control arm of ZS-004[18]
Day 4–14	[redacted]	[redacted]	[redacted]	[redacted]	
Day 15–28	[redacted]	[redacted]	[redacted]	[redacted]	
Day >28	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: N/A, not applicable; SD, standard deviation; S-K, serum potassium.

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- Please provide the mathematical equation of the model that was fitted.

In the following notation:

- [redacted]

Acute phase (day 0–3), SZC and standard care

[redacted]

Maintenance phase (day 4 onwards), SZC

[redacted]

Maintenance phase (day 4 onwards), standard care

[redacted]

- Also, please provide examples of how the values in Tables 30 and 31 relate to the parameters within the potassium worksheet.

Corrections have been made to table 30 and 31 as depicted in Table 13 and Table 14 above. The estimates presented in these amended tables now directly match those reported in the potassium worksheet.

- If this model is different to the model used for the clinical-effectiveness analysis then please state the justification for this, and the anticipated effect on the data simulated in the model (e.g. is all heterogeneity accurately represented).

Statistical models were used in the clinical effectiveness analysis for the following endpoints:

- ZS-004:
    - Acute phase: exponential rate of change in (log transformed) serum potassium concentration at 48 hours following treatment
    - Maintenance phase: mean serum potassium concentration inclusive of maintenance phase study days 8 to 29
- ZS-005:
    - Extended phase: mean (log transformed) serum potassium concentration in months 3–12

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The models used in the clinical effectiveness analysis were of the same functional form as those used to estimate serum potassium trajectories, i.e. mixed effects linear regression models of serum potassium, including fixed effects representing variables of interest and a random intercept to account for intra-patient correlation in serum potassium.

Differences in the precise specification of the models are as follows:

- The models used in the clinical effectiveness analysis were fitted to log transformed serum potassium, while no transformation was taken before fitting the potassium trajectory models.
- The models used in the clinical effectiveness analysis included fixed effects to control for patient demographics and clinical characteristics, while no such control variables were included in the potassium trajectory models.

These differences in model specification arise because the models have different purposes; the models used in the clinical effectiveness analysis were intended to provide estimates for the ZS-004 and ZS-005 study endpoints, while those used to estimate potassium trajectories were required to provide specific inputs to the economic model.

When developing the potassium trajectory models, the ZS-004 and ZS-005 study data were empirically analysed with respect to:

- The need to transform serum potassium prior to modelling: no transformation was required.
- The need to include additional fixed effects to control for non-time-related factors (baseline age, sex, RAASi usage, and history of HF, CKD or diabetes): no additional control covariates improved the predictive performance of the models.

As the mixed effects models were optimised on the observed clinical trial data for the purpose of estimating serum potassium trajectories to populate the economic model, and this process involved testing for and subsequently rejecting the need to include transformations and control covariates, it is anticipated that the models are fit for purpose, and that all relevant heterogeneity has been appropriately accounted for.

- Please provide the full results of the fitted model including parameter estimates, CIs and p-values for all fitted variables, or clarify the results provided in Table 30/31, including the points below:

Model output relating to the fixed effects in each of fitted mixed effects models (i.e. estimates of the ‘fixed’ and ‘time-dependent’ components presented in tables 30 and 31 of the CS) is presented below. Standard deviations for the random effects (i.e. the ‘patient’ and ‘measurement’ components) are presented in the response to the first bullet point from the ERG above.

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Table 15: Mixed effects model inferences, acute phase (day 0–3), SZC and standard care

Variable	Estimate	95% CI	P-value
Intercept	[redacted]	[redacted]	[redacted]
Day	[redacted]	[redacted]	[redacted]

Table 16: Mixed effects model inferences, maintenance phase (day 4 onwards), SZC

Variable	Estimate	95% CI	P-value
Intercept	[redacted]	[redacted]	[redacted]
Day >28 (1/0)	[redacted]	[redacted]	[redacted]

Table 17: Mixed effects model inferences, maintenance phase (day 4 onwards), standard care

Variable	Estimate	95% CI	P-value
Intercept	[redacted]	[redacted]	[redacted]
Day >14 (1/0)	[redacted]	[redacted]	[redacted]

- Please clarify what components of the heterogeneity are captured by the observation component (Table 30) and measurement component (Table 31). Does this account for variation in the measurement process (repeated tests on the same sample may yield different results) as well as other sources of uncorrelated error in the data (for example, patient fluctuations in S-K levels)?

For both ZSC (Table 30) and standard care (Table 31): the patient component captures random variation between patients (i.e. heterogeneity in mean serum potassium concentration between patients); the measurement component captures random variation between measurements (i.e. heterogeneity in serum potassium concentration between measurements, within patients). The patient and measurement components are random residuals, capturing all sources of unobserved patient- and measurement-level heterogeneity that lead to differences between observed serum potassium concentrations and the corresponding fitted values generated by each model's linear predictor.

- Please clarify the values presented under patient component (SD) and observation observation/measurement component (SD). Do these numbers relate to different parameters used in the acute and maintenance phase? Were they estimated from fitting separate models to both phases, or in a combined model of both phases?

The values presented in the patient and observation component columns of tables 30 and 31 are transcription errors. Please refer to the amended set of tables at the beginning of the response to ERG question A20.

- Please provide all the results for (1) the entire population and (2) only in those who meet the criteria eligible for treatment (S-K >5.5 at baseline).

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All modelling outputs for (1) the entire population are presented above. Estimated serum potassium profiles and model inferences for (2) only those patents with serum potassium >5.5 mmol/L at baseline are presented below.

Table 18: S-K profile for SZC, patients with S-K >5.5 mmol/L at baseline: mixed-effects model parameters

	Fixed component	Time-dependent component	Patient component	Observation component	Source
Day 0–3	[redacted]	[redacted]	[redacted]	[redacted]	Pooled data from ZS-004 and ZS-005
Day 4–14	[redacted]	[redacted]	[redacted]	[redacted]	
Day 15–28	[redacted]	[redacted]	[redacted]	[redacted]	
Day >28	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: N/A, not applicable; SD, standard deviation; S-K, serum potassium; SZC, sodium zirconium cyclosilicate.

Table 19: S-K profile for standard care, patients with S-K >5.5 mmol/L at baseline: mixed effects model parameters

	Fixed component	Time-dependent component	Patient component	Measurement component	Source
Day 0–3	[redacted]	[redacted]	[redacted]	[redacted]	Control arm of ZS-004
Day 4–14	[redacted]	[redacted]	[redacted]	[redacted]	
Day 15–28	[redacted]	[redacted]	[redacted]	[redacted]	
Day >28	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: N/A, not applicable; SD, standard deviation; S-K, serum potassium.

Table 20: Mixed effects model inferences, acute phase (day 0–3), SZC and standard care, patients with S-K >5.5 mmol/L at baseline

Variable	Estimate	95% CI	P-value
Intercept	[redacted]	[redacted]	[redacted]
Day	[redacted]	[redacted]	[redacted]

Table 21: Mixed effects model inferences, maintenance phase (day 4 onwards), SZC, patients with S-K >5.5 mmol/L at baseline

Variable	Estimate	95% CI	P-value
Intercept	[redacted]	[redacted]	[redacted]
Day >28 (1/0)	[redacted]	[redacted]	[redacted]

Table 22: Mixed effects model inferences, maintenance phase (day 4 onwards), standard care, patients with S-K >5.5 mmol/L at baseline

Variable	Estimate	95% CI	P-value
Intercept	[redacted]	[redacted]	[redacted]
Day >14 (1/0)	[redacted]	[redacted]	[redacted]

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A21. CS Section B.2.8 page 67.

- The CS states that the ZS-003 trial population is not consistent and generalisable to UK clinical management of patients with HK and CKD or HF due to approximately three-quarters of patients having a baseline S-K level < 5.5 mmol/L. However, ZS-004 also had a considerable proportion of patients with baseline S-K <5.5%. Perform a meta-analysis using data at 28 days (or close to it) from randomisation to the maintenance phase of ZS-005, ZS-003 and ZS-004 using just the subgroup of patients with S-K level >5.5% mmol/L.

Due to the reasons outlined in our response to Question A6 above, AstraZeneca do not consider it relevant to include study ZS-003 in the model, as the trial population is not relevant to the current decision problem. Furthermore, study ZS-003 has been superseded by ZS-004 and ZS-005 which have longer study durations, a larger patient population, a significant number of patients relevant to the decision problem (i.e. with S-K levels ≥5.5 mmol/L), and have a dosing regimen aligned with the licensed dose for SZC.[1]

Section B: Clarification on cost-effectiveness data

Following the correction of the VBA coding errors as highlighted by the ERG in B7, B8, and B9, the base case ICER of SZC decreased from £21,835 to £21,606 in the chronic setting, whilst SCZ remained dominant in the acute setting. A comparison of the submitted and updated cost-effectiveness results is presented in Table 23.

All the scenario analyses presented in Section B below incorporate the VBA coding corrections highlighted by the ERG in B7, B8 and B9. The results from the scenario analyses are presented alongside the updated base case ICER throughout Section B.

Table 23. Base case cost-effectiveness results based on a cohort of 60,000 patients

Scenario	ICER (incremental costs, incremental QALYs)	
	Chronic setting	Acute setting
Base case in CS	£21,835 (£16,688, 0.764 QALYs)	Dominates (£-1,060, 0.049 QALYs)
Updated base case with VBA coding corrections	£21,606 (£16,543, 0.766 QALYs)	Dominates (£-997, 0.049 QALYs)

B1. **Priority question**: As stated on p26 of the company submission NICE Guidelines for CKD state that RAASi should be stopped if the S-K level increases to ≥6.0 mmol/L. The model assumes in the chronic phase that NICE guidance is not followed for patients treated with SZC as all remain on RAASi treatment. Please provide a scenario analysis where patients on SZC treatment with an S-K level ≥6.0 mmol/L have RAASi treatment discontinued.

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RAASi therapies are the mainstay treatment for patients with HF or CKD due to their cardio-renal protective effects and proven reduction in the risk of mortality and morbidity.[2,13,21-23] As such, RAASi therapy is widely used in the UK, and treatment is recommended by clinical guidelines and consensus statements, including those published by NICE, European Society of Cardiology – Heart Failure (ESC-HF) and British Society for Heart Failure.[13,24,25] However, since RAASi therapy is associated with an increase in S-K potassium levels, RAASi-induced hyperkalaemia results in clinicians often having to make the difficult decision to down-titrate their patients' RAASi medication or discontinue treatment completely. This offsets the cardio-renal and survival benefits offered by these therapies, but down-titration/discontinuation is often required to reduce the risk of adverse outcomes associated with hyperkalaemia.[26,27] Due to the distinct lack of alternative pharmacological interventions for the management of hyperkalaemia, down-titration and/or discontinuation of RAASi therapy for the management of hyperkalaemia is supported by UK, European, and International guidelines, and clinical experts advised that this approach is often adopted in UK clinical practice.[11] However, stopping or reducing RAASi therapy in at-risk populations (e.g. patients with CKD or HF) is associated with significantly worse outcomes compared to RAASi continuation on maximal dose. For example, a study published in 2015 reported that patients who receive a sub-optimal dose of RAASi or discontinue RAASi therapy are at an increased risk of CKD progression, stroke and acute myocardial infarction, coronary artery bypass, and all-cause mortality compared with those on optimal dosing regimens.[27] This was further supported by a European study in 2017 that reached similar conclusions.[28] In addition, a landmark study (RALES) demonstrated that a further 30% reduction in the risk of death can be achieved when RAASi therapy is combined with an MRA.[26]

As discussed in the CS, there is a paucity of treatment options for the management of patients in the chronic setting, with management limited to down-titration or discontinuation of RAASi therapy and implementation of a low-potassium diet. Therefore, clinicians are currently faced with a dilemma, where they can either wait to alter RAASi therapy; thereby exposing patients to an increased risk of death, hospitalisation or MACE due to hyperkalaemia, or reduce their RAASi therapy and lose the cardio-renal protective effects offered by RAASi therapies.

Clinical experts advised that there is a great need to introduce an effective, and well-tolerated pharmacological intervention to optimise the treatment of hyperkalaemia without the need to alter RAASi medication. Feedback from experts in Cardiology, Nephrology, and A&E suggested that the introduction of SZC would offer an alternative treatment option which would alleviate the limitations with current treatment options. It is proposed that SZC would be prescribed to manage hyperkalaemia whilst maintaining or optimising RAASi therapy; thereby ensuring that patients still accrue the cardio-renal protective benefits of RAASi therapy.[11] Therefore, the introduction of SZC would be a step-change in the current treatment pathway. As such, AstraZeneca believe that complete discontinuation of RAASi in patients treated with SZC would not reflect UK clinical practice and therefore this has not been presented. However, a scenario where RAASi is discontinued for a short period of time is presented below.

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For both the SZC and the control arm, provide analyses where RAASi treatment would be withheld for a short period of time in patients with an S-K level ≥6.0 mmol/L, with resumption if the S-K level of a patient fell below 6.0 mmol/L and discontinuation otherwise. If the model is amended provide full details of the changes.

Current treatment guidelines recommend that RAASi therapy is to be discontinued in patients with S-K ≥6.0 mmol/L. However, down-titration/discontinuation of RAASi therapy results in patients no longer benefiting from the cardio-renal protective effects of RAASi. In addition, despite being recommended for use, RAASi therapy is unfortunately seldom re-instated following an episode of hyperkalaemia at or after discharge even if a clear precipitating cause of hyperkalaemia was detected and eliminated.[29] Therefore, UK clinical experts and the European Society of Cardiology consensus statement recommends that therapies, such as SZC, aimed at lowering potassium levels and enabling patients to continue RAASi therapy should be considered.[11,29] In addition, UK clinical experts indicated that the availability of potassium binders, such as SZC would mitigate the need to alter RAASi therapy; particularly due to the fast time to onset, with SZC reducing S-K by 0.2, 0.5 and 0.7 mmol/L within 1,2 and 4 hours, respectively, and 84% of patients being normalised within 24 hours.[18] Therefore, whilst the scenario may be clinically relevant, we anticipate that alterations to RAASi therapy will only be made in a minority of patients treated with SZC in UK clinical practice, with the introduction of SZC resulting in a step change in the management of hyperkalaemia. A summary of ICER is shown in Table 24.

This scenario analysis has been included in the "all relevant" scenario in response to B25, but it has not been included in the new base case presented in B25.

Table 24: Scenario analysis results B1

Scenario	ICER (incremental costs, incremental QALYs)	
	Chronic setting	Acute setting
Updated base case (RAASi not stopped in SZC patients)	£21,606 (£16,543, 0.766 QALYs)	Dominates (£-997, 0.049 QALYs)
B1. Scenario analysis (RAASi treatment is withheld for 12 weeks for SZC patients with an S-K level ≥6.0 mmol/L before they all restart at max RAASi)	£22,851 (£16,590, 0.726 QALYs)	N/A

B2. **Priority question**: Please provide a scenario analysis where SZC treatment is only initiated in patients with an S-K level of ≥6.0 mmol/L. Within these analyses allow RAASi treatment to be withheld in patients with an S-K level ≥6.0 mmol/L for a short period of time with resumption if the S-K level fell below 6.0 mmol/L and discontinuation otherwise.

There is significant burden of disease associated with HK both in terms of increased patient morbidity and mortality. Across different patient groups, such as patients with CKD or HF,

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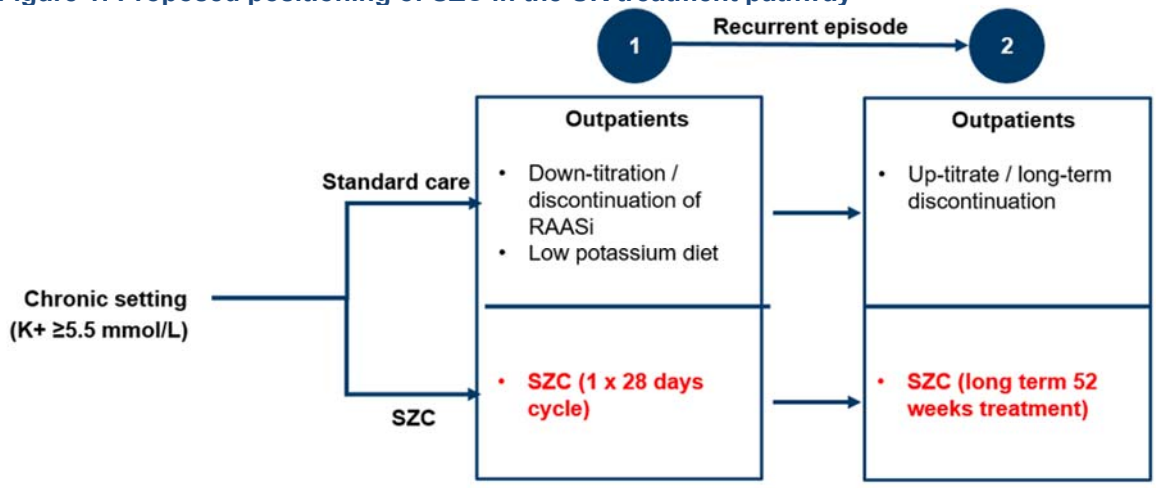
the risk of adverse clinical outcomes, such as major cardiovascular events (MACE) or mortality, has been shown to follow a 'U-shaped' association in which the risk of an event increases at the more extreme S-K levels.[30,31-33] For example, the risk of death is increased by 60% and 231% in patients with CKD who have a S-K of 5.5–5.9 and ≥6.0 mmol/L, respectively, compared with those with S-K 4.5–4.9 mmol/L.[30]

Due to the risk of RAASi-induced hyperkalaemia, UK, European, and International guidelines recommend that treatment with RAASi therapy is either not initiated, used with caution, down-titrated or discontinued; with alterations to therapy generally recommended in patients with S-K ≥5.5 mmol/L.[12,13,24] In patients with S-K ≥5.0 mmol/L NICE clinical guidelines (CG182) recommend that RAASi therapy is not initiated, and the Kidney Disease Outcomes Quality Initiative (KDOQI) recommend down-titrating RAASi therapy by 50%, and complete discontinuation if normokalaemia is not restored.[12,24]. If S-K is ≥5.5 mmol/L, KDOQI guidelines recommend that RAASi therapy should be used with caution, and the European Society of Cardiology Heart Failure guidelines recommend that therapy should be down-titrated. In patients with S-K ≥6.0 mmol, NICE recommend complete discontinuation of RAASi therapy. In UK clinical practice, expert clinical opinion from Cardiologists, Nephrologists, and A&E consultants confirmed that these guidelines are generally followed, and decisions to down-titrate or discontinue are typically made when S-K levels reach ≥5.5 mmol/L.[11] As such, the positioning of SZC in the treatment pathway (see Figure 1 below) to initiate treatment in patients with S-K ≥5.5 mmol/L is based on clinical expert opinion and relevant UK and European guidance on the management of hyperkalaemia. Therefore, a scenario where treatment is not initiated until S-K reaches ≥6.0 mmol/L is not aligned with clinical guidelines, or UK clinical practice, and as such this scenario has not been provided. Furthermore, the European Society of Cardiology consensus statement recommends that therapies aimed at lowering potassium levels and enabling patients to continue RAASi therapy should be considered, and that a similar approach is currently implemented in other fields of medicine (e.g. oncology where antiemetics are used to enable use of cancer therapy).[29]

Figure 1: Proposed positioning of SZC in the UK treatment pathway



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B3. **Priority question**: Provide an analyses for the 'acute population' where the time horizon is 28 days. If possible, incorporate the longer-term consequences of differential mortality rates within the 28-day period via the use of additional estimated QALY gains and costs so that SZC is not disadvantaged. Please provide details of how this analysis is performed.

The results from a scenario analysis of patients in the acute setting, using a time horizon of 28 days are presented in Table 25. As expected, the incremental costs and incremental QALYs are smaller compared to the base case, as there is less time in the scenario analysis to accrue the cost savings and health benefits associated with SZC. Nevertheless, SZC still dominates standard care, even when only short-term costs and benefits are considered.

Due to time constraints, AstraZeneca has not been able to reprogram the model to incorporate the longer-term consequences of differential mortality rates within the 28-day time horizon of the scenario analyses. The exclusion of longer-term consequences from the scenario analysis presented in Table 25 is conservative with respect to SZC. Inclusion of long-term consequences would contribute to the robustness of the dominant result, as SZC would most definitively be associated with greater health benefits in the scenario analysis requested by the ERG compared to the scenario analysis presented in Table 25.

Table 25. Scenario analysis results B3

Scenario	ICER (incremental costs, incremental QALYs)	
	Chronic setting	Acute setting
Update base case (time horizon for the acute setting is lifetime)	N/A	Dominates (-£997, 0.049 QALYs)
B3. Scenario analysis (time horizon for the acute setting is 28 day)	N/A	Dominates (-£10, 0.007 QALYs)

B4. **Priority question**: Please clarify why the values reported in Table 30 of the company submission for SZC treatment do not match those in the model (Potassium worksheet [cells D9:G9]). If the model is incorrect, please amend. If Table 30 is incorrect please provide a scenario analysis where the value for treatment at Day 29+ is [redacted], rather than [redacted]. Comment on the clinical plausibility of the change from [redacted] to [redacted] after day 29 compared with the probability that this is an artefact due to changes in the data sets being used to estimate the values.

As per our response to questions A20, the mixed effects model parameters in Table 30 and Table 31 of the CS are incorrect, but the values used in the model are correct.

AstraZeneca do not believe the change from [redacted] (Day 15–28) to [redacted] (Day >28) in the fixed effect model based on pooled data is an artefact due to the different study durations of ZS-004 and ZS-005, since the decrease in S-K levels from Day 15–28 to

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Day >28 is also observed in the mixed effect model based on data from ZS-005 data only (see Table 26).

From a clinical plausibility perspective, the observed decrease in the S-K level between Day 15–28 to Day >28 may be explained by the discontinuation of SZC in a small proportion of patients prior to day 29. As the patients who discontinue may have been clinically different to those who discontinued treatment, the S-K profile fixed component for Day >28 could therefore be expected to be different to the fixed component for Day 15–28. The use of these results from the fixed effect model in the economic analysis, in combination with treatment discontinuation, would therefore be reflective of the S-K profile evolution of on-treatment patients in Day 15–28 and Day >28.

Table 26. Pre-defined S-K profile for SZC: mixed-effects model parameters

Day	Fixed component	Time-dependent component	Patient component (SD)	Observation component (SD)	Source
Day 0–3	[redacted]	[redacted]	[redacted]	[redacted]	ZS-005
Day 4–14	[redacted]	[redacted]	[redacted]	[redacted]	
Day 15–28	[redacted]	[redacted]	[redacted]	[redacted]	
Day >28	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: N/A, not applicable; SD, standard deviation; S-K, serum potassium; SZC, sodium zirconium cyclosilicate.

To address the ERG's question in full, scenario analyses were carried out to investigate the impact of applying the same fixed component value, either [redacted] to [redacted], to Day 15–28 and Day >28. The results of these scenario analyses show the selected fixed component value to have a minor impact on the ICER (Table 27).

Nevertheless, based on the explanation above, AstraZeneca believe it is appropriate to apply the values from the fixed effect model based on the ZS-004 and ZS-005 pooled data, and that the observed decrease in S-K levels between Day 15–28 and Day >28 is clinically plausible.

The more conservative scenario analysis A (Table 27) has been included in the "all relevant" scenario in response to B25, but it has not been included in the new base case presented in B25.

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Table 27. Scenario analyses results B4

Scenario	ICER (incremental costs, incremental QALYs)	
	Chronic setting	Acute setting
Updated base case (ZS-004 & ZS-005 pooled data: S-K value of 4.753 is used at Day 15-28 and S-K value of [redacted] is used at Day 29+)	£21,606 (£16,543, 0.766 QALYs)	Dominates (£-997, 0.049 QALYs)
B4. Scenario analysis A (S-K value of [redacted] is used at Day 15-28 and at Day 29+)	£22,749 (£16,506, 0.726 QALYs)	Dominates (£-975, 0.044 QALYs)
B4. Scenario analysis B (S-K value of [redacted] is used at Day 15-28 and at Day 29+)	£21,595 (£16,551, 0.766 QALYs)	Dominates (£-986, 0.050 QALYs)

B5. **Priority question**: Clarify whether the model assumes that all of the observational/measurement component (Tables 30 and 31) is patient fluctuation and that there is no measurement error. Clinical advice suggests that tests (bloods and ECG) are undertaken in hospitals to verify the community test result, due to measurement error. Please discuss the likely biases in the ICER that would be caused by assuming no measurement error.

The majority of S-K measurements in the target population are likely to occur in the hospital rather than in the community, and the measurements that occur in the community are routinely repeated once the patient attends the hospital. In addition, S-K measurement in hospitals are usually carried out using point-of-care tests, due to the urgent need to identify life-threatening hyperkalaemia and the need to administer emergency treatment early as per the UK Renal Association guidelines. In addition, blood draws for laboratory analyses are subject to pseudohyperkalaemic results when there is a delay between taking the blood sample and analysing in the lab. As such, S-K measurement errors are expected to be small.

The mixed effect models used to estimate S-K trajectories in the model account for a patient-specific random effect (sampled on Day 0 and Day 4) and a measurement/observation-specific random effect (sampled each time a measurement is drawn). The use of both a patient-specific effect and a measurement-specific effect ensures that measurements taken from the same patient are more likely to be similar than measurements taken from different patients.

The fixed effect models applied in the economic evaluation does not explicitly take measurement errors into account. The lack of measurement error in the model means that it is assumed there are no false positive test results (when patients below the treatment threshold are incorrectly treated) or false negative test results (when patients above the treatment threshold are incorrectly omitted from treatment).

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The SZC treatment threshold in the chronic setting was altered as a proxy in a scenario analysis to estimate the impact of including false positive and false negative test results. By decreasing the SZC treatment threshold in the chronic setting from ≥5.5 mmol/L to ≥5.4 mmol/L, a measurement error of -0.1 mmol/L is introduced to all measurements to represent the impact of false positive test results. Similarly, the impact of false negative test results was investigated by increasing the SZC treatment threshold to ≥5.6 mmol/L in the chronic setting.

Based on the scenario analyses outlined in Table 27, the inclusion of measurement error in the model is expected to only have a small impact on the ICER compared to the base case. The results of the scenario analyses suggest that the cost associated with false positive and false negative results is small.

Finally, it could be argued that the impact of measurement error may to some extent already have been indirectly accounted for, as the S-K measurements in clinical trials inherently contained a degree of measurement error. Therefore, to avoid double-counting it is reasonable to exclude explicit consideration of measurement errors in the model.

In summary, AstraZeneca do not believe that it would be reasonable to explicitly include measurement error in the model. Even if measurement error was to be included, the impact on the ICER would be minimal.

Table 28. Scenario analyses results B5

Scenario	ICER (incremental costs, incremental QALYs)
	Chronic setting
Updated base case (no measurement error; patients treated at S-K ≥5.5 mmol/L in the chronic setting)	£21,606 (£16,543, 0.766 QALYs)
B5. Scenario analysis A (false positive test results included in the model; patients treated at S-K ≥5.4 in the chronic setting)	£22,622 (£17,846, 0.789 QALYs)
B5. Scenario analysis B (false negative test results included in the model; patients treated at S-K ≥5.6 in the chronic setting)	£20,499 (£14,957, 0.730 QALYs)

B6. **Priority question**: Clarify the clinical plausibility that the costs associated with unused doses of SZC can be recouped. Please provide sensitivity analyses where these costs are not recouped and drug wastage is assumed.

Both the 5 g and the 10 g formulations of SZC can be prescribed in pack sizes of 3 sachets or 30 sachets. In clinical practice, there would be minimal wastage associated with SZC as the 3-sachets pack lasts for one full day during the correction phase (multiple 3-sachets

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packs may be used if the correction phase lasts for more than 1 day), and as the 30-sachets packs is prescribed as continuous cycles in the maintenance phase. A maximum wastage of one 30-sachets pack would be incurred if patients die within a SZC treatment cycle. The SZC usage and associated wastage assumptions in the base case are outlined in Table 29.

As per the ERG's request, a scenario analysis with wastage assumptions have been conducted to conservatively incorporate the cost of wastage (scenario analysis A) from cycle 2 onwards (scenario analysis A, Table 29). Wastage is incurred based on the assumption that a proportion of patients use 1 sachet only of the 3-sachet packs in cycle 2 and 3 (1 day cycles). Costs for cycle 4 and cycle 5 (25 days in total) are added at the start of cycle 4 as one pack of 30-sachets. From cycle 6 onwards (28 days per cycle), treatment costs are added at the start of each cycle as one pack of 30-sachets, leading to a 2 sachet wastage in each 28-day cycle.

The assumptions applied in scenario analysis A are highly conservative, as patients who achieve normokalaemia following Day 1 or Day 2 would immediately be prescribed with a 30-sachets pack in clinical practice, rather than incur costs and wastage associated with the use of 3-sachets packs on Day 2 and Day 3 (see Table 29). Additionally, no wastage is expected in clinical practice once the maintenance phase has begun (cycle 5 onwards in the model), as the SZC treatment cycles are continuous and patients would only incur the cost of a new pack of SZC once the previous pack has been fully consumed. The only exception to this is if a patient dies within a SZC treatment cycle, in which case the cost of the ongoing treatment cycle cannot be recouped.

A more realistic scenario analysis, scenario analysis B, was also conducted. In scenario analysis B, the wastage assumption for cycle 2–5 are identical to those in scenario analysis A. However, from cycle 6 onwards in scenario analysis B, each patient incurs the cost of 28-sachets at the start of each cycle instead of a full pack of 30-sachets. The effect of incurring the cost of 28-sachets instead of a 30-sachet pack in this scenario is to avoid the artefact of 2 sachets wasted in each cycle, whilst still accounting for wastage associated with death or discontinuation within a cycle.

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Table 29: Wastage assumed in scenario analysis B6

Day/Cycle	SZC usage based on ZS-005	Cost incurred in the base case	Cost incurred in scenario analysis A	Cost incurred in scenario analysis B
Day 1 / Cycle 1	• 100% of patients receive 3 sachets of 10 g	• 3 sachets [10 g/sachet] (no wastage)	• 1 pack of 3-sachets [10 g/sachet] (no wastage)	• 1 pack of 3-sachets [10 g/sachet] (no wastage)
Day 2 / Cycle 2	• 82.2% of patients receive 1 sachet of 5 g • 0.1% of patients receive 1 sachet of 10 g • 17.7% of patients receive 3 sachets of 10 g	• 82.2% of patients: 1 sachet [5 g/sachet] (no wastage) • 0.1% of patients: 1 sachet [10 g/sachet] (no wastage) • 17.7% of patients: 3 sachets [10 g/sachet] (no wastage)	• 82.2% of patients: 1 pack of 3-sachets [5 g/sachet] (2 sachets wasted†) • 0.1% of patients: 1 pack of 3-sachets [10 g/sachet] (2 sachets wasted†) • 17.7% of patients: 1 pack of 3-sachets [10 g/sachet] (no wastage)	• 82.2% of patients: 1 pack of 3-sachets [5 g/sachet] (2 sachets wasted†) • 0.1% of patients: 1 pack of 3-sachets [10 g/sachet] (2 sachets wasted†) • 17.7% of patients: 1 pack of 3-sachets [10 g/sachet] (no wastage)
Day 3 / Cycle 3	• 96.1% of patients receive 1 sachet of 5 g • 0.1% of patients receive 1 sachet of 10 g • 3.8% of patients receive 3 sachets of 10 g	• 96.1% of patients: 1 sachet [5 g/sachet] (no wastage) • 0.1% of patients: 1 sachet [10 g/sachet] (no wastage) • 3.8% of patients: 3 sachets [10 g/sachet] (no wastage)	• 96.1% of patients: 1 pack of 3-sachets [5 g/sachet] (2 sachets wasted†) • 0.1% of patients: 1 pack of 3-sachets [10 g/sachet] (2 sachets wasted†) • 3.8% of patients: 1 pack of 3-sachets [10 g/sachet] (no wastage)	• 96.1% of patients: 1 pack of 3-sachets [5 g/sachet] (2 sachets wasted†) • 0.1% of patients: 1 pack of 3-sachets [10 g/sachet] (2 sachets wasted†) • 3.8% of patients: 1 pack of 3-sachets [10 g/sachet] (no wastage)
Day 4–28 / Cycle 4 and 5	• 61.7% of patients receive 5 g daily (25 days) • 0.9% of patients receive 5 g every other day (13 days) • 37.4% of patients receive 10 g daily (25 days)	• 61.7% of patients: 25 sachets [5 g/sachet] (no wastage) • 0.9% of patients: 12.5 sachets [5 g/sachet] (no wastage) • 37.4% of patients: 25 sachets [10 g/sachet] (no wastage)	• 61.7% of patients: 1 pack of 30-sachets [5 g/sachet] (5 sachets wasted‡) • 0.9% of patients: 1 pack of 30-sachets [5 g/sachet] (17 sachets wasted‡)	• 61.7% of patients: 1 pack of 30-sachets [5 g/sachet] (5 sachets wasted‡) • 0.9% of patients: 1 pack of 30-sachets [5 g/sachet] (17 sachets wasted‡)

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Day/Cycle	SZC usage based on ZS-005	Cost incurred in the base case	Cost incurred in scenario analysis A	Cost incurred in scenario analysis B
			• 37.4% of patients: 1 pack of 30-sachets [10 g/sachet] (5 sachets wasted‡)	• 37.4% of patients: 1 pack of 30-sachets [10 g/sachet] (5 sachets wasted‡)
Day >29 / Cycle 6 onwards	• 61.7% of patients receive 5 g daily (28 days) • 0.9% of patients receive 5 g every other day (14 days) • 37.4% of patients receive 10 g daily (28 days)	• 61.7% of patients: 28 sachets [5 g/sachet] (no wastage) • 0.9% of patients: 14 sachets [5 g/sachet] (no wastage) • 37.4% of patients: 28 sachets [10 g/sachet] (no wastage)	• 61.7% of patients: 1 pack of 30-sachets [5 g/sachet] (2 sachets wasted‡) • 0.9% of patients: 1 pack of 30-sachets every other cycle [5 g/sachet] (2 sachets wasted every other cycle‡) • 37.4% of patients: 1 pack of 30-sachets [10 g/sachet] (2 sachets wasted‡)	• 61.7% of patients: 1 pack of 28-sachets [5 g/sachet] (no wastage) • 0.9% of patients: 1 pack of 28-sachets every other cycle [5 g/sachet] (no wastage) • 37.4% of patients: 1 pack of 28-sachets [10 g/sachet] (no wastage)

† In clinical practice, these patients would be prescribed with a 30-sachet pack and initiate maintenance phase treatment without incurring this wastage. As such, this assumption is conservative with respect to SCZ.

‡ In clinical practice, maintenance cycles are continuous and therefore there is no routine wastage unless the patient dies within a treatment cycle. As such, this association is conservative with respect to SZC.

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The results of the scenario analyses with explicit wastage assumptions are presented in Table 30, demonstrating the alternative wastage assumptions to have a minimal impact on the ICER.

Whilst AstraZeneca acknowledge that wastage was not been fully accounted for in the base case, AstraZeneca believe scenario analysis A to be overly conservative. The additional scenario analysis B is likely to be more realistic for cycle 6 onwards, whilst the conservative assumptions for cycle 2-5 are still applied.

Scenario analysis B has been included in the "all relevant" scenario in response to B25, and it has also been included in the new base case presented in B25.

Table 30. Scenario analysis results B6

Scenario	ICER (incremental costs, incremental QALYs)	
	Chronic setting	Acute setting
Updated base case (no wastage)	£21,606 (£16,543, 0.766 QALYs)	Dominates (£-997, 0.049 QALYs)
B6. Scenario analysis A (with wastage from cycle 2 onwards)	£23,283 (£17,826, 0.766 QALYs)	Dominates (£-753, 0.049 QALYs)
B6. Scenario analysis B (with wastage in cycle 2–5 only)	£21,930 (£16,791, 0.766 QALYs)	Dominates (£-856, 0.049 QALYs)

B7. **Priority question**: Please clarify whether there is a coding error in the common parameters subroutine. It is believed that:

For i = 1 To 5

dbl_arrAnnRate_CKD_CVDbyEGFR(i) = vnt_arrRiskParams(i + 15, 1)

Should be

For i = 1 To 5

dbl_arrAnnRate_CKD_CVDbyEGFR(i) = vnt_arrRiskParams(i + 1**3**, 1)

A coding error was indeed made. This has been corrected and all analyses provided in this response document have been conducted with the correction. The impact of this change on the cost-effectiveness of SZC is minimal, with the base case ICER decreasing from £21,835 to £21,606 per QALY in the chronic setting and remaining dominant in the acute setting.

This correction has been included in the "all relevant" scenario in response to B25, as well as in the new base case presented in B25.

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Table 31. Results following correction B7

Scenario	ICER (incremental costs, incremental QALYs)	
	Chronic setting	Acute setting
Base case in CS	£21,835 (£16,688, 0.764 QALYs)	Dominates (£-1,060, 0.049 QALYs)
B7. Correction (coding error corrected – this is the updated base case)	£21,606 (£16,543, 0.766 QALYs)	Dominates (£-997, 0.049 QALYs)

B8. **Priority question**: Please clarify whether in the EvaluteKThresholds subroutine the costs being incremented by 1 is a coding error

For example, why is the code:

dbl_arrCostAcuteHK(cycle) = dbl_arrCostAcuteHK(cycle) + dbl_cAcuteHKHigh **+ 1**?

A coding error was indeed made. The code was an error checking code that was not removed and so does not affect the ICER of either setting. This has been corrected.

B9. **Priority question**: Please clarify whether in the fnc_cycleProbACdeath Function cycle weeks being passed as a long rather than a double is a coding error.

A coding error was indeed made. This has been corrected but it has no effect on the ICER.

B10. **Priority question**: Please clarify whether the modelled patients can have both HF and CKD. If not, provide all results separately for the two populations.

The model is not set-up to assess the cost-effectiveness of SZC in patients who have both CKD and HF as there is no data available for this population. Patients with CKD or HF have a progressive disease affecting potassium homeostasis, and are therefore at an increased risk of developing hyperkalaemia. In addition, RAASi therapies are cornerstone treatments prescribed to these patient populations due to their proven cardio-renal protective effects.[29] However, RAASi therapy is often associated with RAASi-induced hyperkalaemia; further exposing this population to an elevated risk of developing the condition. As such, it is clinically relevant to model the treatment of both patient populations, and to determine the cost-effectiveness of treating these patients based on the proportions of CKD and HF patients that present in UK clinical practice with hyperkalaemia. The population included in the model for the base case analysis comprises of patients with CKD (64.3%) or HF (35.7%). These proportions are based on trial data and are representative of the proportions of patients with CKD or HF in UK clinical practice.

Results for the CKD population alone and the HF population alone are presented in the response to question B25 where all the amendments requested are integrated simultaneously.

B11 Please provide an analysis where the maximum dose of RAASi is continued in patients with S-K levels <6.0 mmol/L who are treated with standard of care. That is, the proportion of patients who down-titrate or discontinue are both zero.

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UK, European, and International clinical guidelines recommend cautious or no use of RAASi therapy in patients with S-K levels ≥5 mmol/L, and that down-titration or discontinuation should be implemented if levels increase ≥5.5 mmol/L and ≥6.0 mmol/L, respectively.[12,13,24] In addition, elevated S-K is associated with a significantly increased risk of death, MACE, and hospitalisation,[30,31-33] and therefore there is a need to treat patients earlier, and in line with best-practice. Furthermore, UK clinicians confirmed that RAASi therapy is down-titrated or discontinued when S-K levels are ≥5.5 mmol/L.[11] As the approach suggested in the proposed scenario does not reflect UK clinical practice, AstraZeneca have not provided the results of this analysis.

Please see the response to Question B2 for further information on the current management of patients with hyperkalaemia.

B12. Clarify the rationale for setting the value for the hazard ratio for survival in HF to 1.0 in the model (AA114 in 'Inputs 2') rather than using the value of 1.1 from Table 46 in the company submission. The approach is inconsistent with that taken elsewhere in the modelling, for example in AA122 where a value of 1.01 (Table 44) is used. Please provide sensitivity analyses using a value of 1.1 for AA114.

The hazard ratio of 1.1 was not statistically significant, which would normally mean that the null hypothesis cannot be rejected and a hazard ratio of 1.0 is more appropriate. However, as it is standard practice to accept sensitivity analysis to be more useful than inferential statistics in investigating uncertainty in economic evaluations, we agree that a hazard ratio of 1.1 for survival in HF would have been a more appropriate value to use in the model. The change in ICER is extremely small as presented in Table 32.

This scenario analysis has been included in the "all relevant" scenario in response to B25, and it has also been included in the new base case presented in B25.

Table 32. Scenario analysis results B12

Scenario	ICER (incremental costs, incremental QALYs)	
	Chronic setting	Acute setting
Updated base case (using hazard ratio for survival in HF equal to 1.0)	£21,606 (£16,543, 0.766 QALYs)	Dominates (£-997, 0.049 QALYs)
B12. Scenario analysis (using hazard ratio for survival in HF equal to 1.1)	£21,691 (£16,506, 0.761 QALYs)	Dominates (-£997, 0.049 QALYs)

B13. Clarify the rationale for why there are many variables within the model (for example, all of those contained within the 'Inputs 2' sheet) that appear not to be included in the probabilistic sensitivity analysis (PSA). Please provide a table showing which variables are included in and excluded from the PSA.

The only variables that were not included are those for parameters that define the scenarios and those which are correlated with each other because the covariance matrix is not available. The variables included and excluded from the PSA are provided in Appendix 1.

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B14. Please clarify how the one-way sensitivity analysis for proportions in NYHA groups (company submission, Table 70) is implemented as the current text is not clear.

The lower and upper bound of the one-way sensitivity analyses conducted to test the sensitivity of the model to the proportions of patients in each NYHA class are outlined in Table 33.

Table 33. One-way sensitivity analyses inputs for the baseline NYHA class distribution

Parameter	Base case inputs	OWSA inputs	
		Lower bound	Upper bound
Baseline NYHA class distribution	10% NYHA I 10% NYHA II 43% NYHA III 37% NYHA IV	100% NYHA I (0% for NYHA II, III and IV)	100% NYHA IV (0% for NYHA I, II, III)

B15. Please clarify why patients cannot have multiple experiences of the same adverse event. Provide further detail of why there are 13 cycles for intervention and only 1 for standard of care. For both parts provide additional text to that in Table 74 and page 95. We note that the cycle lengths are the same for SZC treatment and standard of care.

Costs and disutilities associated with AEs are applied to the model, by adding the population average costs and disutilities associated AEs to each simulated patient. The proportions of patients who experience each AE during the 52-week extended dosing phase of ZS-005 and the proportions of patients who experience each AE during the 3-day study by Nasir et al. 2014 are used to calculate the population average costs and disutilities in the SZC arm and the standard care setting, respectively. Therefore, the population average AE costs and disutilities reflect the duration of SZC treatment (52 weeks) and standard care treatment (3 days). Because no pharmacological intervention is used in the standard care arm for chronic treatment of HK patients, no AE costs and disutilities are incurred by standard care patients this this setting.

The model assumes AEs to last for the full 52-week (13 cycles) treatment duration for the SZC arm in the model. As such, the population average 52-week AE costs and disutilities associated with SCZ are divided by 13 before they are applied to each of the 13 on-treatment cycles in the SZC arm. In contrast, as the treatment duration of standard care is 3 days only (in the acute setting and for severe recurrent HK events), the full population average 3-day AE costs and disutilities associated with standard care is applied in one single cycle (as the cycle length exceeds 3 days). No AEs are applied in the standard care arm in the chronic setting as no pharmacological interventions are used (except during severe recurrent HK events).

As the treatment duration for SZC (52 weeks) is significantly longer than for standard care (3 days), the assumption that AEs lasts for the full treatment period is conservative with respect to SZC. This is because certain AEs which are reasonably easy to resolve (for example, constipation) are assumed to last for the full duration of treatment, contributing to more AE costs and disutilities than would be expected in clinical practice.

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The AE assumptions in the model already conservatively account for any costs and disutilities that could be expected with repeat experiences of the same AEs. This is because the costs and disutilities for the "initial" AEs are applied throughout the 52-week treatment duration without any gaps to reflect AE relief. There is currently no data on how diutilities associated with repeat experiences of the same AE may compound, and as such the current AE assumptions are appropriate.

Upon initiation of a new treatment period (52-week SZC treatment or 3-day standard care treatment), the population average AE costs and utilities are reapplied to the simulated patient, representing the occurrence of "repeat AEs" between treatment periods.

AEs are an extremely minor contributor to the overall health benefits and therefore not a driver of the ICER. As such, any assumption made around how AE costs and disutilities accrue will have little to no impact on the ICER and therefore more complicated modelling approaches for computing costs and utilities associated with AEs were considered unnecessary. The Tornado diagram in Figures 30 and 31 of the NICE submission do not include adverse events-related parameters as the ICERs are insensitive to these parameters.

In summary, the AE assumptions in the model are conservative with respect to SZC, as any longer-term AEs associated with standard care treatment have not been incorporated, and as AEs are assumed to last for 52-weeks in the SZC even if the AE can be resolved earlier in clinical practice. In addition, given the lack of sensitivity of the model to AE parameters, the current AE modelling approach is appropriate and sufficient for the current decision problem.

B16. Clarify whether the results in company submission Table 81 when adjusting the 'K+ threshold for treatment' are correct - currently both the upper and lower value are the same side of the deterministic ICER. If this is correct please provide the explanation for these results.

[Please see final response in separate document]~~In line with the corrections to the VBA code as per B7, B8 and B9, the updated lower bound and upper bound one-way sensitivity analysis (OWSA) results for 'S-K threshold for repeat treatment are -£7,740 and -£5,320, respectively (Table 34).~~

~~**Table 34. Updated one-way sensitivity analysis results for 'K+ threshold for repeat treatment'**~~

~~**Parameter**~~	~~**Acute setting**~~		
	~~**Costs**~~	~~**QALYs**~~	~~**ICER (incremental costs, incremental QALYs)**~~
~~**Updated base case** (S-K threshold for repeat treatment is 6.0 mmol/L)~~	~~SZC:~~ [redacted] ~~Standard care:~~ [redacted]	~~SZC:~~ [redacted] ~~Standard care:~~ [redacted]	~~£-20,274 (dominates)~~ [redacted]
~~**S-K threshold for repeat treatment – lower bound** (5.4 mmol/L)~~	~~SZC:~~ [redacted]	~~SZC:~~ [redacted] ~~Standard care:~~ [redacted]	~~£-5,320 (dominates)~~ [redacted]

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Parameter	Acute setting		
	Costs	QALYs	ICER (incremental costs, incremental QALYs)
	Standard care: [redacted]		
S-K threshold for repeat treatment – upper bound (6.6 mmol/L)	SZC: [redacted] Standard care: [redacted]	SZC: [redacted] Standard care: [redacted]	£7,740 (dominates) [redacted]

As elaborated in the CS, there is a U-shaped relationship between S-K levels and morbidity and mortality in patients with CKD and HF, whereby the risk for event (MACE or death) increases at low and high S-K levels, with the risk of death or MACE increasing when S-K levels increase >5.0 mmol/L (Figure 2 and Figure 3). The upper and lower bound results from the OSWA are at the same side of the base case ICER, because of this U-shaped relationship.

Due to the risk of RAASi-induced hyperkalaemia, , current treatment guidelines by NICE recommend RAASi therapy to be discontinued in patients with S-K ≥6.0 mmol/L, in the acute setting. Based on current treatment guidelines (e.g. UK Renal Association and local Trust guidelines) and clinical expert opinion, the 'S-K threshold for repeat treatment' in the acute setting is set to ≥6.0 mmol/L in the base case i.e. this is the threshold at which hyperkalaemia would be managed in the A&E/acute care setting. At this threshold, all patients discontinue RAASi in the acute setting, and receive either SZC treatment or standard care treatment.

When the S-K threshold for repeat treatment is set to ≥5.4 mmol/L (lower bound), patients in both the SZC arm and the standard care arm discontinue RAASi treatment at a lower S-K threshold. In this scenario, patients in both the SZC arm and the standard care arm experience a higher event risk associated with their underlying CKD or HF conditions due to discontinuation of RAASi and therefore accrue less of a benefit vs continuation until a S-K of 6.0 mmol/L is reached. Overall, the ICER changes due to loss of cardiorenal protection from RAASi discontinuation at lower thresholds vs clinical guidelines, but still accrue to benefits from the management of HK treatment.

Conversely, when the S-K threshold for repeat treatment is set to ≥6.6 mmol/L (upper bound), patients in both the SZC arm and the standard care arm continue to receive RAASi treatment at higher S-K levels. As RAASi treatment is maintained for longer in this scenario, the event risk associated with patients' underlying CKD or HF can be expected to be reduced. However, due to the high event risk associated with high S-K levels; particularly between S-K levels between 6.0 and 6.6 mmol/L, the delay to treat at higher levels accrues fewer benefits, but still remains dominant.

Overall, SCZ remains dominant in both the lower bound and upper bound OWSA for 'S-K threshold for repeat treatment'.

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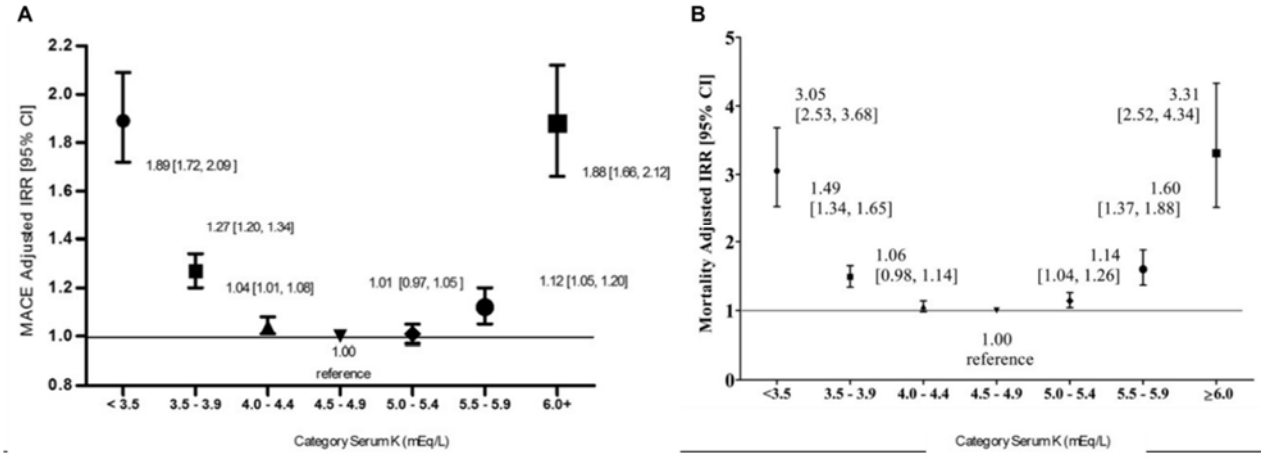
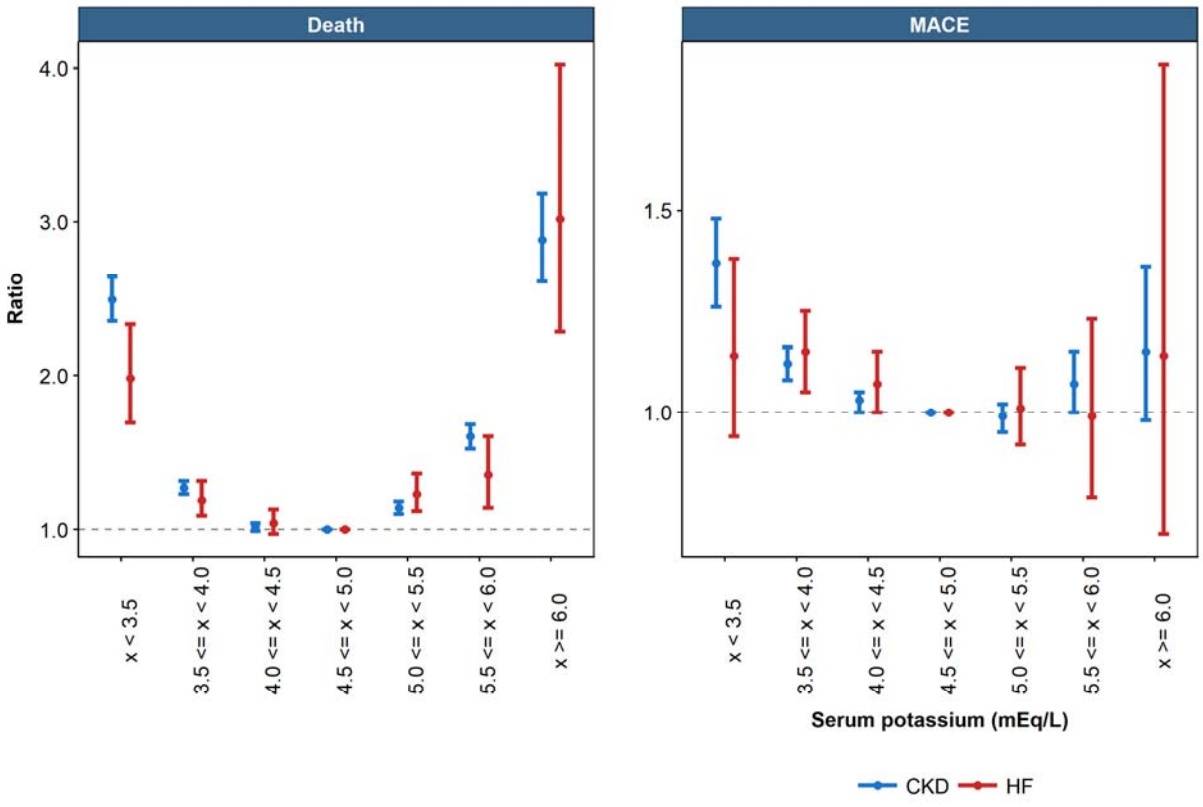
Figure 2: Adjusted IRRs for A) MACE and B) mortality in CKD patients according to S-K – pooled across eGFR data



Abbreviations: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IRR, incidence rate ratio; MACE, major adverse cardiovascular event; S-K: serum potassium.
Source: Luo et al.[30]

Figure 3: UK CPRD risk equation study: adjusted IRRs for mortality and MACE by levels of S-K in CKD and HF patients



Abbreviations: CKD, chronic kidney disease; CPRD, Clinical Practice Research Datalink; HF, heart failure; IRR, incidence rate ratio; MACE, major adverse cardiovascular events; S-K, serum potassium.
Source: Qin et al. 2017, Qin et al. 2017, McEwan et al. 2017.[31-33]

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B17. Please clarify why, within an individual patient model, the age and eGFR values are assumed equal for all patients.

The base case model does not account for patient heterogeneity when running mean values analysis. Consistent with other patient level simulation models, the sensitivity of the model to baseline patient characteristics is assessed through one-way and probabilistic sensitivity analysis (the latter explicitly sampling baseline along with other model parameters).

As with other patient level simulation models, model results convergence may require a large number of iterations. AstraZeneca intend to run additional analyses ahead of the committee meeting with the aim to provide further results.

To at least partially address the ERG's question at this stage, a scenario with baseline eGFR sampling was conducted with baseline eGFR sampling based on the CKD distributions reported in Gifford et al. 2011,[34] as UK study of 123,121 patients (Table 35).

Table 35. Baseline eGFR sampling distribution based on Gifford et al. 2011 in scenario analysis B17

CKD stage	eGFR range (mL/min/1.73 m^2)	Proportion of CKD 3–5 patients	Distribution applied in the model
3b	≥30, <45	79%	Patients' baseline eGFR is assumed to be the upper range eGFR for each category
4	≥15, <30	18%	
5	≥0, <15	3%	

The results from this scenario analysis, based on the baseline eGFR distribution outlined in Table 35 and based on 60,000 patient simulations, do not significantly differ from the base case.

A scenario analysis with baseline age sampling was not carried out due to time constraints.

Table 36. Scenario analysis results B17

	ICER (incremental costs, incremental QALYs)	
	Chronic setting	Acute setting
Update base case (no baseline eGFR sampling; baseline eGFR is 44.66 for all patients)	£21,606 (£16,543, 0.766 QALYs)	Dominates (£-997, 0.049 QALYs)
B17. Scenario analysis (baseline eGFR sampling)	£21,720 (£15,600, 0.718 QALYs)	Dominates (£-951, 0.047 QALYs)

B18. Please clarify whether the results are sensitive to time with CKD, or time since MACE event?

The model does not take into account the time with CKD or the time since MACE event.

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However, as renal function deteriorates with time with CKD, the 'baseline eGFR' can be considered as a proxy for 'time with CKD'. Scenario analyses with different baseline eGFR levels show the model to be robust to a wide range of baseline eGFR levels (Table 37).

Table 37. Scenario analysis results B18

Baseline eGFR (mL/min/1.73 m^2)	ICER (incremental costs, incremental QALYs)	
	Chronic setting	Acute setting
Updated base case (baseline eGFR is 44.66 for all patients)	£21,606 (£16,543, 0.766 QALYs)	Dominates (£-997, 0.049 QALYs)
B18. Scenario analysis A (baseline eGFR is 60 for all patients)	£23,176 (£21,956, 0.947 QALYs)	Dominates (£-1,889, 0.052 QALYs)
B18. Scenario analysis B (baseline eGFR is 45 for all patients)	£21,840 (£16,807, 0.770 QALYs)	Dominates (£-1,028, 0.050 QALYs)
B18. Scenario analysis C (baseline eGFR is 30 for all patients)	£20,933 (£11,733, 0.561 QALYs)	Dominates (£-600, 0.038 QALYs)
B18. Scenario analysis D (baseline eGFR is 15 for all patients)	£20,277 (£6,370, 0.314 QALYs)	Dominates (£-376, 0.021 QALYs)

B19. Clarify further how the values in Table 66 of the company submission were derived. Do these use the most recent HRG costs? If possible, please provide an example of how weighting was performed to calculate mean and standard error. Are there typographical errors (for example, the source for nausea appears to be the same as for diarrhoea)?

The most recent NHS reference costs (2017) are used. The values are obtained by calculating a weighted average from the activity and unit costs for a day case. The standard errors have been assumed as 10% of the cost/mean.

An example is given for oedema in the table below. Calculations are presented in red and the numbers in blue are taken directly from NHS reference costs spreadsheet.

Table 38. Example calculation of adverse event unit costs

Day Case			
Currency Description	**Activity**	**Unit Cost**	**Weighted cost (Unit cost x Activity)/Total Activity**
DZ20E - Pulmonary Oedema without Interventions, with CC Score 6+	3	£292.64	£146.32
DZ20F - Pulmonary Oedema without	3	£197.00	£98.50

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Day Case			
Currency Description	**Activity**	**Unit Cost**	**Weighted cost (Unit cost x Activity)/Total Activity**
Interventions, with CC Score 0-5			
Total	**6**		**£244.82-**

The standard error (SE) is assumed to be 10% of £244.82 which is £24.48.

There are no typographical errors – the source for nausea and diarrhoea is the same as the cost of nausea is assumed equivalent to half the cost of diarrhoea.

B20. Please evaluate the sensitivity of the model to changes in the costs assumed for each NYHA state. It is unlikely the costs are zero.

The base case model accounts for costs associated with RAASi treatment, RAASi down-titration and up-titration, adverse cardiovascular outcomes and hospitalisation. These components capture the typical costs associated with managing heart failure and, as such, the base case model did not consider any additional NYHA cost components.

To evaluate the impact of additional annual costs associated with each of the NYHA states, a targeted literature review of NYHA state costs was conducted. In the absence of any studies conducted in the UK, Ford et al. 2012 was selected to inform the NYHA stage annual costs for the scenario analysis. Ford et al. 2012, a study conducted Australia, was also used in the base case model to inform the monthly probability of hospitalisation by NYHA class. As the study was conducted in Australia, the costs reported may not be fully generalisable to the UK.

The annual NYHA state costs reported in Ford et al. 2012, included the cost of GP visits, pathology tests, echocardiograms, specialist visits, and the cost of medication (Table 40). As the cost of GP and specialist visits for RAASi titration and cost of RAASi treatment are already included in the model, the use of the annual NYHA state costs are likely to be associated with double-counting of some costs. Hospitalisation costs were nevertheless reported separately in Ford et al. 2012 and therefore excluded from the current scenario analysis to reduce double-counting. The costs reported in Ford et al. 2012 were converted to GBP at the 30/06/2012 exchange rate and inflated to 2017 GBP using the PSSRU Index (Table 39).

Table 39. Annual NYHA state costs from Ford et al. 2012 in scenario analysis B20[35]

NYHA state	Annual NYHA state cost reported in Ford et al. 2012	Annual NYHA state costs converted to 2017 GBP
I	AUS$130.30	£90.99
II	AUS$150.11	£104.82
III	AUS$194.69	£135.95
IV	AUS$207.79	£145.10

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Table 40. Resource use for each NYHA class

Cost item	NHYA I	NYHA II	NYHA III	NYHA IV
GP visits	6 visits per year	12 visits per year		
Pathology	Every 3 months			
Echocardiogram	1 performed every 2 years			
Specialist visits	Twice a year (initial visit and repeat visit)			

The results of a scenario analysis incorporating these additional costs are presented in Table 41, showing the additional NYHA stage annual costs to have a minimal impact on the ICER. The scenario analysis is likely to be conservative with respect to SZC, as there is likely to still be some degree of double-counting of costs, as outlined above, in terms of GP visits costs, specialist visits costs and RAASi treatment costs.

This scenario analysis has been included in the "all relevant" scenario in response to B25, and it has also been included in the new base case presented in B25.

Table 41. Scenario analysis results B20

Scenario	ICER (incremental costs, incremental QALYs)	
	Chronic setting	Acute setting
Updated base case (no annual NYHA state costs)	£21,606 (£16,543, 0.766 QALYs)	Dominates (£-997, 0.049 QALYs)
B20. Scenario analysis (costs were added for each NYHA state)	£21,672 (£16,593, 0.766 QALYs)	Dominates (-£994, 0.049 QALYs)

It is worth noting that CKD stage annual costs were included in the model, in addition to the costs associated with RAASi treatment and hospitalisation, as the cost of RAASi therapy is not a substantial cost component of the management of CKD. In addition, CKD patients without HK do not incur substantial hospitalisation costs. The only annual CKD stage costs identified in the literature were aggregated CKD care costs from CG182. Therefore, the current implementation of CKD stage annual costs may result some limited double-counting (e.g. GP visits and secondary care appointments for eGFR monitoring may overlap with appointments for RAASi titration), which is conservative with respect to SZC.

B21. Provide a scenario analysis where patients remain in CKD5 at a fixed eGFR score rather than receiving renal replacement therapy and exiting the model. Please highlight the changes made in the VBA to enable this change.

AstraZeneca understand that the ERG may have asked this question to explore the sensitivity of the model with regards to RRT and the exiting of patients on RRT from the model. However, we would like to emphasise that this scenario is highly unrealistic, as the natural history of CKD is associated with eGFR decline over time and eventual need for RRT. Post-hoc analyses of a clinical trial show that the use of RAASi may slow down, but not, stop the eGFR decline.[36]

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To address the ERG's question in full, a scenario analysis is provided in Table 42 where patients remain in CKD5 at a fixed eGFR level, without further eGFR deterioration and without renal replacement therapy. There is a small increase in the ICER associated with this scenario compared to the baseline. AstraZeneca would like to emphasise that this scenario is highly unrealistic.

Table 42. Scenario analysis results B21

Scenario	ICER (incremental costs, incremental QALYs)	
	Chronic setting	Acute setting
Updated base case (patients with CKD5 exit the model)	£21,606 (£16,543, 0.766 QALYs)	Dominates (£-997, 0.049 QALYs)
B21. Scenario analysis (patients remain in CKD5 at fixed eGFR)	£22,818 (£17,566, 0.770 QALYs)	Dominates (£-496, 0.063 QALYs)

Changes in the VBA code:

The location of the new code can be found by searching for "'B21 new code" in the VBA. The changes were made in the simulateCohort subroutine and the original code has been commented out to highlight the changes made.

Original Code:
Else
blnPatientFlag_RRT = True
Exit For

New Code:
Else
dbl_arrEGFR(cycle + 1) = sng_RRTthreshold

B22. Please clarify whether the utilities for NYHA categories and CKD categories are absolute values from the source reference or are multipliers as they have been used within the model.

The health state utility values (HSUVs) used in the model are the product of the disease stage utility values reported in the literature (Table 50 of CS) and the relevant age-specific UK general population utility value (Table 49). This approach was chosen as it is conservative with respect to SZC and as it prevents the HSUVs from exceeding the UK general population utility values.

AstraZeneca understand that this approach is likely to underestimate the HSUV, as age-related utility decrements are likely to have been accounted for twice:

- Firstly, utility values in the literature were derived from subjects with a mean age of 64 ± 12 years (Göhler et al. 2009) and 62.8 ± 12.7 years (Gorodetskaya et al. 2005) and as such these utility values can be considered to already intrinsically account for age-related utility decrements (for the age of the subjects in the studies)

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- Secondly, age-related utility decrements are explicitly accounted for through the multiplication of the utility values from the literature with the age-specific UK general population utility values

Overall, this "multiplicative" approach to calculate age-specific HSUVs is conservative with respect to SZC as the total QALYs gained in both the SZC arm and the standard care arm are likely to have been underestimated by a similar proportion, and as a result the incremental QALYs gained is also likely to also have been underestimated.

One additional advantage with the current approach is that the HSUVs calculated for use in the model never exceed the UK general population utility values. AstraZeneca note that an alternative approach for calculating the HSUVs for the model would be to use a "subtractive" approach, whereby the utility values from the literature are adjusted for age by subtracting an age-related utility decrement per additional year of age. As some of the utility values from the literature are greater than the UK general population utility values, the "subtractive" utility approach would need to be combined with "capping" whereby the maximum possible HSUVs would be set to be the UK general population utility values. As several of the utility values from the literature are greater than the UK general population values, "capping" would disregard utility value deteriorations expected with disease progression and therefore compromise the clinical validity of the model.

Whilst responding to the above question, we further investigated the HSUVs currently used in the model and recommend that the HSUV for CKD stage 5 in the model should be updated from 0.570 (based on Lee et al. 2005) to 0.850 (based on Gorodetskaya et al. 2005) so that the same reference study is used to inform all the HSUVs by CKD stage. This change improves the internal validity of the model and avoids the abrupt drop in HSUV between CKD stage 4 and CKD stage 5, which lacks clinical justification. The change in HSUV for CKD stage 5 only has a negligible impact on the ICER in both the acute and the chronic scenarios. Nevertheless, AstraZeneca believe this scenario to be more clinically relevant compared to the base case presented in the CS.

The scenario analysis presented in Table 44 has been included in the "all relevant" scenario in response to B25, and it has also been included in the new base case presented in B25.

Table 43: Health state utility values applied in the CS and in scenario analysis B22

Health state	As submitted in CS		Scenario B22	
	Utility	Source	Utility	Source
NYHA I	0.855	Göhler et al.[37]	0.855	Göhler et al.[37]
NYHA II	0.771		0.771	
NYHA III	0.673		0.673	
NYHA IV	0.532		0.532	
CKD 3 a	0.870	Gorodetskaya et al.[38]	0.870	Gorodetskaya et al.[38]
CKD 3b	0.870		0.870	
CKD 4	0.850		0.850	

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Health state	As submitted in CS		Scenario B22	
	Utility	Source	Utility	Source
CKD 5 (pre-RRT)	0.570	Lee et al.[39]	0.850	

Abbreviations: CKD, chronic kidney disease; NYHA, New York Heart Association; RRT, renal replacement therapy; SE, standard error.

Table 44. Scenario analysis results B22

Scenario	ICER (incremental costs, incremental QALYs)	
	Chronic setting	Acute setting
Updated base case (HSUV for CKD 5 is 0.570)	£21,606 (£16,543, 0.766 QALYs)	£-20,274 (£-997, 0.049 QALYs)
B22. Scenario analysis (HSUV for CKD 5 updated to 0.85)	£19,870 (£16,543, 0.833 QALYs)	£-9,359 (£-997, 0.107 QALYs)

B23. Please provide the supplementary tables associated with Sullivan et al 2011 and confirm that these contain the disutility values for the conditions incorporated in the model.

Please find the supplementary tables from Sullivan et al. 2011 in Appendix 2 of this response, with the disutility values from Sullivan et al. 2011 applied in the model highlighted in red text.

There were minor referencing errors in Table 51 of the CS. An updated table is provided below (Table 45) with the corrections highlighted in red text.

Table 45. Summary of AE disutilities (Table 51 of CS)

Health state	No. cycles applied for	Utility	SE	Dist.	Source
Oedema	13 (1 year)	−0.0029	0.000	Beta	Sullivan et al.[40]
Constipation	13 (1 year)	−0.0056	0.001	Beta	
Diarrhoea	13 (1 year)	−0.0008	0.001	Beta	Kristiansen et al.[41]
Nausea	13 (1 year)	−0.0037	0.001	Beta	Nafees et al.[42]
Hypomagnesaemia	13 (1 year)	−0.0028	0.002	Beta	Sullivan et al. [40]
Anorexia	13 (1 year)	−0.0029	0.001	Beta	
Hypokalaemia	13 (1 year)	0.0000	0.000	Beta	Assumption – no study identified
Anaemia	13 (1 year)	−0.0015	0.001	Beta	Sullivan et al. [40]
UTI	13 (1 year)	−0.0004	0.001	Beta	Sullivan et al. [40]
MACE event	1	−0.050	0.040	Beta	Palmer et al.[43]
Hospitalisation	1	−0.024	0.007	Beta	Göhler et al.[37]

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B24. Clarify why the number of weeks in the year is set to 52 rather than a more accurate value. If producing new analyses based on the potential coding errors/changed assumptions then please change this value.

The number of weeks in the year has been set to 52 rather than a more accurate value because of the 28-day cycle length (4 weeks) which reflects the study design of ZS-004 trial and the need to have an entire number of cycles per year. The anticipated duration of treatment and length of the treatment cycle is also aligned with expected UK clinical practice. Choosing 52 weeks over a more accurate value has limited impact on the ICER.

B25. Please perform analyses that consider all of the requested amendments simultaneously.

The updated base case based on correction of errors identified by the ERG in B7, B8 and B9 are presented in Table 46.

Table 46. Updated base case results with B7, B8 and B9 corrections

Population	ICER (incremental costs, incremental QALYs)	
	Chronic setting	Acute setting
CKD or HF (base-case)	£21,606 (£16,543, 0.766 QALYs)	Dominates (£-997, 0.049 QALYs)
CKD only	£26,359 (£14,394, 0.546 QALYs)	Dominates (£-1,163, 0.033 QALYs)
HF only	£12,928 (£9,527, 0.737 QALYs)	Dominates (£264, 0.054 QALYs)

AstraZeneca believe the following scenario analyses proposed by the ERG to be clinically relevant, in some situations, as discussed in the response to each individual question: B1, B4, B6, B7, B8, B9, B10, B12, B17, B20, B22. The combined effect of the changes associated with these scenarios are presented in Table 47.

New base case results have also been generated for the chronic and acute setting, representing the most likely ICER based on the clinical relevance of the scenarios incorporated (Table 47).

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Table 47. Results of combined scenarios analyses for the combined CKD and HF population and for HF only and CKD only subpopulations

Population	ICER in the Chronic setting (incremental costs, incremental QALYs)		ICER in the Acute setting (incremental costs, incremental QALYs)	
	All relevant scenarios (B1, B4†, B6‡, B7, B8, B9, B10, B12, B17, B20, B22	New base case (B6‡, B7, B8, B9, B10, B12, B20, B22	All relevant scenarios (B1, B4†, B6‡, B7, B8, B9, B10, B12, B17, B20, B22	New base case (B6‡, B7, B8, B9, B10, B12, B20, B22
CKD or HF	£24,575 (£15,867, 0.646 QALYs)	£21,849 (£16,803, 0.769 QALYs)	Dominates (£-641, 0.047 QALYs)	Dominates (£-853, 0.052 QALYs)
CKD only	£28,487 (£20,111, 0.706 QALYs)	£25,363 (£14,623, 0.577 QALYs)	Dominates (£-1,105, 0.051 QALYs)	Dominates (-£1027, 0.037 QALYs)
HF only	£15,244 (£9,370, 0.615 QALYs)	£13,458 (£9,772, 0.726 QALYs)	£6,022 (£291, 0.048 QALYs)	£7,380 (£393, 0.053 QALYs)

† The more conservative scenario analysis of using a S-K value of 4.753 at Day 15–28 and at Day 29+
‡ The more realistic scenario analysis with wastage assumed in cycle 2–5 only

Section C: Textual clarifications and additional points

C1. Please clarify whether there is a typo in Table 80. If so, what should the life year gained value for standard care be?

There was indeed a typographic error in Table 80 of the NICE submission. This has been corrected and the correct values can be found in Table 48 below.

Table 48: Amends to Table 80 of the CS

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Sodium zirconium cyclosilicate	[redacted]	[redacted]	[redacted]			
Standard care	[redacted]	[redacted]	[redacted]	16,451	0.76	21,655

C2. Please clarify the apparent contradiction within Table 11. Table 11 reports baseline SK in the randomised phase as approximately 4.5 in each arm although the acute phase values in the rows below appear to give an average higher than 4.5 (for example in the SZC 10 g

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dose 63% of patients have values greater than, or equal, to 5.5). Clarify what is meant by acute phase S-K in Table 11.

The row 'Acute phase S-K baseline' reports the distribution of patients in the 3 categories of S-K (i.e. <5.5, 5.5 to <6.0, and ≥6.0) at the start of the acute phase of the study (i.e. the corrective phase of treatment as per the SmPC). This acute phase of this study represents the open label phase where all patients received SZC 10g TID at entry in the trial. Patients who achieve normokalaemia are randomised to receive 5 g, 10 g, or 15 g SZC in the maintenance phase. Therefore, it is expected that the baseline values of S-K in the acute phase (or open label phase) are higher than those at the baseline of the randomised maintenance phase, as patients entered the maintenance phase after having achieved normokalaemia during the acute phase.

C3. Please clarify whether in the model 'lng_ageCatIndirect' is an orphan variable.

'lng_ageCatIndirect' is an orphan variable as indirect costs have been removed from the model. This has no effect on the ICER.

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Priority: Please clarify whether S-K levels within the model are independent of RAASi use. If yes, provide a rationale for this, or amend the model if this is an oversight

Thank you for seeking additional clarification on the model structure. We agree that the relationship between RAASi down-titration or discontinuation with S-K reductions is not currently explicitly modelled. However, due to the methods and data used to model the S-K trajectory in the model, AstraZeneca believe any S-K related benefits from RAASi down-titration or discontinuation to be more than accounted for in the model, as explained below.

Down-titration or discontinuation of RAASi therapy is the mainstay intervention for the management of hyperkalaemia, but there is a lack of robust published evidence to quantify the magnitude of S-K reduction associated with RAASi down-titration/discontinuation that limits the feasibility to model this relationship. Nevertheless, a published literature review suggests the initiation and use of RAASi to be associated with a S-K increase of 0.1–0.3 mmol/L in HF patients and 0.06–0.8 mmol/L (typically ≤0.5 mmol/L) in CKD patients.[1] In the absence of other data, the magnitude of S-K *change* associated with RAASi *initiation* could reasonably be considered to be the maximum magnitude of S-K *reduction* associated with RAASi *discontinuation*. Based on UK clinical experts' input,[2] the majority (80%) of patients would be managed through RAASi down-titration if their S-K levels are ≥5.5–6.0, with only 20% of patients being managed by RAASi discontinuation if their S-K levels are ≥5.5–6. Therefore, since not all patients discontinue RAASi therapy, the population mean reduction in S-K levels following RAASi down-titration/discontinuation in clinical practice is likely to be smaller than the S-K change reported in the literature.

As discussed in the CS, the S-K trajectories modelled are based on data from ZS-004 and ZS-005. In these clinical trials, all patients were treated with SZC in the correction phase (Day 1–3), followed by either continued SZC or placebo treatment in the maintenance phase. Data from patients who received placebo in the maintenance phase were used in the mixed effect models to generate the S-K profiles for the standard care arm from Day 4 onwards. Due to the lack of placebo data, the S-K profiles in the SZC arm and the standard care arm are assumed to be the same on Day 1–3, with the same time-dependent reduction in S-K levels from baseline ([redacted] mmol/L per day). Based on this assumption, the S-K reduction in the standard care arm over the first 3 days is [redacted] mmol/L, which more than compensates for any reductions in S-K levels associated with RAASi down-titration or discontinuation (see above).

From Day 4 onwards, the mixed-effects models of the S-K profiles in the SZC and the standard care arms become treatment specific with a population mean of [redacted] mmol/L for patients treated with SZC based on pooled data from ZS-004 and ZS-005 and [redacted] mmol/L for patients treated with standard care based on data from ZS-004. This corresponds to a [redacted] mmol/L reduction from baseline S-K level in the standard care arm, which is greater than the reductions that would be expected due to RAASi down-titration or discontinuation (see above).

As patients treated with "placebo" initially received treatment with SZC during the correction phase of the ZS-004 clinical trial, it is expected that these patients have lower S-K levels compared to patients treated by standard care who would not benefit from the use of SZC. As above, it is possible that patients treated by standard care in UK clinical practice may benefit from some reductions in S-K levels following RAASi down-titration or discontinuation

that is currently not directly modelled, however, the “placebo” data used to model the S-K trajectories is likely to more than account for the RAASi discontinuation benefits.

When patients in the standard care arm receive RAASi up-titration in the model, the model does not account for any S-K level increases that may be expected with RAASi up-titration.[1] This means that the model is conservative with respect to SZC both when RAASi is down-titrated/discontinued and up-titrated in the standard care arm.

Overall, it is likely that the reduction in S-K levels due to the use of SZC in patients during the correction phase who were subsequently randomised to receive placebo are greater than any reductions in S-K levels that would be expected due to RAASi discontinuation in UK clinical practice. In addition, the change in S-K reported in the literature is likely to conservatively overestimate the magnitude of S-K change associated with *down-titration/discontinuation* in clinical practice and additionally the S-K reduction is clinical practice is likely to be attenuated further as some patients with S-K levels of ≥5.5–6.0 mmol/L down-titrate rather than discontinue RAASi therapy. Therefore, the use of data in the current model is conservative with respect to SZC in terms of estimating the S-K associated morbidity and mortality risk in standard care patients, and intrinsically accounts for S-K reductions associated with RAASi down-titration/discontinuation in the standard care arm.

B16. Clarify whether the results in company submission Table 81 when adjusting the ‘K+ threshold for treatment’ are correct - currently both the upper and lower value are the same side of the deterministic ICER. If this is correct please provide the explanation for these results.

Upon further consideration of the questions highlighted by the ERG in B16, AstraZeneca would like to provide an updated response to B16 to correct our original response.

Whilst the U-shaped associations between S-K levels and risk of MACE and mortality, outlined in our original response to B16, is an important consideration in the management of HK patients, this relationship is not the driver of the observations highlighted by the ERG in B16. Furthermore, AstraZeneca would like to clarify that in the acute setting of the model, RAASi treatment is discontinued in all patients at the index HK event, with no subsequent up-titration. As such, even if repeat treatment is withheld, no additional benefits from RAASi treatments are acquired as all patients in the acute setting have already discontinued RAASi at the index HK event.

AstraZeneca would like to emphasise that many of the scenarios evaluated as part of the OWSA may not be clinically relevant. The S-K threshold for repeat treatment at ≥6.0 mmol/L is clearly outlined in acute-care protocols and the Renal Association guidelines for the emergency management of hyperkalaemia in adults,[3-11] and supported by expert clinical opinion from A&E consultants, nephrologists, and cardiologists. As such, the lower and upper bound analysis of the ‘S-K threshold for repeat treatment’ at 5.4 and 6.6 mmol/L, respectively, is not clinically relevant. In addition, even if the S-K threshold for repeat treatment differs from 6.0 mmol/L, associated parameters in the model including the ‘Threshold for index HK event’ and ‘Threshold high acute HK event’ (threshold at which costs for acute HK management are incurred) would need to change concurrently to align

with the S-K threshold for repeat treatment. When these associated parameters are not varied concurrently, some of the scenarios generated are not clinically relevant, e.g. it would not be clinically relevant for the costs of acute HK management to be incurred at 6.0 mmol/L if the S-K threshold for repeat treatment is assumed to be 5.4 mmol/L (lower bound OWSA).

Nevertheless, OWSAs are an important tool for evaluating the drivers of models, as long as the results are interpreted carefully, even if some of the scenarios generated are not clinically relevant. The results in Table 81 of the company submission are correct. However, as SZC dominates standard care in the deterministic base case analysis, the results of the OWSA are easiest to interpret when presented as net monetary benefits (NMBs). As such, the results of the OWSA based on the model in the original CS and based on the new base case model (as per B25) are presented below as NMBs.

Results from original model displayed as net monetary benefits

The results of the OWSA of the new base case model show the lower and upper bound of the 'S-K threshold for repeat treatment' OSWA fall either side of the mean deterministic NMB result, at willingness to pay thresholds of £20,000 and £30,000 (Figure 1 and Figure 2).

The OWSA results with respect to 'S-K threshold for repeat treatment' are summarised in Table 2, based on the original company submission model, showing SZC to be dominant and associated with positive NMBs in both the lower and upper bound scenarios.

Figure 1. Results from OWSA of original CS model presented as net monetary benefits (NMBs) (λ=£20,000)

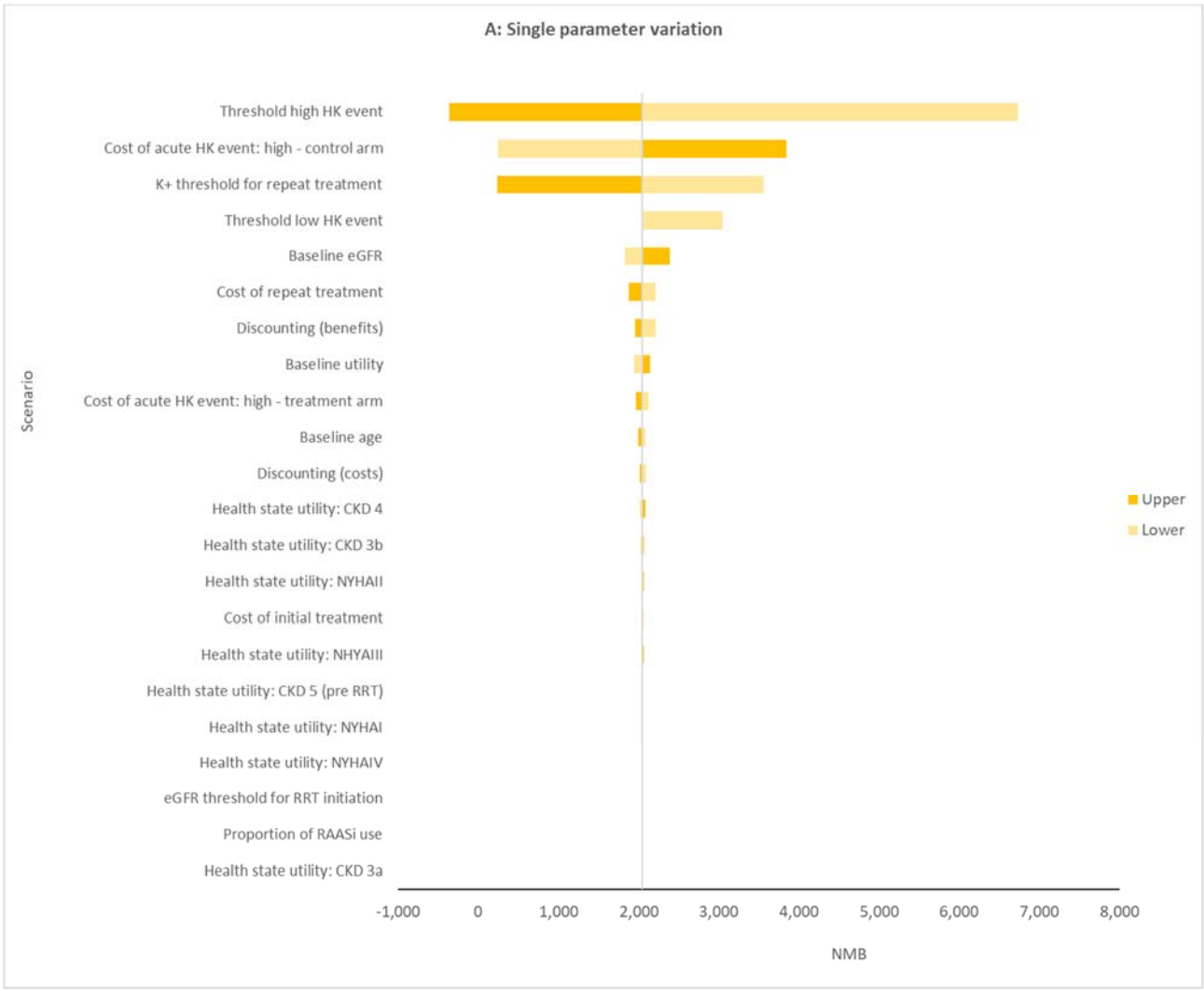

Figure 2. Results from OWSA of original CS model presented as net monetary benefits (NMBs) (λ=£30,000)

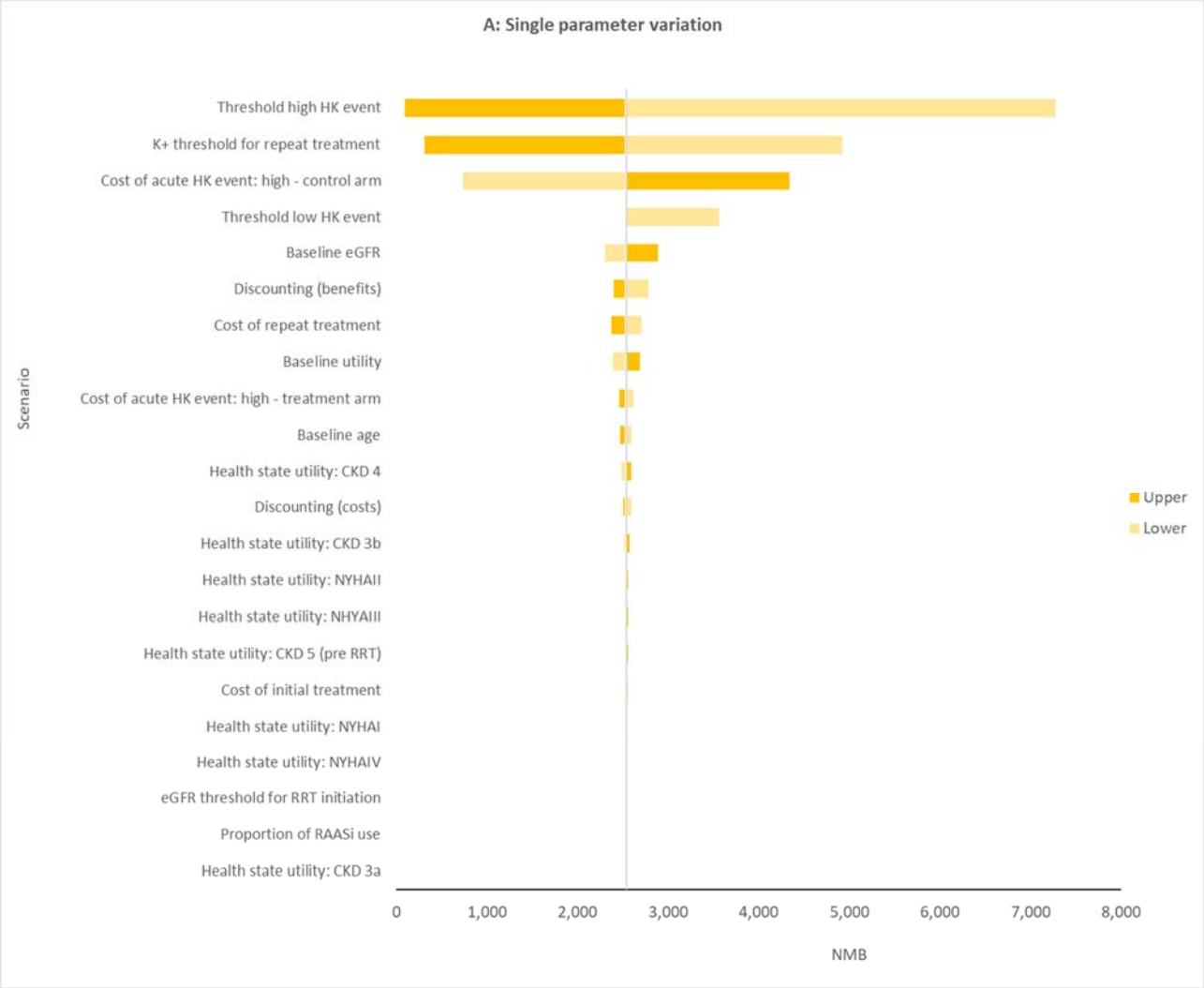

Table 1. OWSA results of original CS model for 'S-K threshold for repeat treatment'

Parameter	**Acute setting**				
	Costs	**QALYs**	**LYs**	**NMB at λ=£20,000 (incremental costs, incremental QALYs)**	**NMB at λ=£30,000 (incremental costs, incremental QALYs)**
Original CS base case (S-K threshold for repeat treatment is 6.0 mmol/L)	SZC: [redacted] Standard care: [redacted]	SZC: [redacted] Standard care: [redacted]	SZC: [redacted] Standard care: [redacted]	£2,048.08 (-£1,060, 0.049 QALYs)	£2,542,00 (-£1,060, 0.049 QALYs)
S-K threshold for repeat treatment – lower bound (5.4 mmol/L)	SZC: [redacted] Standard care: [redacted]	SZC: [redacted] Standard care: [redacted]	SZC: [redacted] Standard care: [redacted]	£3,562.88 (-£840, 0.136 QALYs)	£4,924.14 (-£840, 0.136 QALYs)

S-K threshold for repeat treatment – upper bound (6.6 mmol/L)	SZC: [redacted] Standard care: [redacted]	SZC: [redacted] Standard care: [redacted]	SZC: [redacted] Standard care: [redacted]	£232.18 (-£71, 0.008 QALYs)	£313.01 (-£71, 0.008 QALYs)

Results from new base case model displayed as net monetary benefits

The results of the OWSA of the new base case model show the lower and upper bound of the 'S-K threshold for repeat treatment' OSWA fall either side of the mean deterministic NMB result, at willingness to pay thresholds of £20,000 and £30,000 (Figure 3 and Figure 4).

The OWSA results with respect to 'S-K threshold for repeat treatment' are summarised in Table 2, based on the new base case model (B25), showing SZC to be associated with positive NMBs in both the lower and upper bound scenarios.

Figure 3. Results from OWSA of new base case model presented as net monetary benefits (NMBs) (λ=£20,000)

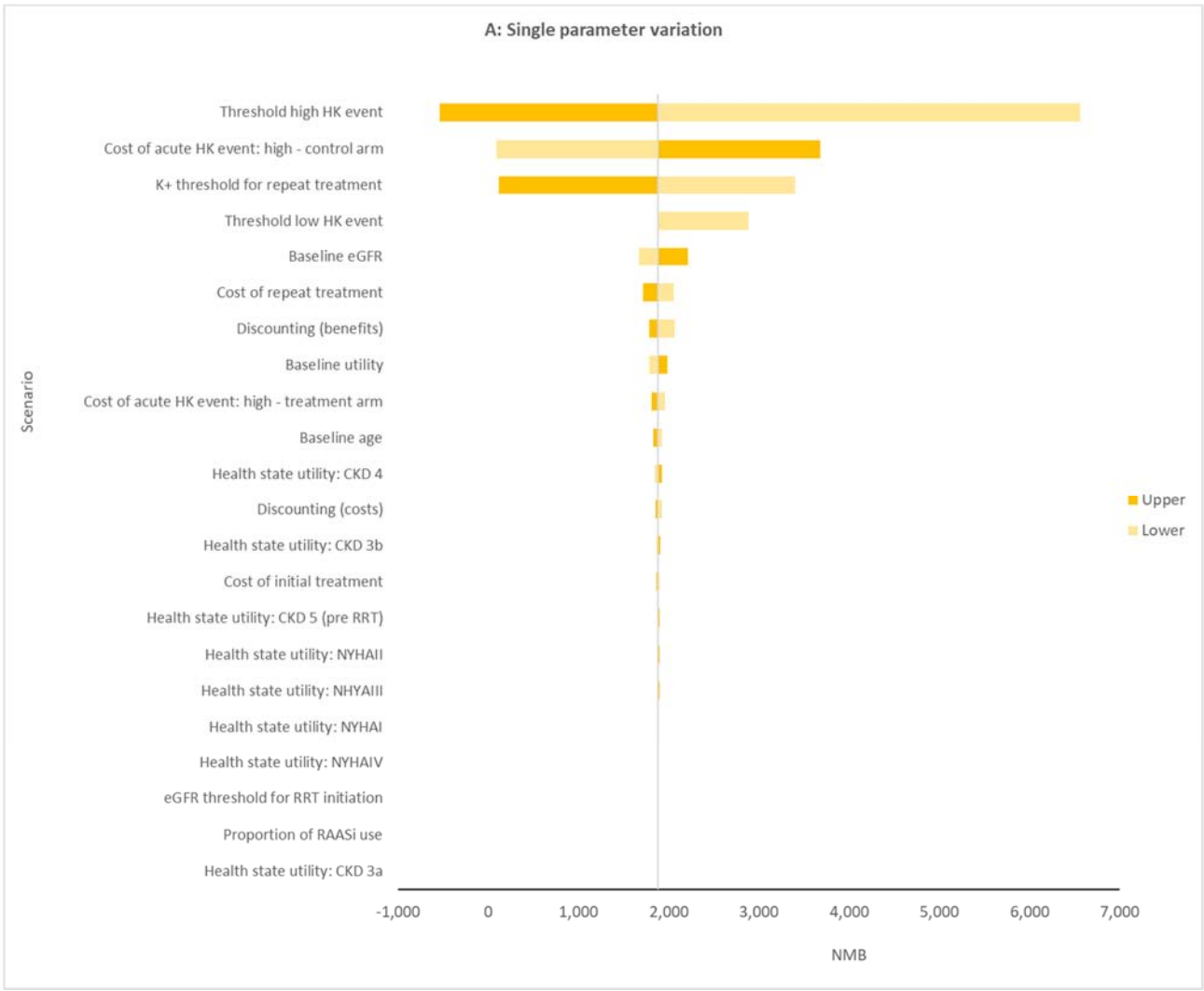

Figure 4. Results from OWSA of new base case model presented as net monetary benefits (NMBs) (λ=£30,000)

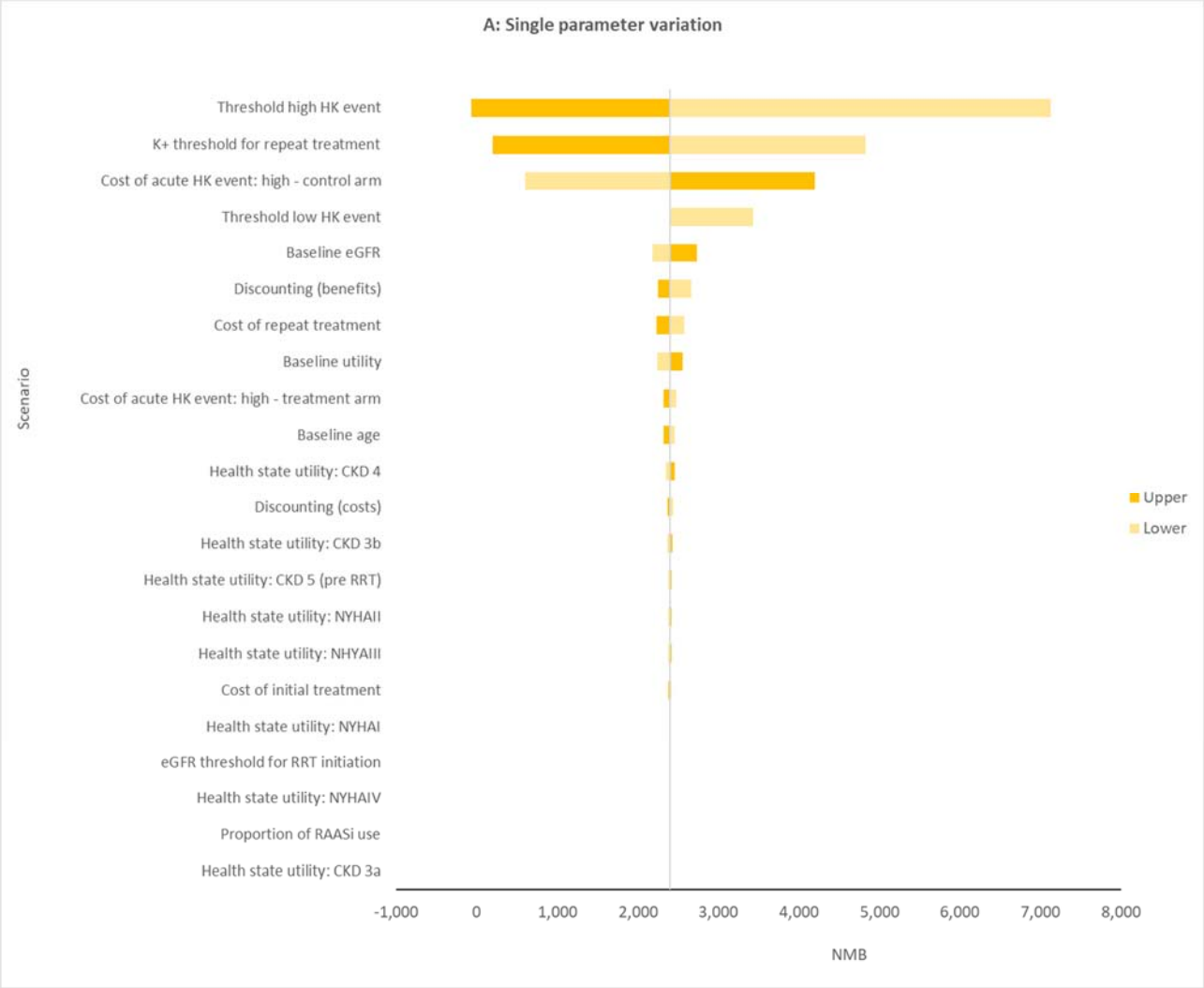

Table 2. OWSA results of new base case model for 'S-K threshold for repeat treatment'

Parameter	Acute setting				
	Costs	**QALYs**	**LYs**	**NMB at λ=£20,000 (incremental costs, incremental QALYs)**	**NMB at λ=£30,000 (incremental costs, incremental QALYs)**
New base case (S-K threshold for repeat treatment is 6.0 mmol/L)	SZC: [redacted] Standard care: [redacted]	SZC: [redacted] Standard care: [redacted]	SZC: [redacted] Standard care: [redacted]	£1,885.15 (-£853, 0.052 QALYs)	£2,401.43 (-£853, 0.052 QALYs)
S-K threshold for repeat treatment – lower bound (5.4 mmol/L)	SZC: [redacted] Standard care: [redacted]	SZC: [redacted] Standard care: [redacted]	SZC: [redacted] Standard care: [redacted]	£3,402.68 (-£563, 0.142 QALYs)	£4,822.52 (-£563, 0.142 QALYs)

S-K threshold for repeat treatment – upper bound (6.6 mmol/L)	SZC: [redacted] Standard care: [redacted]	SZC: [redacted] Standard care: [redacted]	SZC: [redacted] Standard care: [redacted]	£114.12 (£53, 0.008 QALYs)	£197.57 (£53, 0.008 QALYs)

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Sodium zirconium cyclosilicate for treating hyperkalaemia [ID1293]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Prof Sunil Bhandari**
2. Name of organisation	**Representing The Renal Association and Royal College of Physicians**

3. Job title or position	**Consultant Nephrologist/Honorary Professor and Vice Chair of Education and Training Committee of The Renal Association**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**The Renal Association is the leading professional body for the UK Renal Community, dedicated to improving services and outcomes for patients and families through education, research and training for prevention and effective treatment of kidney disease. It is funded through the subscription of its members.**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**NONE**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or	Sodium zirconium cyclosilicate is indicated for the treatment of hyperkalaemia in adults. For renal services it would allow clinicians to maintain medications for patients with chronic kidney disease and hypertension and heart failure and thus prevent unnecessary admissions to hospital for acute hyperkalaemia. It would also potentially reduce the frequency of follow-up. This use may lead to improvements in quality of life for patients via a more relaxed diet (unknown). In addition Angiotensin converting enzyme inhibitors (ACE-I), a low cost therapy, is recommended by NICE

disability.)	for people with proteinurica chronic kidney disease, hypertension and an ACR of 30mg/mmol and diabetics with an ACR of 3mg/mmol or more. Sodium zirconium cyclosilicate also has a rapid effect on reducing potassium
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	I would expect a reduction in measured serum potassium levels of the order of 1 mmol/L and this to be maintained throughout the duration of therapy. I would apply this for all treatment groups. The rate of reduction is less important in the management of chronic hyperkalaemia but it should occur within a week of therapy. In addition I would expect that if there was a future plan to manage acute hyperkalaemia – I would want data to confirm a 0.5 mmol/l fall in serum potassium within the first 2 hours of therapy. Again this should persist with therapy.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	This is a new field of therapy which is niche to certain medical fields including nephrology, diabetes, cardiology and medicine for the elderly. Therapies directed at augmenting gastrointestinal potassium excretion In the form of resonium has been in use for many years, it has been unreliable in the acute setting and generally poorly tolerated. Despite this there is an unmet need in this field of hyperkalaemia to assist in optimal patient care. A recent "real world" study of use of ACE-I and ARB, suggests an overall low rate (<2%) of hyperkalaemia (e.g., >5 mmol/L), but this is increasing with increased optimisation of these therapies and the aging population with chronic kidney disease.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Calcium Polystyrene Sulfonate – (Resonium) is the current treatment. This is ineffective and poorly tolerated. In addition there are significant complications such as constipation and major issue in chronic kidney disease. Finally in the majority of cases the treatment is to discontinue important medications such

	as those that block the Renin Aldosterone Angiotensin System (RAAS) such as Angiotensin converting enzyme inhibitors (ACEi) which have a wealth of data in proteinuric chronic kidney disease and diabetes mellitus. In addition reduction or discontinuation of medications known to increase the risk of hyperkalaemia. Finally dietary restriction of foods rich in potassium is used in renal services mainly.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are recognised guidelines for the treatment of acute hyperkalaemia – see The Renal Association web pages. This does not include Sodium zirconium cyclosilicate, However the data does suggest a rapid effect on potassium concentrations and hence a likely use in the medium term future in this field in addition to current acute therapy. Currently there are no guidelines for the treatment of chronic hyperkalaemia except current best practice which includes reduction or discontinuation of those drugs which may exacerbate hyperkalaemia and introduction of potassium restricted diets. There are however recommendations about the level of potassium (5.0mmol/L) at which one should consider use of drugs such as ACE-I with caution and close monitoring.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	International guidelines are clear on the optimal therapy for those patients with chronic kidney disease (CKD), hypertension and heart failure with reduced ejection fraction (HF) and the benefits of blocking the RAAS. Therefore there is a well-defined universal pathway of care which is evidence based. NICE heart failure guidelines also recommend ACE-I as the mainstay therapy for heart failure in addition to beta-blockers, both of which may cause hyperkalaemia. The KDIGO guidelines endorse these views for CKD. However there is tittle well defined evidence on the optimal method of potassium control in these populations and is based on the recent trial data from a number of studies in this field. As this is a relatively new area there are few opinions and most of the current experience emanates from the USA where the drug has been in use for much longer. It is clear from these views that the ability to reduce the need to down titrate or discontinue RAAS inhibitors is of value in view of the associated worsening clinical outcomes in chronic kidney disease patients (at least in the early stages G1-4).

• What impact would the technology have on the current pathway of care?	Sodium zirconium cyclosilicate is indicated for the control of hyperkalaemia. This may enable optimisation of RAAS inhibitors in patients who develop elevated K^+, after the use of the normal potassium reducing measures such a diet restriction. In addition it will reduce unnecessary hospital admission with acute high potassium levels.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	I would suggest that Sodium zirconium cyclosilicate should be used selectively for those challenging patients who require numerous samples and repeat admissions with hyperkalaemia in the first instance with the aim to achieve long-term control of serum K^+; prevent recurrence of elevated K^+ and allow optimal dosing for RAAS inhibitors. This is a change in clinical practice from that in current practice. I would also suggest consideration of use in acute hyperkalaemia to reduce potassium in conjunction with current therapy as this may reduce a need for more intensive interventions.
• How does healthcare resource use differ between the technology and current care?	This is an additional therapy not previously available and adds to the armoury for the clinician in the effective management of a group of patients with relative high co-morbidity and mortality
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	It is my opinion that this technology should be initially restricted to secondary care in view of the monitoring required and treatment optimisation for maximum benefit. However in the longer term once there is a wealth of real world clinical experience I see no reason why it could not be extended to primary care. My one reservation for the latter is the current, evidence of the poor adherence to guidelines and detailed recommendations for the monitoring of patients on RAAS inhibitors in primary care
• What investment is needed to introduce the technology? (For example, for facilities,	The main investment will be education of clinicians and prescribers of medications and implementation of a strategy of use in targeted patients who are likely to have the most benefit.

equipment, or training.)	Although it may lead to an increase in measures of potassium in the early stages of introduction, in the longer term it is likely to lead to a reduction in the frequency of tests, and monitoring.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes: Potential use of a potassium binder may lead to positive outcomes for patients on ACE-I. There is no long term data to conclusively prove this outcome. It must be remembered that these are uncontrolled, open label studies of up to one year, with a total of approx 800 participants examining the ability to maintain a normal serum potassium levels, hence data is limited but evolving at present.
• Do you expect the technology to increase length of life more than current care?	Yes: - Real world data suggest that there is an odds ratio of discontinuation of RAAS medication in the order of 1.19, 1.66 and 2.69 for potassium levels of >5; >5.5;>6.0 respectively while the odds ratio of dose reductions were 1.76; 2.81 and 3.81 respectively. Therefore potential use of a potassium binder may reduce this effect and lead to positive outcomes for patients. There is no long term data to conclusively prove this outcome.
• Do you expect the technology to increase health-related quality of life more than current care?	This is unknown and no data currently exists. What is known is that patients with a higher that average potassium concentration have a reduced length of life from epidemiological data. Recent published retrospective observational trials in haemodialysis patients has showed that potassium levels 5.5–6.0 mmol/L were associated with higher risk for subsequent hospitalization, emergency department visits, and mortality. This is also seen in non-dialysis patients from observational data.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The use of Sodium zirconium cyclosilicate may be most appropriate in patients with advancing CKD (stages 3b or worse) and comorbidities such as heart failure/severe hypertension/diabetes, who have had repeated hospital re-admissions due to episodes of hyperkalaemia or exacerbation of their blood pressure or heart failure HF from sub optimal dosing of medications due to high potassium levels. As with all studies the data on subgroups analysis is difficult to interpret with any reliability and should be viewed with caution.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Implementation, including the resource availability to support implementation should not be an issue and I would expect that clinical practice would not be impacted, indeed it may possibly allow reduced monitoring, and assuming there is no significant increase in adverse effects, a better outcome. Currently KDIGO guidelines and NICE recommend monitoring of patients between one - two weeks after initiation of ACEI therapy and at each dose increment. This will not change as the impact on renal function needs to be assessed.
14. Will any rules (informal or	There will need to be a clear guidance on the measurement and duration of medication used to ensure that

formal) be used to start or stop treatment with the technology? Do these include any additional testing?	effectiveness is obtained. I expect a reduction of at least 0.5 mmol/L of potassium within a two week period, should be used as a bench mark. Additional testing will be needed within the first 2 weeks and after any dose escalation but based on the literature the potassium levels are stable. In addition testing of magnesium levels may be necessary within the first month of therapy as these may fall.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Sodium zirconium cyclosilicate may enable optimal RAAS inhibitor therapy in patients with HF and/or CKD who would otherwise be at risk of elevated K+. This should lead to an increase in cost from more effective use of these therapies. Currently, patients with HF and/or CKD receive RAAS inhibitor therapy as the mainstay of their treatment; however, RAAS inhibitor therapy may be suboptimal owing to the risk of elevated K+, leading to compromised outcomes for patients. NICE recommends discontinuation of RAAS inhibitors if the serum potassium is >6mmol/l and this additional treatment could reduce this need and allow maintenance of therapy.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	This is a new area on management of patients with electrolyte disorders mainly as a consequence of medications and in part diet. This addition may transform our ability to effectively manage patients with chronic hyperkalaemia. Normalising the diet of patients and maximising treatments (ACE-I and ARB) may have long term benefits but these are yet to be confirmed in randomised controlled trials.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Calcium Polystyrene Sulfonate is licensed for the treatment of hyperkalaemia associated with anuria or severe oliguria. It is also used to treat hyperkalaemia in patients requiring dialysis and in patients on regular haemodialysis or on prolonged peritoneal dialysis. There is no licensed drug therapy currently indicated for the treatment of elevated K+ in adult patients, including patients treated with RAAS inhibitor therapy who develop elevated K+. However I would expect over time that Resonium, which is used occasionally, becomes obsolete as this technology is added and replaces it.
• Does the use of the technology address any particular unmet need of the patient population?	Yes: an unmet need in several groups of patients including those on medications which tend to increase potassium (beta blockers; ACE-I; ARB; mineralocorticoid antagonists) but are essential to reduce risk of cardiovascular; cerebrovascular events and renal progression: 1. Elderly 2. Patients with Acute Kidney Injury (AKI) 3. Dialysis patients 4. Kidney transplants and those with CKD patients 5. Patients post myocardial infarction
17. How do any side effects or adverse effects of the technology affect the management of the condition	There is limited data on this but overall there appears to be great tolerability. The main symptoms or adverse effects which have been described include: -gritty taste associated with the medication; flatulence; abdominal pain and diarrhoea.

and the patient's quality of life?	
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Current UK practice is still in evolution and the introduction and use of this new medication is low and not universal in the UK. Sometime will be required before this data is available for analysis and interpretation. The international data would potentially translate to a UK population who have similar co-morbidities.
• If not, how could the results be extrapolated to the UK setting?	The data are encouraging on use in the USA patient population and elsewhere and equally applicable to a UK population.
• What, in your view, are the most important outcomes, and were they measured in the trials?	The outcome measures which are important to examine should include, hard end points and qualitative measures: These would consist of: - Potassium levels which have been measured in trials - Effect on ability to use RAAS inhibitors which appear in real world data - Adverse events which have been measured in trials. Other measures are important but have not been studied to in detail in trials: - Hospitalisations - Survival - Health related quality of life In addition I would record episodes of moderate hyperkalaemia (6.0-6.4) as these levels precipitate a visit to the emergency department for a further blood test and possible intervention and reduction of these would have a significant health gain for the patient and economic gain for the NHS.

	Some data on the ability to relax dietary restrictions and thus allow consumption of “healthier foods may be useful but I am not sure easily measurable (it might be captured in the health related quality of life assessment). I would record cardiovascular death separately
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Surrogate outcome measures are open to extreme bias and should be avoided. They are of interest only scientifically in hypothesis generation.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None that I am aware of when speaking to colleagues who use the drug in the USA as there is limited use in the UK currently but more extensive use in the USA.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	None again and on speaking with colleagues from other countries.
20. How do data on real-world experience compare with the trial data?	Similar data on real world experience with no new findings. The main findings are the large percentage of patients discontinuing or reducing the dose of important

	therapies to reduced comorbidity risk.
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Need to ensure access for elderly patients
21b. Consider whether these issues are different from issues with current care and why.	No
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Ability of optimise use of RAAS inhibitors in patients with chronic kidney disease; hypertension; diabetes and heart failure
- Reduction of potential episodes of acute hyperkalaemia requiring hospitalisations
- Relative safety but need to measure magnesium levels
- Sustained effect of the drug on potassium concentrations
-

Thank you for your time.

NICE National Institute for Health and Care Excellence

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Sodium zirconium cyclosilicate for treating hyperkalaemia [ID1293]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Kathryn Ryan**
2. Name of organisation	**Royal College of Pathologists**

3. Job title or position	**Chair of Clinical Biochemistry Specialty Advisory Committee (RCPath)** Consultant Chemical Pathologist
4. Are you (please tick all that apply):	x☐ an employee or representative of a healthcare professional organisation that represents clinicians? x☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The College is a professional membership organisation with charitable status, concerned with all matters relating to the science and practice of pathology. It is a body of its Fellows, Affiliates and trainees, supported by the staff who are based at the College's London offices. As such it is funded by subscription from its members. The majority of members are doctors and scientists working in hospitals and universities in the UK. The College oversees the training of pathologists and scientists working in 19 different specialties, which include cellular pathology, haematology, clinical biochemistry and medical microbiology. (adapted from RCPath website https://www.rcpath.org/about-the-college.html)
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of the treatment is to reduce potassium levels in patients with hyperkalaemia. This is often due to chronic kidney disease (CKD) and the hyperkalaemia is exacerbated by drugs such as ACEi. ACEi, ARBs, and spironolactone have been shown to improve cardiovascular outcomes and ideally these would be continued in patients with CKD, as adverse cardiovascular events are the major cause of mortality in this patient group. Reducing potassium levels with this treatment may lead continued use of ACEi, ARBs and spironolactone could prolong survival in these patients.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A significant response would be reduced hospitalisation for hyperkalaemia treatment, reduced cardiovascular events and increased time to renal replacement therapy.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	

9. How is the condition currently treated in the NHS?	The condition is currently treated by adjusting doses of potassium raising drugs, and administering calcium resonium and treating acute hyperkalaemia with insulin and glucose infusions, inhaled salbutamol and IV calcium gluconate.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are Clinical Practice Guidelines for Management of Acute Hyperkalaemia published in 2014 by the UK Renal Association. Sodium zirconium cyclosilicate is recommended for use in chronic but not acute hyperkalaemia.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is not clearly defined and often in involves a number of the steps outlined in the first part of question 9.
• What impact would the technology have on the current pathway of care?	The technology might reduce the frequency of admission for treatment of acute hyperkalaemia and enable doses of potassium raising drugs to be maintained at optimum levels.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No

• How does healthcare resource use differ between the technology and current care?	There is no equivalent medication (calcium resonium is poorly tolerated and so infrequently used in clinical practice).
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	It should be used in primary care, outpatient secondary care and specialist clinics.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment is needed. Blood tests would be checked frequently in any case in the patient group in whom this would be used.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	If the technology is well tolerated and produces significant sustained reductions in potassium levels it is likely to provide meaningful benefits.
• Do you expect the technology to increase length of life more than current care?	If the technology is well tolerated and produces significant sustained reductions in potassium levels it is likely to increase length of life.

• Do you expect the technology to increase health-related quality of life more than current care?	If the technology is well tolerated and produces significant sustained reductions in potassium levels it is likely to increase health-related quality of life.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with CKD.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	It will add an extra step to the treatment pathway for patients with CKD and recurrent or chronic hyperkalaemia but should not be more difficult than current care.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Rules which may be required around this technology would be assessing if it reduces potassium levels in individuals and stopping treatment if it is ineffective. I do not think this will result in additional testing as the patients underlying condition requires frequent blood tests.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial	It has potential to be innovative

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No
• Does the use of the technology address any particular unmet need of the patient population?	No
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	This medication can cause gastrointestinal side effects and this would adversely affect the patient's quality of life.
Sources of evidence **Clinicaltrials.gov website**	

18. Do the clinical trials on the technology reflect current UK clinical practice?	No current equivalent treatment, but the treatment with this medication (if effective) would allow continuation of medication which is used in current practice for treatment of conditions such as heart failure and hypertension.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Prevention of hyperkalaemia Reduction in adverse cardiovascular outcomes including death (if able to remain on ACEi and other medication)
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	No
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not aware of any
19. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	N/A
21. How do data on real-world experience compare with the trial data?	unknown
Equality	
22a. Are there any potential equality issues that should be	No

taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.

- This is a potentially useful treatment which would enable drugs known to improve cardiovascular outcomes to be continued longer or at a more effective dose.
- It could potentially reduce hospitalisation for management of acute hyperkalaemia.
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Patient expert statement

Sodium zirconium cyclosilicate for treating hyperkalaemia [ID1293]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Fiona Loud**
2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? ☒ a patient organisation employee or volunteer?

	☒ other (please specify): Someone who has had the condition
3. Name of your nominating organisation	Kidney Care UK
4. Did your nominating organisation submit a submission?	☐ yes, they did ☒ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☒ I am drawing on others' experiences. Please specify how this information was gathered: through working with other patients over the past 15 years, through our Facebook support group and from being on dialysis with other patients for 5 years
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Hyperkalaemia can come in bouts, if dialysis has not been enough to reduce potassium levels, especially in between dialysis sessions. This can be particularly bad for people on 3 days a week dialysis in hospitals/satellite units during the 2 day gap at weekends when eating or drinking something with a high potassium level which the body is not able to process. In my personal experience it makes a person feel sick, shake, have a racing heart and feel disoriented. Living with someone who develops hyperkalaemia is difficult for partners/carers especially if they are struggling to work out what food to buy and cook.
Current treatment of the condition in the NHS	
9. What do patients or carers	Patients say that current treatments are extremely unpalatable. Sometimes they struggle to get enough dialysis, or to eat. For people not on dialysis they may not recognise the symptoms and be in great need

think of current treatments and care available on the NHS?	of dietary advice, although amending diet is not always effective. A low potassium diet is very demanding, especially as it restricts common items like bananas, coffee and chocolate and if alongside other restrictions on dairy food if phosphate levels are also too high and accompanied by the very common liquid restriction of 500ml/day.
10. Is there an unmet need for patients with this condition?	There is an unmet need for effective strategies to reduce or ideally avoid hyperkalaemia.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Patients are looking forward to new developments in this area.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Not being able to benefit from it if it is restricted in some parts of the country, or only made available or effective for pre-dialysis patients.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so,	Those on dialysis, with CKD 5 but not on dialysis, such as those on conservative care, people with failing transplants would all be likely to benefit but special care should be taken with the latter 2 groups. For those on conservative care they may be looked after in the community and there is (unsurprisingly) often a reluctance to prescribe specialist drugs by non-specialists, so patients can lose out.

please describe them and explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**Please consider how the medication could be taken and those who would need to receive it in liquid form rather than by tablets.**
Other issues	
15. Are there any other issues that you would like the committee to consider?	
Key messages	
17. In up to 5 bullet points, please summarise the key messages of your statement: • Hyperkalaemia is dangerous and distressing	

- Current treatments are not adequate
- Dietary intervention is not always effective
- Dietary restrictions are very difficult
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Sodium Zirconium Cyclosilicate for Hyperkalaemia: A Single Technology Appraisal

Produced by School of Health and Related Research (ScHARR), The University of Sheffield

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Date completed Date completed (05/09/2018)

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Declared competing interests of the authors

No author declares a conflict.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

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Contributions of authors

Matt Stevenson and Andrew Rawdin critiqued the health economic analysis submitted by the company. Lesley Uttley summarised and critiqued the clinical effectiveness data reported within the company's submission. Jean Hamilton critiqued the statistical aspects. Mark Clowes critiqued the company's search strategy. Annette Alfonso provided clinical advice. All authors were involved in drafting and commenting on the final report.

Tables

Figures

ABBREVIATIONS

CKD	chronic kidney disease
CPRD	Clinical Practice Research Datalink
CPS	calcium polystyrene sulfonate
CS	company submission
eGFR	estimated glomerular filtration rate
EQ-5D	Euroqol 5-Dimensions
ERG	Evidence Review Group
HF	heart failure
HK	hyperkalaemia
HUI3	health utilities index mark 3
ICER	incremental cost effectiveness ratio
K	potassium
MACE	major adverse cardiovascular events
N/A	not Appropriate
NICE	National Institute for Health and Care Excellence
NYHA	New York Heart Association
OR	odds ratio
PBO	placebo
QD	once daily
RAASi	renin-angiotensin-aldosterone system inhibitors
RCT	randomised controlled trials
RRT	renal replacement therapy
SHFM	Seattle Heart Failure Model
S-K	serum potassium
SOC	standard of care
STA	Single Technology Appraisal
SZC	sodium zirconium cyclosilicate
TEAE	treatment emergent adverse event
TID	three times daily
TTO	Time trade-off

Executive Summary

Critique of the decision problem in the company's submission

The decision problem in the company submission was generally appropriate. The company base case assumed that patients identified in the acute clinical setting would not subsequently be treated in the chronic clinical setting which was not believed appropriate by the clinical advisors to the ERG.

Summary of the key issues in the clinical effectiveness evidence

The clinical evidence provided in the CS comprised the description of two Phase 3 trials (ZS-004 and ZS-005) in the main submission document and data from three further trials (ZS-002, ZS-003 and ZS-004E) in the appendices. No comparative data are available for people in the acute clinical setting or for the acute phase of the chronic clinical setting.

Summary of the key issues in the cost effectiveness evidence

The company model did not model the relationship between renin-angiotensin-aldosterone system inhibitor (RAASi) treatment and serum potassium (S-K) levels. This was believed to be a major limitation as a key benefit of SZC is that it may allow RAASi treatment to continue despite RAASi treatment being associated with increased S-K levels.

The company base case model did not withdraw RAASi treatment for patients receiving SZC despite having S-K levels of ≥6.0 mmol/L. The ERG believes that this is not aligned with NICE guidance, and prefer a sensitivity analysis conducted by the company.

The company assigned time trade off utility (TTO) values for patients with chronic kidney disease (CKD) rather than health utilities index mark 3 (HUI-3) values. The latter are preference-based and are believed to be more appropriate by the ERG.

The company used a relationship between S-K level and heart failure (HF) mortality that could not be verified by the ERG and were based on patients with hypertension.

The acute clinical setting model is based on patients in the chronic clinical setting who have been simulated to have high S-K levels.

The modelled benefits in terms of reduced mortality and hospitalisations related to S-K levels are based on observational data and surrogate endpoints. It is not known whether these relationships will hold in patients who have S-K levels reduced with SZC.

Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG present two base cases dependent on the assumed level of S-K increase associated with RAASi treatment. The ERG prefers base case 1, but has provided the second to allow the committee to assess an alternative plausible value. The components of the ERG base-cases are:

- Withdrawing RAASi treatment for 12 weeks for all patients with an S-K level ≥ 6.0 mmol/L
- Assuming that S-K levels drop when RAASi treatment is discontinued (0.23 mmol/L; 0.10 mmol/L)
- Using HUI3 utilities than TTO utilities for patients with CKD
- Using an alternative relationship between S-K levels and HF mortality derived from patients with HF.
- Allowing wastage (assumed to be 30 sachets over a 28-day period)
- Assuming that the costs associated with RAASi discontinuation or down-titration were lower than those assumed by the company

Further exploratory analyses in the chronic setting included

- Assuming lifetime treatment with SZC
- Assuming that the length of hospitalisation was independent of whether a patient was treated with SZC or standard of care (SOC)

In the acute setting the time horizon was reduced to a period of 52 weeks to allow patients with subsequent HK events to be treating in the chronic setting.

These changes are described in further detail Section 5.1 of the report.

The results of the ERG's exploratory analyses are presented in Table 1 to

Table 4, which are contained, along with interpretation of the results in Section 5.2 of the report. These results are deterministic but the model appeared linear with probabilistic estimates were similar to deterministic ones. The ERG comments that the incremental cost-effectiveness ratios (ICERs) are driven by the relative effect of SZC and SOC within the correction and maintenance phase, for which no evidence exists. The ERG base cases are likely to be unfavourable to SZC in the chronic setting as the assumed decrease in S-K levels in the correction phase for SOC is assumed to be that associated with SZC although the assumption of no effect of SOC is extremely favourable. Assuming that the surrogate relationships between S-K levels and clinical endpoints hold the ERG believes that the ICER in the chronic clinical setting for HF patients is likely to be in the range of £10,000 to £29,000; for CKD

patients in the chronic clinical setting the ICER is likely to be in the range of £16,000 to £46,000. If the surrogate relationships do not hold then the ICERs for all analyses are uncertain and likely to be higher than the ranges quoted.

Caution must be used when looking at the results in the acute clinical setting due to the reduced time horizon. More people are alive in the SZC arm at 52 weeks and this will produce additional quality-adjusted life year (QALY) gains, and incur some costs, over longer time horizons; only small future QALY gains are required to produce cost per QALY gained values of £30,000. The robustness of the results in the acute clinical setting are uncertain due to the reliance on data generated from chronic patients who have been simulated to have high S-K levels.

Table 1: Exploratory deterministic results for HF patients in the chronic setting*

Analysis	Discounted costs		Discounted QALYs		Life years		ICER
	SZC	SOC	SZC	SOC	SZC	SOC	
Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£13,458**
1) Withdrawing RAASi treatment for twelve weeks when S-K ≥ 6 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,063
2a) Assuming a decrease in S-K levels of 0.23 post-RAASi discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,012
2b) Assuming a decrease in S-K levels of 0.10 post-RAASi discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,333
4) Assuming an alternative relationship between S-K level and HF mortality	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,952
5) Adding in wastage: the cost of 30 sachets assumed over a 28-day period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,329
6) Reducing the costs associated with RAASi changes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,301
7) Assuming no reduction in S-K level due to SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,641
ERG base case 1 (1, 2a, 4, 5 and 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£29,239**
ERG base case 1 with lifetime SZC treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,668
ERG base case 1 with hospitalisation stay independent of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,257
ERG base case 1 with no effect of SOC on S-K levels	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8817
ERG base case 2 (1, 2b 4, 5 and 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£23,296**
ERG base case 2 with lifetime SZC treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,056
ERG base case 2 with hospitalisation stay independent of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,313
ERG base case 2 with no effect of SOC on S-K levels	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6949

*Note that ERG exploratory analysis 3 relates to CKD utilities and does not change the HF results.

Table 2: Exploratory deterministic results for CKD patients in the chronic setting

Analysis	Discounted costs		Discounted QALYs		Life years		ICER
	SZC	SOC	SZC	SOC	SZC	SOC	
Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£25,363**
1) Withdrawing RAASi treatment for twelve weeks when S-K ≥ 6 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,056
2a) Assuming a decrease in S-K levels of 0.23 post-RAASi discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,200
2b) Assuming a decrease in S-K levels of 0.10 post-RAASi discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,851
3) Using HUI3 utilities rather than TTO utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,537
5) Adding in wastage: the cost of 30 sachets assumed over a 28-day period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,882
6) Reducing the costs associated with RAASi changes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,683
7) Assuming no reduction in S-K level due to SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,532
8) Using EQ-5D values identified by the company	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,928
ERG base case 1 (1, 2a, 3, 5 and 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£46,936**
ERG base case 1 with lifetime SZC treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£53,685
ERG base case 1 with hospitalisation stay independent of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,965
ERG base case 1 with no effect of SOC on S-K levels							£15,877
ERG base case 2 (1, 2b, 3, 5 and 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£40,731**
ERG base case 2 with lifetime SZC treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,135
ERG base case 2 with hospitalisation stay independent of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,761
ERG base case 2 with no effect of SOC on S-K levels	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,173

*Note that ERG exploratory analysis 4 relates to HF and does not change the CKD results.

Table 3: Exploratory deterministic results for HF patients in the acute setting (52-week analysis)*

Analysis	Discounted costs		Discounted QALYs		Life years		ICER
	SZC	SOC	SZC	SOC	SZC	SOC	
Company base case (lifetime)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£7,380**
Company base case (52-weeks)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£10,263**
1) Withdrawing RAASi treatment for twelve weeks when S-K ≥ 6 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,263†
2a) Assuming a decrease in S-K levels of 0.23 post-RAASi discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,652
2b) Assuming a decrease in S-K levels of 0.10 post-RAASi discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,223
4) Assuming an alternative relationship between S-K level and HF mortality	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
5) Adding in wastage: the cost of 30 sachets assumed over a 28-day period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,098
6) Reducing the costs associated with RAASi changes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,263†
ERG base case 1 (1,2a, 4, 5 and 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£100,093**
ERG base case 1 plus restarting on RAASi treatment at 12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£196,049
ERG base case 2 (1,2b, 4, 5 and 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£37,097**
ERG base case 2 plus restarting on RAASi treatment at 12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£72,109

*Note that ERG exploratory analyses 3 and 8 relates to CKD utilities and do not change the HF results. Analysis 7 applies only in the chronic setting.
†This does not affect the ICER as the company models assumes that all patients in the acute setting discontinue RAASi treatment and never have RAASi treatment restarted

Table 4: Exploratory deterministic results for CKD patients in the acute setting (52-week analysis)

Analysis	Discounted costs		Discounted QALYs		Life years		ICER
	SZC	SOC	SZC	SOC	SZC	SOC	
Company base case (lifetime)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominating**
Company base case (52-weeks)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominating**
1) Withdrawing RAASi treatment for twelve weeks when S-K ≥ 6 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating†
2a) Assuming a decrease in S-K levels of 0.23 post-RAASi discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£289,171
2b) Assuming a decrease in S-K levels of 0.10 post-RAASi discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9627
3) Using HUI3 utilities rather than TTO utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
5) Adding in wastage: the cost of 30 sachets assumed over a 28-day period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
6) Reducing the costs associated with RAASi changes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating†
8) Using EQ-5D values identified by the company	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
ERG base case 1 (1, 2a, 3, 5 and 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£346,485**
ERG base case 1 plus restarting on RAASi treatment at 12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£140,264
ERG base case 2 (1, 2b, 3, 5 and 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£28,760**
ERG base case 2 plus restarting on RAASi treatment at 12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,566

*Note that ERG exploratory analysis 4 relates to HF and does not change the CKD results. Analysis 7 applies only in the chronic setting.
†This does not affect the ICER as the company models assumes that all patients in the acute setting discontinue RAASi treatment and never have RAASi treatment restarted

1 BACKGROUND

With the consent of the National Institute for Health and Care Excellence (NICE) this report pilots the proposed new NICE template for single technology appraisals (STAs) and is therefore necessarily shorter in length that historic STA reports written by the Evidence Review Group (ERG). Attempts have been made to avoid duplication with the company submission unless necessary and to concentrate on the most salient issues in terms of clinical plausibility and impact on the incremental cost-effectiveness ratio (ICER).

1.1 Disease Background

Sodium Zirconium Cyclosilicate (SZC) is marketed by AstraZeneca UK for the treatment of hyperkalaemia (HK). HK is associated with increased rates of mortality and major adverse cardiovascular events (MACE) which can be life-threatening. Within the company submission (CS)[1] there is an acceptable summary of HK, which details the definition, which is a serum potassium (S-K) concentration of > 5.0 mmol/L, and risk factors for HK which include chronic kidney disease (CKD) and heart failure (HF). Common treatments for patients with CKD or HF are collectively known as renin-angiotensin-aldosterone system inhibitors (RAASi). Whilst RAASi treatment is protective in patients with CKD or HF against mortality, worsening of CKD, and MACE such treatment increase S-K levels and can endanger patients by inducing HK. NICE Guidelines for CKD in adults recommend that patients are not routinely offered RAASi treatment if their S-K levels are > 5.0 mmol/L and that RAASi treatment should be discontinued if S-K levels > 6. 0 mmol/L and other drugs that increase S-K levels have been discontinued.[2]

1.2 The technology and the company's anticipated positioning of SZC

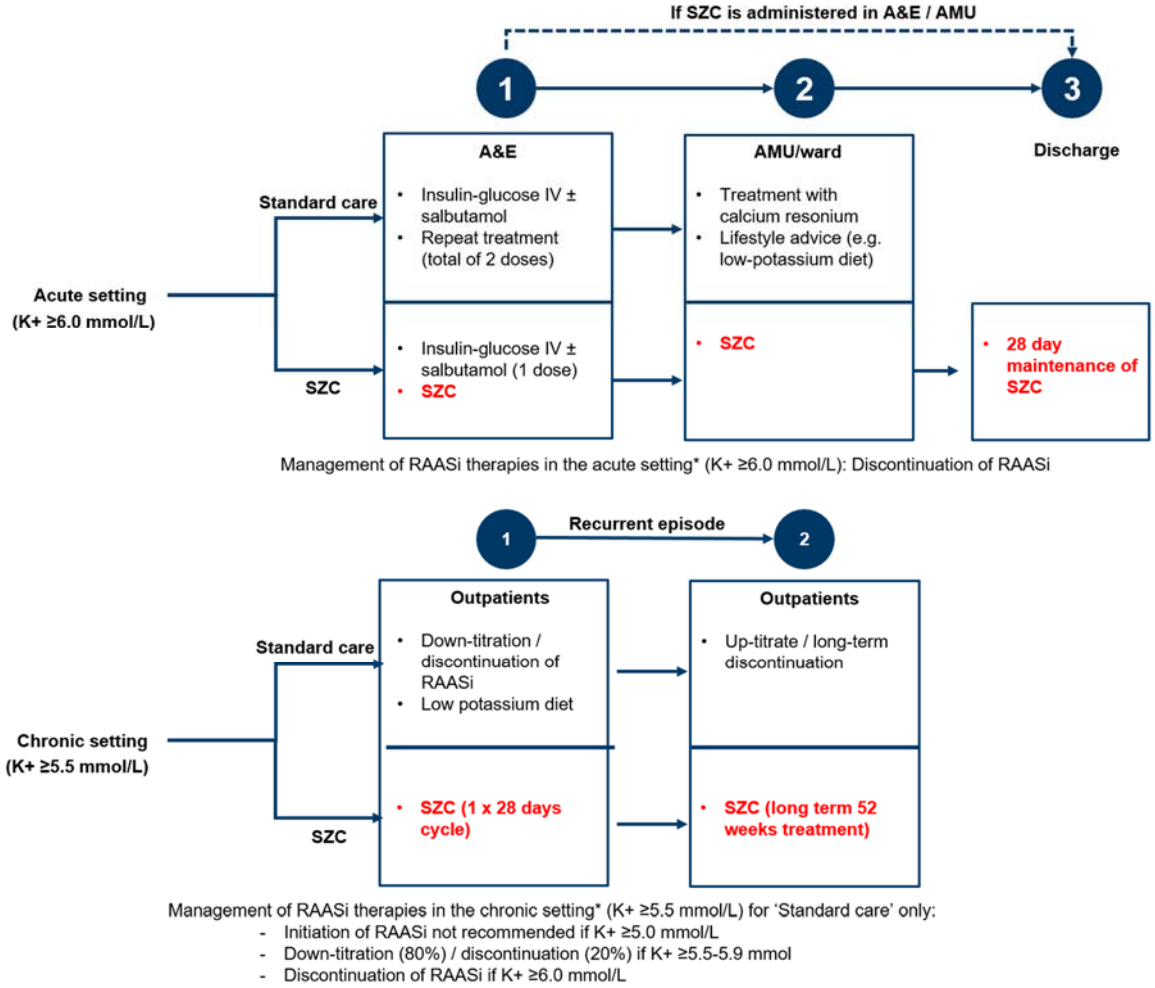
A description of SZC is provided in Section 1.2 of the CS. The intervention is available as either a 5g or 10g powder for oral suspension. During the correction phase of treatment, the recommended dose is 10g three times a day until normokalaemia is achieved. This is typically with 24-48 hours, although 10g may be continued for an additional 24 hours. If normokalaemia is not achieved after 72 hours other treatments should be considered. Once normokalaemia is achieved maintenance regimens should be followed with the recommended dose of 5g once daily, although if required a possible titration, both upwards and downwards is possible in order to maintain normokalaemia.

Figure 6 in the CS depicts the company's intended positioning of SZC and is reproduced in Figure 1. The company have provided separate estimates of the ICER for patients identified within the acute setting and those within the chronic setting. Patients identified in the CS as in the acute setting represent those with acute medical problems, such as sepsis, dehydration/acute kidney injury, or pneumonia, whereas patients within the chronic setting will have already been identified as having HK and will be

regularly monitored by clinicians in secondary care. Patients identified within the acute setting in the CS are assumed to have S-K levels ≥ 6.0mmol/L and would all be eligible for SZC treatment; patients in the chronic setting would be eligible to receive SZC treatment with S-K levels ≥ 5.5mmol/L, although clinical advice to the ERG suggests that this will vary by clinician and circumstances, and that it is possible that SZC treatment would not be given until S-K levels of > 6.0mmol/L unless RAASi treatment was being down-titrated or if patients were experiencing recurrent episodes of moderate HK.

SZC treatment was assumed to impact on continuation of treatment with RAASi, with a greater proportion of patients remaining on RAASi treatments, and/or at a greater dose. As these relationships are relatively complex these are discussed in further detail in Section 4.2.4.

Figure 1: The company's anticipated positioning of SZC



1.3 Critique of company's definition of decision problem

The company's definition of the decision problem compared with the final NICE scope[3] is summarised in Table 5.

Table 5: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	Adults with HK	Adults with HK in a comorbid patient population comprising CKD (stage 3–5) HF	HK occurs predominantly in patients with an underlying degree of CKD or HF due to disease pathophysiology and the wide use of cardio-renal protective medicines, such as RAASi, which significantly increase the risk of developing HK. The CKD or HF population represents the most relevant patient population in UK clinical practice.	The ERG understands the rationale for the reduced population. No cost-effectiveness results are presented for patients with HK that do not have CKD or HF.
Intervention	SZC	SZC	Not appropriate (N/A)	N/A
Comparator(s)	Standard care. This includes a low potassium (K^+) diet with or without agents that reduce levels of potassium in the body	Acute setting: Intermittent use of calcium resonium (with some patients receiving a repeat dose of insulin-glucose) Chronic setting: no therapy administered. All patients are managed with lifestyle interventions (e.g. dietary intervention)	N/A	The ERG does not know to what level lifestyle interventions had been recommended within the key randomised controlled trials

		and modification of concomitant medications, such as RAASi		(RCTs) that form the evidence base for SZC
Outcomes	The outcome measures to be considered include: Serum potassium level Use of RAASi therapy Mortality Time to normalisation Adverse effects (AE) of treatment Health-related quality of life (HRQoL)	Outcomes included in the submission, include: • S-K level • Time to normalisation • AEs of treatment • Use of RAASi therapy (exploratory endpoint)	Mortality was not an outcome in the clinical trial programme for SZC as this would be confounded by underlying comorbidities. HRQoL was not collected in the clinical trial programme for SZC as HK symptoms often go unnoticed and outcomes such as cardiovascular events and mortality were not captured in the trials.	The ERG is content with the reasons provided by the company.
Economic analysis	The reference case stipulates that cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life-year (QALY). The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or	As per scope	N/A	N/A

	outcomes between the technologies being compared. Costs will be considered from a National Health Service (NHS) and Personal Social Services perspective			
Subgroups	If the evidence allows, the following subgroups will be considered People with acidosis People with acute HK People with CKD People with HF	The base-case analysis includes adults with HK and comorbidity for CKD or HF. Patients can present in the acute (S-K ≥6.0 mmol/L) and chronic (S-K ≥5.5 mmol/L) settings. Those presenting in the acute setting are those with acute HK.	The clinical trial programme for SZC did not evaluate people with acidosis.	The ERG comments that no analyses were presented for people with HK but who did not have CKD or HF.
Special considerations including issues related to equity or equality	None	None	N/A	N/A

2 CLINICAL EFFECTIVENESS

2.1 Critique of the methods of review(s)

The main submission document does not describe the systematic review that was used to inform the clinical effectiveness but Appendix D of the CS describes that the company performed an update to a recently published relevant systematic review (Palaka *et al*. 2018[4]) on the management of HK covering the period between April 2017 and April 2018.

2.1.1 Searches

As an update to the Palaka *et al.* 2018[4] review, the CS clinical effectiveness searches presented in Appendix D cover only the period from April 2017-April 2018. Evidence prior to this date was drawn from the published review by Palaka *et al*. 2018[4] which was based on a more restrictive search strategy and narrower inclusion criteria than the decision problem in the NICE scope. Specifically, the published review is less inclusive of foreign language studies with an English abstract, studies with mixed populations, and does not include safety data. Additionally, the Palaka *et al*. (2018[4]) review is based on two search strategies, in 2016 and 2017, that were less sensitive than that used in the CS update, with the 2016 search strategy using titles and major headings only to search for HK, and not abstracts.

The review question in Appendix D of the CS (page 2) asked 'what randomised controlled trials have been conducted in HK?'. However, the search strategy used for Medline, EMBASE and Cochrane for the period since 2017 would retrieve only those studies mentioning at least one of SZC or standard care. It is also noted that this list did not include the term which is a synonym for SZC "zirconium silicate", used in some trials. The identified limitations in the company's search strategy were addressed in clarification questions A8, A9 and A10 which result in the searches being to the satisfaction of the ERG.[5]

2.1.2 Inclusion Criteria

The inclusion and exclusion criteria for clinical effectiveness studies are listed in Table 7 of Appendix D in the CS. The population, intervention, comparators, and outcomes of interest are broadly in accordance with the decision problem in the final NICE scope.[3] The CS criteria differ from the Palaka *et al*.[4] review in that the former uses 5.0 as a cut-off whereas the latter uses 4.9 but this difference is unlikely to be clinically meaningful.

2.1.3 Study Selection

The company describe that study selection were performed by two independent reviewers with disagreement discussed with a third reviewer when required. Reference lists of systematic reviews and included studies were not checked for RCTs meeting the inclusion criteria.

Details of study selection using appropriate methods with more than one reviewer are described. 73 references were considered for extraction. Two trials of patiromer were appropriately excluded as it is not a comparator in the decision problem. [6] The remaining 71 references related to 13 RCTs that were identified as relevant to the review question.

Table 6: SZC trials included and reported in the CS

Trials included in main submission document	Trials included in CS appendices	Ongoing trials discussed but results not included in CS
ZS-004[7] (Kosiborod 2014)[8] ZS-005[9] (no peer reviewed published paper but clinical study report provided)	ZS-002[10] ZS-003[11] ZS-004E[12] (CS Appendix M and all clinical study reports provided)	ENERGIZE (NCT03337477).[13] Phase 2 RCT enrolling 132 patients to assess SCZ plus insulin and glucose versus placebo (PBO) plus insulin and glucose in patients with S-K ≥5.8 mmol/L DIALIZE (NCT03303521).[14] Phase 3b RCT enrolling 180 patients to assess efficacy and safety for patients on stable haemodialysis

Clinical advice to the ERG stated that the ongoing trials (ENERGISE, DIALIZE) will provide the data for the patients with acute HK that they would be most interested in treating with SZC and that the data from the included trials in the CS is limited to chronic, stable patients.

The Palaka *et al*. 2018[4] review is the published journal article of a full report of a systematic literature review (Buchanan-Hughes *et al.*[15]) which states some justifications for not formally comparing RCTs of SZC. During a request for clarification from the ERG (question A13)[5], the company clarified that studies of temporising agents (such as insulin dextrose) were excluded from the review as they are '*administered earlier in the treatment pathway to shift potassium into the cells*'. The ERG considers that the reasons provided in the CS of different routes of administration and mechanisms of action are not valid reasons to justify the company's decision not to formally compare SZC with temporising agents via an indirect comparison. Additionally, whilst temporising agents may not be '*used for prolonged administration*', the comparison of SZC with relevant comparators such as insulin for the initial hours would provide evidence for its relative efficacy and safety compared to temporising agents in the correction phase of treatment. It is in this situation which is where head-to-head data with any comparator, including PBO, is lacking from the trials submitted (ZS-004[7] and ZS-005[9]). However, the ERG considers that the company's decision not to conduct an indirect comparison due to the absence

of evidence at comparable time points for SZC and temporising agents in the correction phase of treatment was appropriate.

Following a request for clarification, the company stated that only three SZC trials (additional to ZS-004[7] and ZS-005[9]) are relevant to the decision problem (question A13)[5] from the systematic review. These are the published papers for the trials ZS-002[10] (Ash 2015)[16], ZS-003[11] (Packham 2015)[17] and ZS-004[7] (Kosiborod 2014).[8]

2.1.4 Data Extraction

Results are provided for primary and secondary endpoints narratively in turn for each included trial. The company do not provide any data extraction from the trials to summarise the results of all the relevant RCTs in the systematic literature review. Reasons were not provided in the CS for why a systematic review which includes data extraction and data synthesis of the trials identified was not performed. Neither of the two referenced reports of the systematic literature reviews (Buchanan-Hughes *et al.*[15] or Palaka *et al.*[4]) includes the results from RCT evidence. The Buchanan-Hughes *et al.*[15] full report of the SR, which the CS aims to update, only provides results for non-randomised evidence for down-titration or discontinuation of RAASI and diet.

2.1.5 Quality Assessment

Quality assessment is provided in tabulated form for the 13 RCTs stated as relevant and also for trials ZS-004E[12] and ZS-005[9] in Appendix D of the CS. Summaries of the critical appraisal were not provided. The ERG requested clarification from the company about which of the 13 trials which were subjected to quality assessment were regarded as relevant to the decision problem. The company responded that three of the 13 trials (ZS-002[10], ZS-003[11] and ZS-004[7]) were relevant to the decision problem. Reasons for exclusion for the other ten trials were provided in the clarification response to question A13,[5] and can be viewed in Appendix 1.

2.1.6 Data Synthesis

No meta-analysis of studies is performed and results across studies are not provided in either tabulated or narrative form.

The CS cites reasons for not conducting a meta-analysis as clinical and methodological heterogeneity within the CS trials of SZC including:

- Smaller proportions of baseline S-K levels above 5.5 in trial ZS-003[11] than the other SZC trials
- shorter trial duration in ZS-002[10]

- titration (both increase and decrease) allowed in ZS-005[9] but not in ZS-004[7] (only decrease)
- shorter maintenance phase in ZS-004[7] (28 days) than ZS-005[9] (52 weeks)
- enrolment to ZS-004E[12] at investigator's discretion and not part of original statistical analysis plan

During a request for clarification the ERG (question A19)[5] asked the company to clarify why the argument relating to different treatment regimens in ZS-004[7] and ZS-005[9] is not consistent with the statement in the cost-effectiveness section which stated that participants in these studies "*received the same treatment… for the first 28 days*". This issue is still not clear after the company's response, which referred to "*differences in dosing regimens*" as a reason for not conducting the meta-analysis. The ERG considers that it is potentially appropriate to pool data from ZS-004[7] and ZS-005[9] for the analysis presented in the cost-effectiveness section (assuming that the treatments received are considered sufficiently similar). However, the ERG notes that this is inconsistent with arguments provided earlier in the submission. Irrespective of this inconsistency, the ERG is satisfied that it was not possible to conduct a meta-analysis of studies ZS-004[7] and ZS-005[9] due to the lack of comparator arm in ZS-005.[9]

The ERG also asked the company (question A21)[5] to conduct a meta-analysis, using just the subgroup of patients from trials ZS-003[11], ZS-004[7] and ZS-005[9] with S-K >5.5%. This was not conducted by the company as they considered that ZS-003[11] was "*not relevant to the current decision problem*". The ERG considers the exclusion of ZS-003 to be appropriate on the basis of small numbers of patients in the licensed dose study arms.

2.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

2.2.1 Key Clinical Trials

The two trials included in the CS (ZS-004[7] and ZS-005[9]) were relevant to the decision problem outlined in the final NICE scope and were good quality, adequately powered, multi-centre international trials. The majority of patients in the trials ZS-004[7] and ZS-005[9] were from the USA, Australia and South Africa. During a request for clarification by the ERG from the company clarified that ZS-005[9] enrolled ten patients from one UK site only (clarification response to question A5).[5] In the study populations for ZS-004[7] and ZS-005[9] approximately one-third of patients had HF and two-thirds of patients had CKD although these were not mutually exclusive. Approximately two-thirds of the study populations used RAASi medication.

2.2.1.1 ZS-004

Trial ZS-004[7] features an open-label acute phase where all patients are treated with SZC 10g until normokalaemia is reached at which point they are randomised to either SZC, 5g, 10g, 15g or PBO. Separate analyses were performed for the acute and maintenance phases.

Maintenance phase

The primary efficacy endpoint was the model-based mean of all available S-K values during maintenance phase study days 8-29 (see

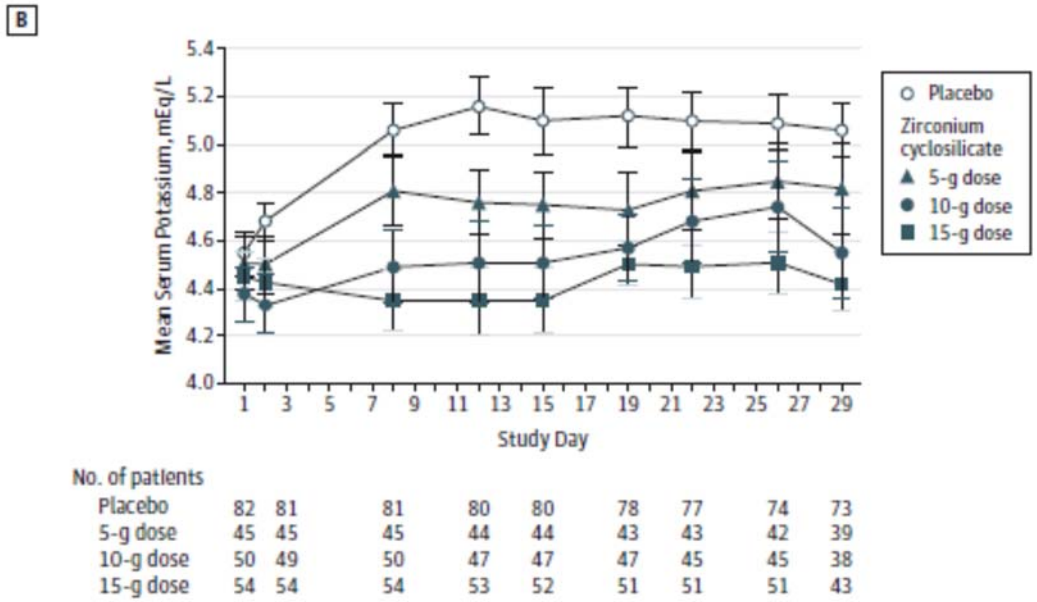
Figure 2) Mean S-K levels during days 8-29 in ZS-004[7] were significantly lower for SZC 10 g and 5 g daily dose (4.5 mmol/L and 4.8 mmol/L) than PBO (5.1 mmol/L) ($p<0.0001$). The raw data were analysed using a longitudinal model as shown below

[redacted] (1)

[redacted]

Full results of the fitted model to the maintenance phase of ZS-004[7] are provided in Appendix 2 Table 18. All treatment groups showed statistically significant reductions in S-K levels compared with placebo ($p<0.001$). Acute phase baseline S-K ($p=0.026$) and maintenance phase baseline S-K ($p=0.002$) were also statistically significant at the 5% level. Heterogeneity estimates for the patient level random effect and random error terms, were not provided by the company.

Figure 2: Serum potassium levels during the randomised phase of ZS-004 replicated from the CS (Figure 10)



Secondary outcomes reported but not repeated here included; the number of normokalaemic days during the maintenance phase inclusive of days 8-29, change and percent change from acute phase baseline to each maintenance phase follow-up time point, the proportion of patients who achieved normalisation in S-K values at Day 29 of the maintenance phase, and the time to hyperkalaemia.

Acute phase

A key secondary efficacy outcome was the proportion of patients who achieved normalisation in S-K values at 24 and 48 hours after the start of dosing. 168/254 patients (66.1%) normalised at 24 hours and 221/251 patients (88.0%) normalised at 48 hours after the first dose of SZC. Other secondary outcomes reported but not repeated here included: the exponential rate of change in S-K values during the initial 48 hours of study drug treatment; the change and percent change from baseline in S-K values at 24 and 48 hours after start of dosing; and the time to normalisation of S-K (as defined by S-K values of 3.5 to 5.0 mmol/L, inclusive).

2.2.1.2 ZS-005

Trial ZS-005[9] is open-label SZC use and thus does not have a comparator arm. Trial ZS-005 is an open-label study containing an acute phase where all patients are treated with SZC 10g three times a day for 24-72 hours. A long-term maintenance phase (up to 12 months) follows where patients initially receive SZC 5 g QD which may be increased up to 15g QD depending on is STAT measurements monitored weekly throughout the first month of the study and every four weeks thereafter.

Acute phase

The primary endpoint for the acute phase was the restoration of normal S-K levels (3.5-5.0 mmol/L). 77.9% of patients achieved normokalaemia (95% CI: 74.8%, 80.9%) within 72 hours.

Other outcomes reported but not repeated here included the proportion of patients who achieved normalisation in S-K values at 24 and 48 hours after start of dosing.

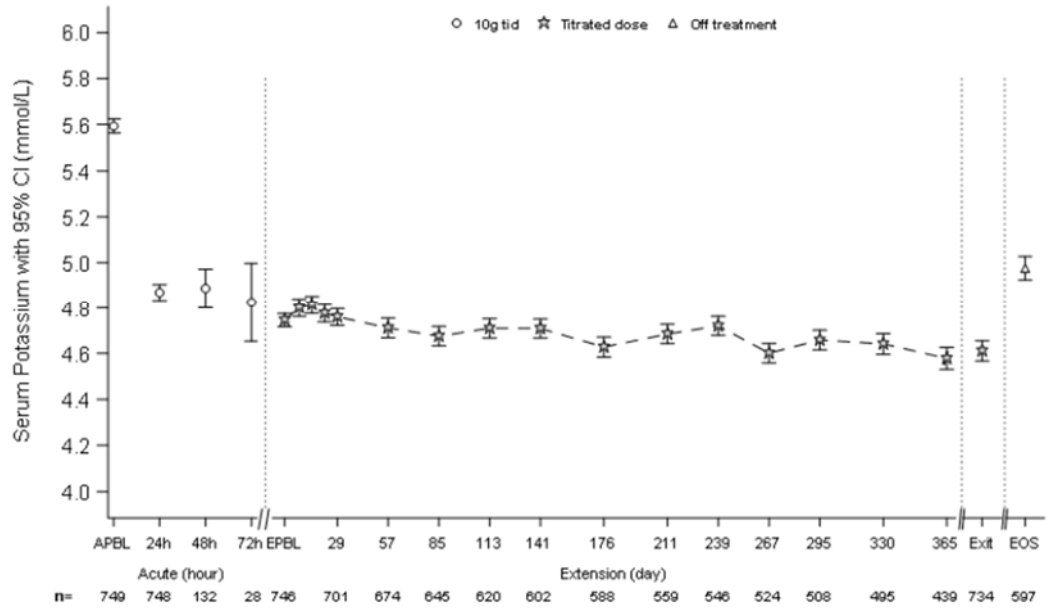
Extended/maintenance phase

The primary endpoint for the extended phase of the trial (which provides data for the maintenance phase of treatment) was the percentage of patients with mean S-K levels ≤ 5.1 mmol/L during days 85-365 (see

Figure 3). 88.4% (95% CI: 85.7%, 90.8%) maintained a mean S-K of ≤ 5.1 mmol/L during days 85-365.

Mean S-K levels for the extended phase of ZS-005[9] were also analysed using a longitudinal model as described in equation (1). Full results of the fitted model are shown in Appendix 2 Table 5. Acute phase baseline S-K (p=0.0006), extended dosing baseline S-K (p<0.0001), and acute phase baseline eGFR (p=0.0061) were statistically significant at the 5% level.

Figure 3: Serum potassium levels during the extended phase of ZS-005 replicated from the CS (Figure 12)



Other secondary efficacy outcomes included the proportions of patients with mean S-K values between 3.5 and 5.5 mmol/L, inclusive, across extended dosing phase days 85–365, as well as the proportions at

each visit during extended dosing. Across extended dosing phase days 85–365, 98.5% (95% CI: 97.2, 99.3) of patients had mean S-K values between 3.5 and 5.5 mmol/L, inclusive. During the extended dosing phase time points, the proportions of patients with S-K values between 3.5 and 5.5 mmol/L, inclusive ranged from 91.3% (95% CI: 89.0, 93.2) to 95.6% (95% CI: 93.5, 97.2).

Other secondary and additional outcomes reported but not repeated here included: the mean S-K levels at each visit; the mean change and mean percent change from acute phase baseline in S-K; nominal and percent change from the acute phase baseline in bicarbonate levels at each visit; proportion of subjects with normal bicarbonate values at acute phase day 1 and each extended phase visit.

2.2.2 Safety data

Adverse event data from trial ZS-004[7] indicate that between 29.4% and 53.3% patients experienced a treatment-emergent adverse (TEAE) with SZC 10 g and 5 g respectively compared with PBO (31.8%). Adverse event data from trial ZS-005[9] indicate that the overall incidence of TEAEs was 65.5% during the 12-month extended dosing phase.

The most frequent adverse events in the trials included oedema, gastrointestinal disorders, hypertension, urinary tract infection and hypokalaemia. The overall incidence of serious treatment-emergent adverse events was low. In ZS-005[9], eight patients died during the extended dosing phase. A further two patients had serious events considered related to study drug by the investigator (pulmonary oedema, and cardiac failure congestive).

Frequent occurrence of oedema as an adverse event is likely related to SZC's mechanism of action for exchanging potassium for sodium and is most likely to prompt treatment with diuretics.

2.2.3 Attrition

Premature discontinuation of study drug occurred in over one third of patients in trials with long-term data (ZS-004E[7] and ZS-005[9]). Attrition was 35.8% (n=44) in the extended maintenance trial ZS-004E[12] (CS Appendix D, Table 13) and 37.5% (n=280) in the extended dosing phase of trial ZS-005.[9] Therefore, less than two thirds of patients adhered to SZC in the extended phase of the CS clinical trials.

Clinical advice to the ERG stated that discontinuation of SZC could lead to potentially dangerous clinical scenarios if SZC approval encourages clinicians to use extra RAAS drugs and the goal of SZC treatment is to protect patients from the risks associated with potassium-increasing drugs for serious conditions, such as those for HF. Clinical advice stated that patients may be more likely to discontinue SZC treatment because it is a powder/drink formulation as opposed to a pill which is easier to take.

Both clinical advisors highlighted that it is preferable to attempt dietary interventions or at least to provide brief diet information before considering drugs such as SZC as patients may not welcome dietary advice later in their treatment pathway than earlier.

2.2.4 Dose modification during treatment:

SZC exchanges potassium indiscriminately, therefore some monitoring/dose modification was required to ensure normokalaemia is maintained, and to prevent hypokalaemia in the trials included in the CS. In ZS-004[7], potassium was measured on days 1, 2, 5, 8, 12, 15, 19, 22, 26, and 29. If a patient's potassium value was between 3.0 and 3.4mEq/L at any time during the randomised phase, the dose was reduced from once daily to every other day for the remainder of the study.

In ZS-005[9], 417 patients had at least one dose modification with 32 patients down-titrated to 5 g every other day, 396 titrated to the 10 g daily dose, and 87 titrated to the 15 g daily dose. At least two dose modifications were needed in 16.5% of patients with <4% requiring at least three dose modifications.

Clinical advice to the ERG was that HK would be closely monitored and that it is unlikely that SZC would require additional monitoring to standard care in the acute setting.

2.2.5 Company's interpretation of clinical data

Randomised and blinded data is only for the maintenance phase position in the CS included trials but is not compared with an active intervention such as protocol-mandated dietary restriction, insulin glucose or calcium resonium.

No randomised, blinded data for SZC are available for the correction phase position. In clinical practice patients in the correction phase in the acute setting are treated with temporising agents such as insulin dextrose and SZC to stabilise S-K levels within 48 hours but as patients in the study population were chronic and stable (not acute HK patients), insulin dextrose was not administered. As the company do not conduct an indirect comparison, insulin dextrose is not considered as a comparator in the base case.

Clinical advice to the ERG is that patients in the "acute" phase in the included studies are not fully representative of real-world patients with acute HK, as the CS included trials were conducted in an outpatient setting, excluding acutely unwell patients, dialysis patients.

2.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The CS (page 68) describes that it was not necessary to conduct an indirect or mixed treatment comparison because head-to-head data for the maintenance phase are available via ZS-004[7] which has a valid comparator (PBO). However, there is no head-to-head data from either ZS-004[7] or ZS-005[9] in the acute phase of treatment.

The CS provides justification for not conducting an indirect comparison with insulin glucose for the correction phase of treatment due to identifying RCTs with "*very small population and only reported outcomes within the first few minutes or hours of administration*". The CS identified one RCT[18] of calcium resonium, however this did not share a common comparator with the company's trial and the dose of calcium resonium considered was not relevant to UK clinical practice.

The ERG consider that the comparison of SZC with insulin glucose for the initial hours of hospitalisation could provide evidence for its relative efficacy and safety to temporising agents in the correction phase of treatment which is where head-to-head data with any comparator, including PBO, is lacking from the trials considered in the CS (ZS-004[7] and ZS-005[9]). However, the ERG considers that the company's decision not to conduct an indirect comparison due to the absence of evidence at comparable time points for SZC and temporising agents in the correction phase of treatment was appropriate.

2.4 Additional work on clinical effectiveness undertaken by the ERG

The ERG searched for and reviewed records of completed and ongoing clinical trials of SZC. Six further registered trials which are relevant to the decision problem were identified. One was conducted by ZS Pharma and collected data on real-world standard of care for HK. Despite being completed in May 2016, results have not been published. Three further trials by AstraZeneca of patients, mainly located in Asia, have been completed more recently (see

Table 7). Two further early trials by AstraZeneca are not yet recruiting.

Table 7: Trials not included or not reported in the CS

Clinical trial no. **Status** **Sponsor**	**Description**
NCT02607085[19] Completed May 2016 Sponsor: ZS Pharma	Prospective observational study of 203 subjects with standard of care admitted to the emergency department with HK (≥ 5.5 mmol/L). Subjects receiving IV calcium, insulin/glucose, beta2-agonists, diuretics, IV bicarbonate, SPS, dialysis and/or other intervention measured at 30 minutes, 1, 2, & 4 hours after treatment. Subjects receiving no intervention during the initial 4-hour period measured 4 hours after baseline measurement.
NCT03283267[20] Completed Nov 2017 Sponsor: AstraZeneca	Open-label safety and pharmacodynamic study of 22 healthy Chinese subjects administered with 5g or 10g SZC over 4 days.
NCT03127644[21] Completed Feb 2018 Sponsor: AstraZeneca	Phase 2/3 dose-response trial of 103 Japanese patients with HK (≥ 5.1 mmol/L and ≤ 6.5 mmol/L). SZC 5g or 10g, 3 times per day versus PBO.
NCT02875834[22] Completed in Feb 2018 Sponsor: AstraZeneca	HARMONIZE GLOBAL. Phase 3 multicentre RCT of 239 patients from Japan, Republic of Korea, Russian Federation & Taiwan with HK (≥ 5.1 mmol/l). SZC 5g or 10g vs PBO once daily following two days of initial SZC 10g TID
NCT03172702[23] (not yet recruiting). Sponsor: AstraZeneca	Open-label study enrolling 150 Japanese patients with HK (≥ 5.1 mmol/L). Includes 24 to72-hour correction phase of SZC 10g TID and 12-month long-term maintenance phase or SZC 5g QD.
NCT03528681[24] (not yet recruiting) Sponsor: AstraZeneca	HARMONIZE ASIA. Phase 3 multicentre RCT of 337 patients from China and India with HK (≥ 5.1 mmol/L). SZC 5g or 10g vs PBO once daily following two days of initial SZC 10g TID

2.5 Conclusions of the clinical effectiveness section

The ERG is satisfied that the trials presented are accurately described and relevant to the decision problem subject to the following limitations.

The CS provides evidence that SZC lowers S-K levels in the study population of chronic, stable patients versus PBO. It does not provide direct evidence for:

- SZC as plausible alternative for protocol mandated dietary modification or versus any comparator in the correction phase
- SZC efficacy or safety in acutely unwell patients

The CS does not present a systematic review that includes trials for potential comparators to SZC. Whilst the reasons for excluding trials presented in the CS may be valid with regards to meta-analysis, using conventional systematic review methods the CS should have summarised the characteristics and results (by tabulation or narratively) of studies which were identified but subsequently excluded but may have been relevant to the decision problem.

3 COST EFFECTIVENESS

3.1 ERG comment on company's review of cost-effectiveness evidence

The ERG is satisfied with the company's review of the cost-effectiveness literature. Three studies with a UK perspective were found that evaluated interventions for the treatment of HK.[25-27] These are summarised in Table 22 of the CS: one was a Markov model[27] and two were individual patient models.[25, 26] The company stated that a Markov model would have resulted in an unreasonable number of health states and that a patient-level simulation model, which simulates individual patients and can use their simulated histories to influence future events would be more appropriate and thus a *de novo* model was constructed. The ERG does not find this position unreasonable.

3.2 Summary and critique of the company's submitted economic evaluation by the ERG

3.2.1 NICE reference case checklist

The concordance between the *de novo* model in the company submission and the NICE reference case is detailed in Table 8.

Table 8: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The CS is appropriate
Perspective on costs	NHS and PSS	The CS is appropriate
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The CS is appropriate
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The CS is appropriate
Synthesis of evidence on health effects	Based on systematic review	Health effects are based on data longitudinal models fitted to pooled data from ZS-004 and ZS-004. This is potentially appropriate but there is inconsistency between the clinical-effectiveness and cost-effectiveness sections regarding

		whether treatments in the two trials are sufficiently similar to pool. No information regarding the longitudinal model selection and diagnostic checking was provided to allow verification of the selected model.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The Euroqol 5-Dimensions (EQ-5D) is the preferred measure of health-related quality of life in adults.	Health effects are measured in QALYs. Utilities for CKD are generated from time trade-off exercises rather than a preference-based measure.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	The CS is appropriate
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The utilities for CKD are from time trade-off (TTO) exercises valued by US patients rather than a representative sample of the UK population.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The CS is appropriate
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The CS is appropriate
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The CS is appropriate

PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.

3.2.2 Population

Patients considered within the company's model are patients with HK and with either CKD (Stages 3a to 5 (non-dialysed)) or with HF (NYHA functional class I, II, III, or IV). The company assumed that no patient had both CKD and HF (response to clarification question B10).[5]

It was assumed within the model that the population are 63% male and 37% female, pooled from studies ZS-004[7] and ZS-005.[9] All of these patients were assumed to be 64.1 years of age, with 70.2% of patients on RAASi treatment on entry to the model in accordance with data from ZS-005.[9] Patients with CKD were assumed to have an eGFR of 44.66 mL/min/1.73m^2 as detailed in Table 69 of the CS which was based on the weighted average eGFR between CKD and HF patients (64.3% CKD, 35.7% HF). This differs from the value of 31.63 mL/min/1.73m^2 for CKD patients and of 68.14 mL/min/1.73m^2 reported in Table 28 of the CS.

Patients in the chronic clinical setting are assumed to have S-K levels ≥ 5.5mmol/L. Patients in the acute clinical setting are assumed to have S-K levels ≥ 6.0mmol/L. Hypothetical patients are assumed to have an underlying S-K level of [redacted], which is also influenced by a patient component and an observational component which are described in more detail in Section 3.2.8. Patients that are sampled with an S-K level <5.5 mmol/L in the chronic setting are assumed, and <6.0 mmol/L in the acute setting are discarded and resampled.

3.2.3 Clinical Setting

The CS evaluated patients within two designated clinical settings: chronic and acute. The distinction between these settings were detailed in the company's response to clarification (question A3)[5] with the company stating that the decision to adopt two distinct settings was based on discussions with UK experts in the management of HK.

Patients within the chronic setting are assumed to be regularly monitored through routine nephrology / cardiology appointments and will have a history of persistently elevated potassium that is available to the treating clinician. The company suggest that low potassium diets have been recommended to such patients but that adherence is low.

The company stated that patients within the acute setting '*generally attend A&E due to an acute medical problem, such as sepsis, dehydration/acute kidney injury, or pneumonia. As a result of these acute conditions, patients are likely to suffer from hyperkalaemia, and are therefore managed in line with local acute-care protocols and the Renal Association guidelines for the emergency management of hyperkalaemia in adults*'. (Clarification response question A3).[5] Clinical advice to the ERG states that people with S-K levels of >6.5 mmol/L who are not acutely unwell would also be admitted for emergency treatment, although this group of patients would usually require a shorter hospital stay.

These populations were kept distinct throughout the model. As such, patients who are identified in the acute setting cannot be subsequently treated in the chronic setting. Clinical advice provided to the ERG suggests that this assumption is incorrect as further episodes would be considered chronic. The ERG performs sensitivity analyses that uses a time horizon of 52 weeks in the acute clinical setting.

3.2.4 Treatment Pathway and assumed use of RAASi based on clinical setting and treatment

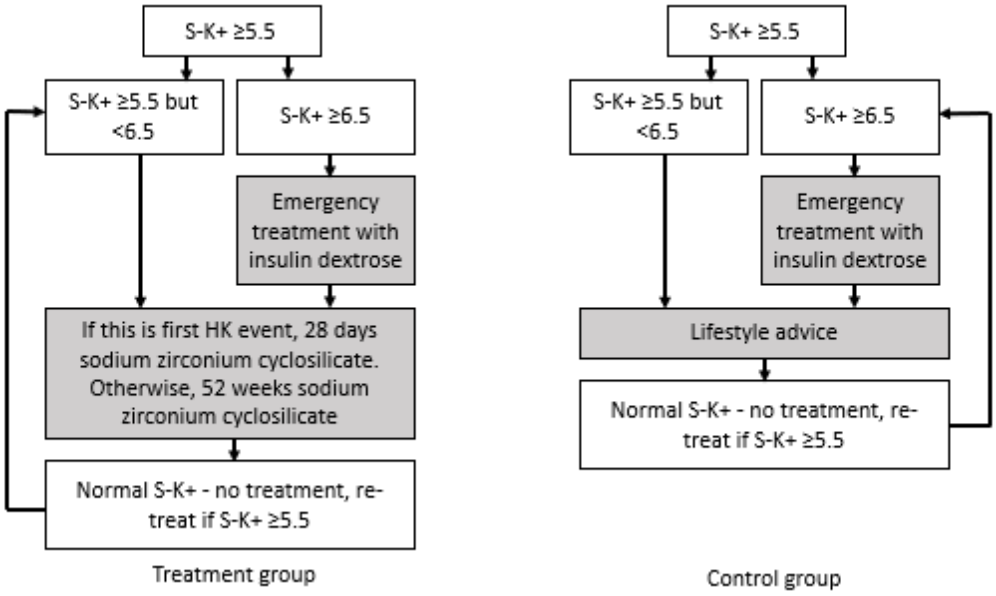
The treatment pathways assumed for the patient populations differ according to clinical setting as does assumption related to subsequent retreatments with SZC.

3.2.4.1 Chronic Setting

The treatment pathway in the chronic setting is reproduced from Figure 16 in the CS in

Figure 4.

Figure 4: The assumed treatment pathway in the chronic setting



3.2.4.1.1 With current standard of care

The model assumes that currently, in the chronic setting patients will be monitored and if S-K levels are 6.5 mmol/L or above would receive emergency treatment with insulin dextrose. If S-K levels are > 5.5 mmol/L but < 6.5 mmol/L lifestyle advice will be provided to the patient. The model assumes that currently, in the chronic setting all patients will discontinue RAASi if their S-K levels are equal to, or greater than, 6.0 mmol/L. In contrast, only 20% of patients with an S-K level equal or > 5.5 mmol/L, but < 6.0 mmol/L would discontinue RAASi, with the remaining 80% intended to down-titrate their RAASi dose. Patients who have discontinued, or down-titrated their RAASi dose have a 49.7% chance

per cycle, based on Luo *et al*.[28] of returning to maximum RAASI dose. Clinical input stated that the minimum time before RAASi would be restarted was 12 weeks. Within the company's model the RAASi dose is linked to clinical outcomes; this is discussed in detail in Section 3.2.12

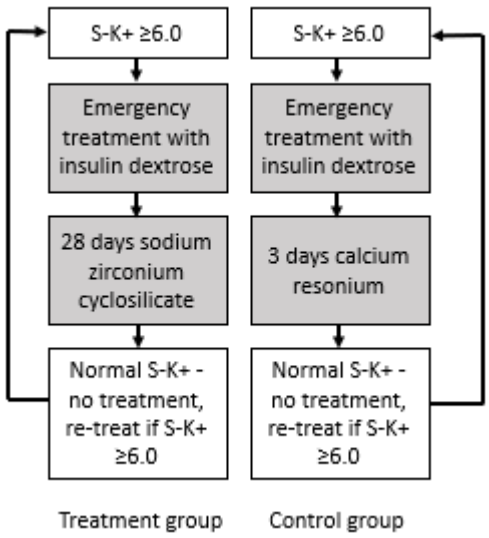
3.2.4.1.2 With SZC being prescribed

The company anticipate that if SZC was available in the chronic setting then patients would be provided with SZC for 28 days following their first HK event. For patients who have a second or subsequent HK event, SZC treatment would be prescribed for a period of 52 weeks. The model initially submitted by the company assumed that no-one would discontinue or down-titrate the dose of RAASi whilst on SZC. This is in direct contradiction to NICE guidance which states '*1.6.11: Stop RAASi if the serum potassium concentration increases to 6.0 mmol/L or more and other drugs known to promote HK have been discontinued.*'[2] Following the clarification process, question B1,[5] the company provided an analyses where RAASi treatment was withheld for 12 weeks in patients with an S-K level ≥6.0 mmol/L for those patients prescribed SZC.

3.2.4.2 Acute Setting

The treatment pathway within the acute setting is shown in Figure 5 (reproduced from Figure 15 from the CS).

Figure 5: The assumed treatment pathway in the acute setting



3.2.4.2.1 With current standard of care

The model assumes that currently, all patients treated in the acute setting will receive emergency treatment with insulin dextrose followed by 3 days of calcium resonium treatment. Retreatment for 28 days would occur if patients' S-K levels rose to 6.0 mmol/L or greater. The model assumes that currently all patients will discontinue RAASi if their S-K levels are equal to, or greater than, 6.0 mmol/L (which

includes all patients in the acute setting). In contrast, only 20% of patients with an S-K level equal or greater than 5.5 mmol/L, but less than 6.0 mmol/L would discontinue RAASi, with the remaining 80% intended to down-titrate their RAASi dose. Patients in the chronic setting who have discontinued, or down-titrated their RAASi dose have a 49.7% chance per cycle, based on Luo *et al*.[28] of returning to maximum RAASI dose. Clinical input stated that the minimum time before RAASi would be restarted was 12 weeks. Patients are not allowed to re-initiate RAASi treatment in the acute setting of the model.

3.2.4.2.2 With SZC being prescribed

The company anticipate that if SZC was available in the acute setting then patients would be provided with SZC correction treatment for up to 3 days and SZC maintenance treatment for 28 days following their first HK event. For patients who have a second or subsequent HK event, SZC correction and maintenance treatment would be prescribed also for a period of 3 days and 28 days, respectively. As with the chronic setting model, the acute setting model initially submitted by the company assumed that no-one would discontinue or down-titrate the dose of RAASi whilst on SZC, however, following the clarification process, question B1,[5] the company provided an analyses where RAASi treatment was withheld for 12 weeks in patients with an S-K level ≥6.0 mmol/L for those patients prescribed SZC.

3.2.5 Model structure

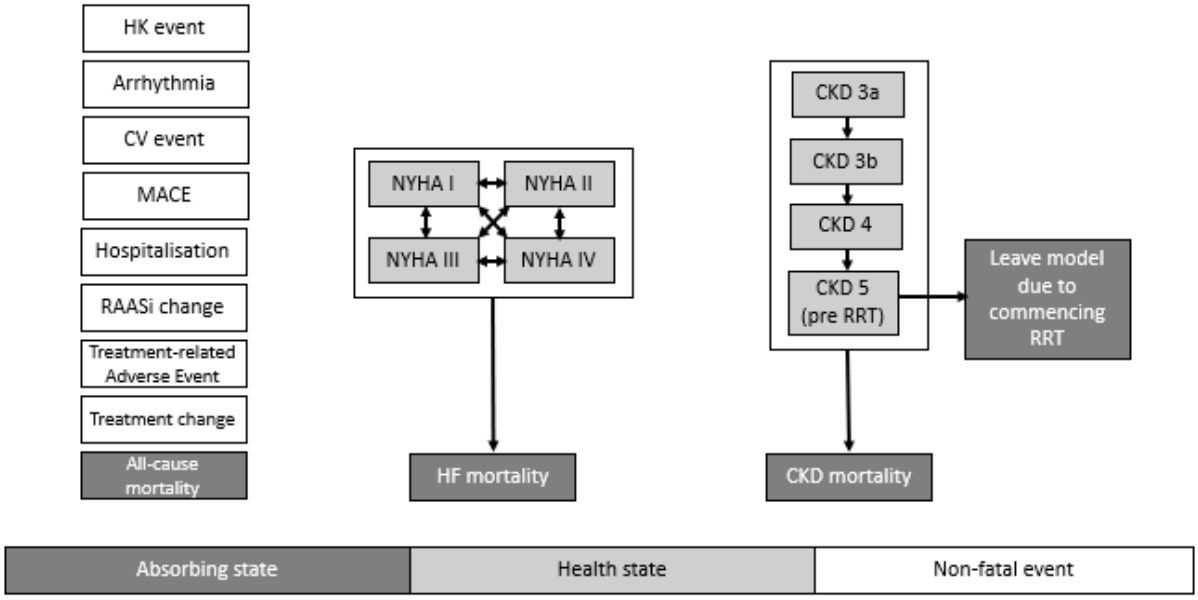
The company submitted a *de novo* patient-level simulation model in Microsoft Excel® employing time cycles of 28 days. The calculations within the model were predominantly driven by Visual Basic for Application modules. The standard of programming and annotation was very good and the ERG identified few implementation errors.

A reproduction of Figure 17 in the CS is provided in

Figure 6. There are health states related to the level of severity of a hypothetical individual's HF or CKD (the conditions of HF and CKD are mutually exclusive and exhaustive.). Additionally, there are a number of events that are tracked over time for each simulated individual that are shown in white in

Figure 6. Absorbing health states were death (due to HF, CKD, or another cause) and a patient being simulated to receive renal replacement therapy (RRT). Responding to question B21the clarification letter,[5] the company provided a scenario analysis where patients did not exit the model when receiving RRT but remained in the CKD5 health state with a stable eGFR.

Figure 6: The conceptual model presented by the company



3.2.6 Interventions and comparators

Information on SZC and the comparator lifestyle advice has been provided in Section 2.2.

3.2.6.1 The costs of SZC and SOC

The list price of SZC is [redacted] for a 5g sachet and [redacted] for a 10g sachet. Based on commercial in confidence dosage data and long-term data from the ZS-005 study[9] the company estimate a cost of [redacted] over the initial 28 days of treatment and a cost of [redacted] for 52 weeks of treatment.

The costs for lifestyle advice appear to be zero in the model. The costs of calcium gluconate were used instead of calcium resonium, although the low cost of £1.50 per patient meant that this did not concern the ERG.

3.2.6.2 Adverse events associated with SZC and SOC included in the model

Table 36 in the CS details the ten adverse events that are included in the model. These were based on events recorded in the ZS-005 trial[9] that had an incidence of ≥5% in either arm in the SZC arm, whereas the adverse events for SOC came from Nasir *et al*.[18]

3.2.7 Perspective, time horizon and discounting

The model takes an NHS and Personal Social Services perspective and discounts both health and costs at 3.5% per annum as recommended by NICE.[29] The time horizon was for 80 years or until RRT both for patients in the acute setting and for patients in the chronic setting. As stated, following the clarification process,[5] the company provided an analysis where patients remained in the CKD5 health

state and were assumed to not have RRT (question B21). Additionally, on request by the ERG an analysis was undertaken where the time horizon for the acute setting was 28 days. (clarification question B3).[5]

3.2.8 Treatment effectiveness and discontinuation rates

3.2.8.1 Treatment effectiveness in reducing S-K levels

For both SZC and standard of care it was assumed that there was a fixed trajectory of S-K level for the average patient. This trajectory was assumed to be different depending on whether the patient was on SZC treatment or standard of care (SOC). The mean trajectory for each treatment is provided in **Error! Reference source not found.**. These underlying trajectories are used regardless of the S-K level at presentation which may represent a limitation of the model. Following discontinuation of SZC it was assumed that the S-K level in the next cycle would increase to be equal to that of SOC. Importantly, the company assumed that the absolute levels of reduction that were observed in chronic patients would also apply to patients identified in the acute clinical setting. This adds uncertainty to the results for patients in the acute clinical setting, which in time will be reduced by the publication of results from the ENERGIZE[13] and the DIALIZE[14] studies.

The trajectories were derived by fitting a longitudinal model to pooled data from ZS-004 and ZS-005, separately for 3 sections of the data; Acute phase day 0-3 for both SZC and SOC, maintenance phase day 4 onwards for SZC, and maintenance phase day 4 onwards for SOC. Note that the use of separate models does not maintain the correlation of serial measurements within an individual over time. The statistical model is of the same form as that used in the clinical effectiveness analysis (see Section 2.2.1 equation 1) but with two key differences; i) the models used in the clinical effectiveness analysis fitted to log transformed data and ii) the models used in the clinical effectiveness analysis included several fixed effects covariates. The fitted model is shown below:

[redacted] (2)

[redacted]The time component is treated as a continuous variable for the acute phase model, providing a (non-zero) gradient in the mean acute phase trajectory. For the maintenance phase models the time component is an indicator variable which applies only after a certain time point, resulting in piecewise constant trajectories after day 3 (gradient zero). Parameter estimates for all three sections of the data are provided in Appendix 3, based on the company's response to clarification question A20.[5] The trajectories in **Error! Reference source not found.** illustrate the fixed components of this longitudinal model, without the additional patient level variation (captured by u_i and $\varepsilon_{i,t}$). The ERG questioned whether the decrease in S-K level for patients in the SZC arm at 28 days was an artefact of the data particularly as the follow-up in ZS-004[7] ended at 28 days (clarification question B4).[5] The company responded that there was an observed

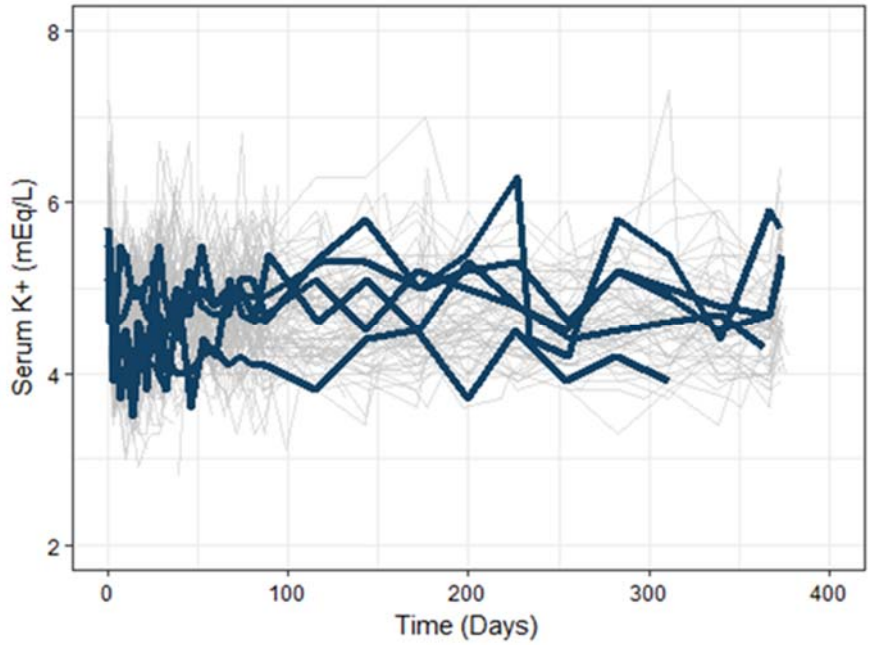
difference between days 4-28 and beyond 29 days in ZS-005,[9] and ran scenario analyses to explore altering this assumption.

[redacted]

The treatment specific trajectories were amended by two components: a patient component and an observation component. The patient component was a measure of the underlying S-K for a particular patient. A value was sampled from a uniform [0,1] distribution which was used to determine the difference between the specific patient and the average patient at all time points, therefore, a patient would maintain higher than (lower than) underlying S-K levels than the average patient throughout the model. The ERG assumes that this was required in the cost-effectiveness model because separate models were used for the acute and maintenance phases. The ERG considers that this is not unreasonable, but does not completely reflect the (independent) statistical models that were fitted to the data. The observation component was a measure of variability in S-K levels due to many factors: this value was sampled for a patient at the start of each cycle. The relative magnitude of the standard deviation of the observational component was large ([redacted] for patients treated with SZC; [redacted] for patients treated with SOC) and could result in large changes in the patient's S-K level as the width of the 95% CI will be in the region of [redacted] mmol/L. Estimates of the heterogeneity parameters were not provided for the results of the clinical effectiveness section, and the modelling was conducted on a different scale, therefore it is not possible to compare the variance estimates with and without the additional covariates.

Variations in the S-K levels for illustrative patients are shown in Figure 7 which is a reproduction of Figure 18 in the CS.

Figure 7: Illustrative patient trajectories presented by the company



3.2.8.2 The rate of discontinuation with SZC treatment

The company model assumes that patients may discontinue treatment before the scheduled end date, or before leaving the model due to progression to RRT. The rate of discontinuation was conditional on the setting in which the patient was identified, and was an annualised discontinuation rate of 37.5% in the chronic setting, based on the observed data in ZS-0005[9] and an annualised discontinuation rate of 85.3% in the acute setting based on the ZS-004 study.[7]

3.2.9 The relationships between S-K level and HF-mortality, CKD-mortality, MACE and hospitalisation

The relationships between S-K levels and HF-mortality, CK-mortality and MACE used within the company base case are shown in Figure 8. These data have been taken from Luo *et al.*[28] (for MACE and CKD mortality) and are stated by the company to be based on Krogager *et al.*[30] for HF mortality. It is seen that as the S-K level increases above 5.5 mmol/L the hazard ratio for HF mortality and the incident rate ratio for CKD mortality increase noticeably compared with patients with an S-K level of 4.3-4.5 mmol/L. The ERG could not verify the values for HF mortality and noted that these values were for people with hypertension; clinical advice to the ERG suggested that this was not appropriate. The ERG comments that these data are from cohort data and it is unknown whether the relationships observed would be maintained if the S-K levels were reduced by an intervention. Further, there is the potential for confounding in that it may be underlying comordities that are resulting in extreme S-K levels rather than the S-K levels being the cause of underlying health conditions. This conclusion has been supported in Collins *et al.*[31] who state that '*Future clinical trials will be required to determine if*

aggressive management of hypokalemia and hyperkalemia may reduce mortality in patients with and without HF, CKD, DM [diabetes mellitis], or CVD [cardiovascular disease].'

The ERG comments that the clinical studies undertaken by the company did not show any changes in clinical endpoints although this is not surprising; ZS-004[7] had a comparative data period of less than 30 days whereas ZS-005[9] was only a single arm study.

Figure 8: Relationships between S-K levels and HF-mortality, CKD-mortality and MACE used in the company base case

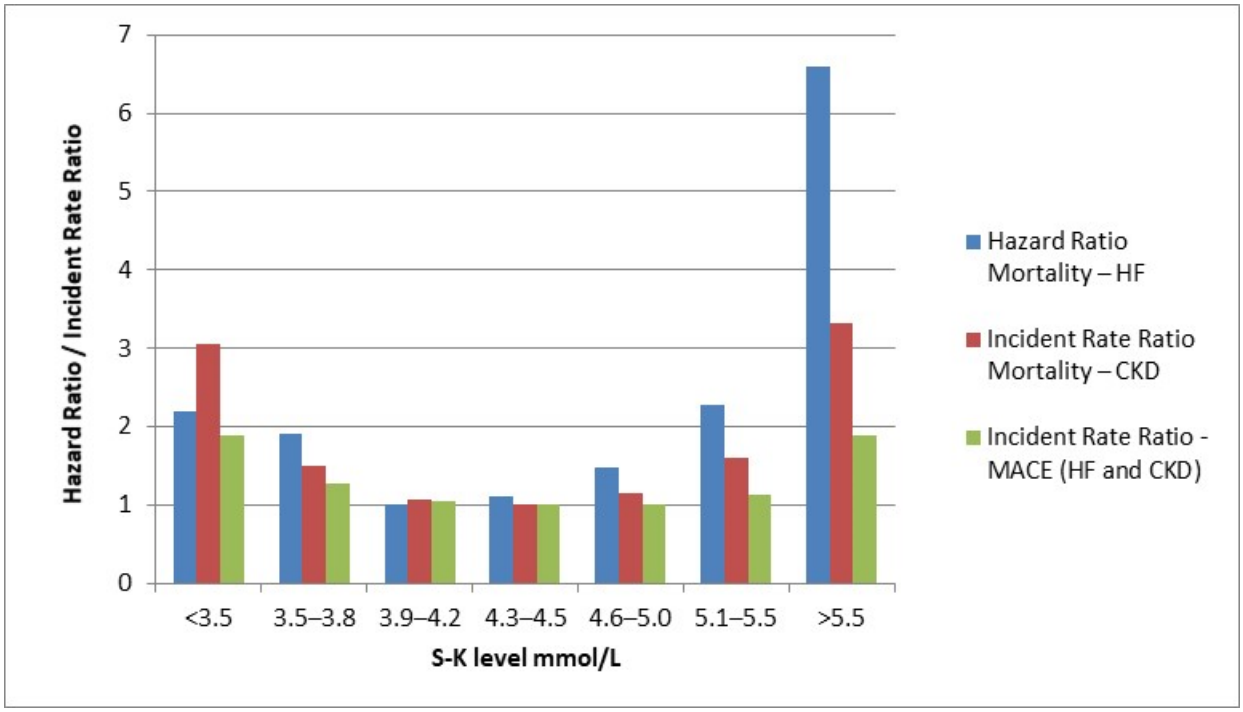


Table 39 of the CS provides data on the incidence risk ratios of hospitalisation that are associated conditional on eGFR level. and on S-K level.[28] Broadly, lower eGFR values are associated with more hospitalisations as are more extreme S-K levels. As with the relationship with S-K levels and mortality it is not known whether the surrogate relationships between S-K levels and hospitalisation hold if S-K levels are changed through SZC treatment.

3.2.10 Progression of CKD

Patients with CKD were assumed to enter the model with an eGFR of 44.66 mL/min/1,73m^2. The company assume that the rate of eGFR decline in patients who are not taking RAASi was 3.52mL/min/1,73m^2.[32] Patients on maximum dose RAASi or on down-titrated RAASi treatment were assumed to have the rate of decline associated with irbesartan treatment, a angiotensin II receptor blocker, which was 2.34mL/min/1,73m^2,[32] although the ERG not that this is from a single study of people with diabetes mellitus and that there may be uncertainty in this value. The eGFR (in

mL/min/1,73m$^{2)}$ value was assumed to allocate a patient to CKD stage as follows: ≥ 45 and <60, stage 3a; ≥ 30 and <45, stage 3b; ≥ 15 and <30, stage 4; and <15 stage 5. When eGFR became ≤ 8.5mL/min/1,73m^2 the patient was assumed to receive RRT and left the model. Sensitivity analyses were performed keeping the patient in CKD stage 5 without receiving RRT. Clinical advice to the ERG stated that decline in eGFR would be more rapid in patients with heavy proteinuria and uncontrolled hypertension, and that there would be more benefit in these patients but ICERs for this population were not presented by the company.

The risks of cardiovascular event, hospitalisation and all-cause mortality by CKD stage are provided in Table 38 of the CS and were taken from Go *et al*.[33] As anticipated, the rates of each event increases as the CKD stage becomes more severe. These values are multiplied by the incidence risk ratios conditional on S-K level as reported by Luo *et al*.[28] which increases the risks for those patients with high or low S-K levels. This methodology introduces some double counting as the average of the adjusted figures will be greater than the observed average, although the ERG does not believe the impact will be large.

3.2.11 Progression of HF

The cohort of patients with HF were assumed to begin the model with 10% in NYHA class I, 10% in NYHA class II, 43% in NYHA class III and 37% in NYHA class IV. The assumed transition probabilities between NYHA states are provided in Table 41 of the CS and are sourced from Yao *et al.*[34] The company state within the model that no evidence was found for the impact of RAASi treatment on transition probability and thus these values were assumed to be independent of RAASi use. The transitions were also assumed to be independent of S-K levels.

The probability of hospitalisation for patients with HF was dependent on NYHA class and whether RAASi treatment was prescribed. The rate of hospitalisation by NYHA class was taken from Ford *et al*.[35] whilst the OR associated with maximum dose RAASi (0.670) was taken from Flather *et al*.[36] and the OR associated with sub-optimal RAASi doses (0.882) was an assumption based on the ATLAS study.[37] The full data are presented in Table 42 of the CS.

The Clinical Practice Research Datalink risk equation was used by the company to determine the annual risk of MACE in HF patients. Table 43 of the CS provides full details. The incident risk ratios for MACE dependent of S-K levels, as shown in Figure 8) were used to estimate the risk for each individual patient.

The Seattle Heart Failure Model was used by the company to estimate the risk of death associated with HF. The coefficients for this model are provided in Table 45 of the CS. Hazard ratios associated with

S-K levels were then applied as shown in Figure 8. This methodology introduces some double counting as the average of the adjusted figures will be greater than the observed average, although the ERG does not believe the impact will be large.

3.2.12 The effectiveness of RAASi treatment in preventing HF and CKD

For CKD patients the odds ratio (OR) for mortality associated with RAASi treatment versus no RAASi treatment was assumed to be 0.870 based on Xie *et al*.[38] The company assumed that patients on sub-optimal RAASi doses would have half the effect of maximum dose and assumed an OR of 0.935. It was stated in the CS that no data were found for the influence of RAASi use on hospitalisations and thus this was set to an OR of 1.

3.2.13 The relationship between RAASi treatment and S-K levels

The ERG comments that the use of RAASi, or not, is excluded from the estimated S-K levels. The ERG believes that this represents a major limitation, given the widely reported effects of RAASi on S-K level,[39-41] as noted in the CS. This is discussed in detail in Section 5.1.

3.2.14 Mortality due to reasons other than HF or CKD

The model incorporates the probability of death based on life table statistics from the Office of National Statistics[42] based on age and sex. These values were assumed to be used if they were greater than the risks of death estimated from HF and CKD reasons.

3.2.15 Health related quality of life

The company use the EQ-5D population utility values reported in Szende *et al*.[43] Disutility associated with HF and CKD was incorporated as utility multipliers, although as acknowledged by the company in the clarification process (question B22)[5] that this may incorporate age-related decrements twice, which may be unfavourable to SZC given that SZC in conjunction with RAASi use prevents HF and CKD events.

Utility multipliers associated with HF were sourced from Gohler *et al*.[44] and were: 0.855 (NYHA Class I); 0.771 (NYHA Class II); 0.673 (NYHA Class III); and 0.532 (NYHA Class IV). Utility multipliers for CKD patients in the revised company analysis were taken from TTO values reported in Gorodetskaya *et al*.[45] which were; 0.870 (Stage 3a and 3b); and 0.850 (Stage 4 and 5 (pre-RRT)). This differed from the initial submission in changing the Stage 5 (pre-RRT) utility value from 0.570, which was an EQ-5D value reported by Lee *et al*.[46]

As discussed in more detail in Section 5.1, the ERG prefers the Health Utilities Index 3 (HUI3) data provided in Gorodetskaya *et al*.[45] Disutilities were applied to AEs as reported in Table 51 of the CS and had little impact on the results so are not discussed further.

In the fact check process the company performed an analysis where the utility for patients in the acute clinical setting was lowered to account for '*for acutely unwell patients*' for the hospitalisation period and stated that the conclusions did not change. The ERG comments that this was highly predictable given that the disutilities were applied to both arms and were effectively cancelled out (barring deaths during hospitalisation). As such, these analyses are not discussed further.

3.2.16 Resources and costs

Acquisition costs of SZC and SOC are reported in Section 3.2.6.

3.2.16.1 Costs associated with CKD

The annual costs associated with CKD were taken from NICE Clinical Guideline 182.[2] These were £3511 (Stages 3a, 3b and 4) and £5478 for CKD Stage 5 pre-RRT.

3.2.16.2 Costs associated with HF

Following the clarification process the company revised the annual costs of HF taking values from Ford *et al*,[35] converting to £ (from Australian $) and inflating to 2017 prices. These values were: £90.99 (NYHA Class I); £104.82 (NYHA Class II); £135.95 (NYHA Class III); and £145.10 (NYHA Class IV).

3.2.16.3 Costs associated with HK events

The costs associated with HK were divided by the company into severe HK events and less severe HK events. In the acute setting, the threshold for both a severe and less severe HK event was 6.0 mmol/L and in the chronic setting, the threshold for the severe event was 6.5 mmol/L and 5.5 mmol/L for the less severe HK event. The costs used in the model for severe HK events do not match those reported in Table 62 of the CS, but are £2297 for patients treated with SZC and £3093 for patients treated with SOC; the difference is due to the company assuming that there is one less day of inpatient care for patients treated with SZC. This assumption is removed in sensitivity analyses. The bulk of the costs of severe HK events for both arms is inpatient stay which is costed at £727 per day.[47] The costs of less severe HK events is that reported in Table 62 of the CS which is £177 for both the SZC and the SOC arm.

3.2.16.4 Costs associated with RAASi treatment

The company assume that the costs of maximum dose RAASi is £46 for CKD patients and £58 for HF patients. These costs are reduced to £25 (CKD patients) and £36 (HF patients) where there is sub-optimal dosing. The company assumed that there were costs involved in changing RAASi treatment which were £481.48 for a discontinuation, £129.72 for an up-titration and £722.22 for a down-titration. Further details are provided on page 129 of the CS.

3.2.16.5 Costs associated with MACE, hospitalisation not due to HK events and adverse events

The company assumed that MACE cost £4952 based on Kent *et al.*[48] and that non HK-related hospitalisation costs were £2522.[49] The costs of adverse events were provided in Table 66 of the CS, but were not key drivers of the ICER.

3.2.17 Probabilistic Sensitivity Analyses

The company undertook probabilistic sensitivity analyses (PSA). Following the clarification process (question B13)[5] the company provided an appendix which detailed the parameters that were and were not included in the PSA. A large number of parameters was not included meaning that the uncertainty in the answers is likely to be underestimated.

4 COST EFFECTIVENESS RESULTS

4.1 Company's cost effectiveness results

During the clarification process the company's base case was amended. The differences between the subsequent base case and the original base case were:

- Incorporating drug wastage within cycles 2 to 5 (Clarification response B6)[5]
- Fixing coding errors that had been identified by the ERG at the clarification stage (Clarification responses B7, B8, B9)[5]
- Providing results for the CKD only population and the HF only population separately (Clarification response B10)[5]
- Using the actual value for the hazard ratio for a variable rather than using 1.0 (Clarification response B12)[5]
- Incorporating costs associated with each NYHA class (Clarification response B20)
- Amended the utility of stage 5 CKD from 0.570[46] to 0.850[45] (Clarification response B22)[5]

These amendments were incorporated into the company's base case analyses which is provided in Table 9.

Table 9: The company's base case results

Population	Incremental cost of SZC treatment	Incremental QALYs of SZC treatment	Cost per QALY
Chronic Setting			
CKD or HF	[redacted]	[redacted]	£21,849
CKD only	[redacted]	[redacted]	£25,363
HF only	[redacted]	[redacted]	£13,458
Acute setting			
CKD or HF	[redacted]	[redacted]	Dominating
CKD only	[redacted]	[redacted]	Dominating
HF only	[redacted]	[redacted]	£7380

4.2 Company's sensitivity analyses

In addition to these amendments the company also undertook an 'all relevant scenarios' analysis which added the following changes to the base case

- Withholding RAASi treatment for 12 weeks for patients in the SZC arm who have an S-K level of > 6.0 mmol/L (clarification question B1)[5]
- Assuming that there was no decrease in S-K levels between day 28 and subsequent time points (clarification question B4)[5]

- Assuming that the eGFR levels was not equal for all patients but were distributed between Stages 3b and 5 (pre-RRT) (clarification question B17)[5]

The 'all relevant scenarios' results were provided in Table 47 of the clarification response.[5] These are summarised in Table 10. It is seen that in the company's analyses that in the chronic setting the ICERs for CKD patients are noticeable greater than those for HF patients.

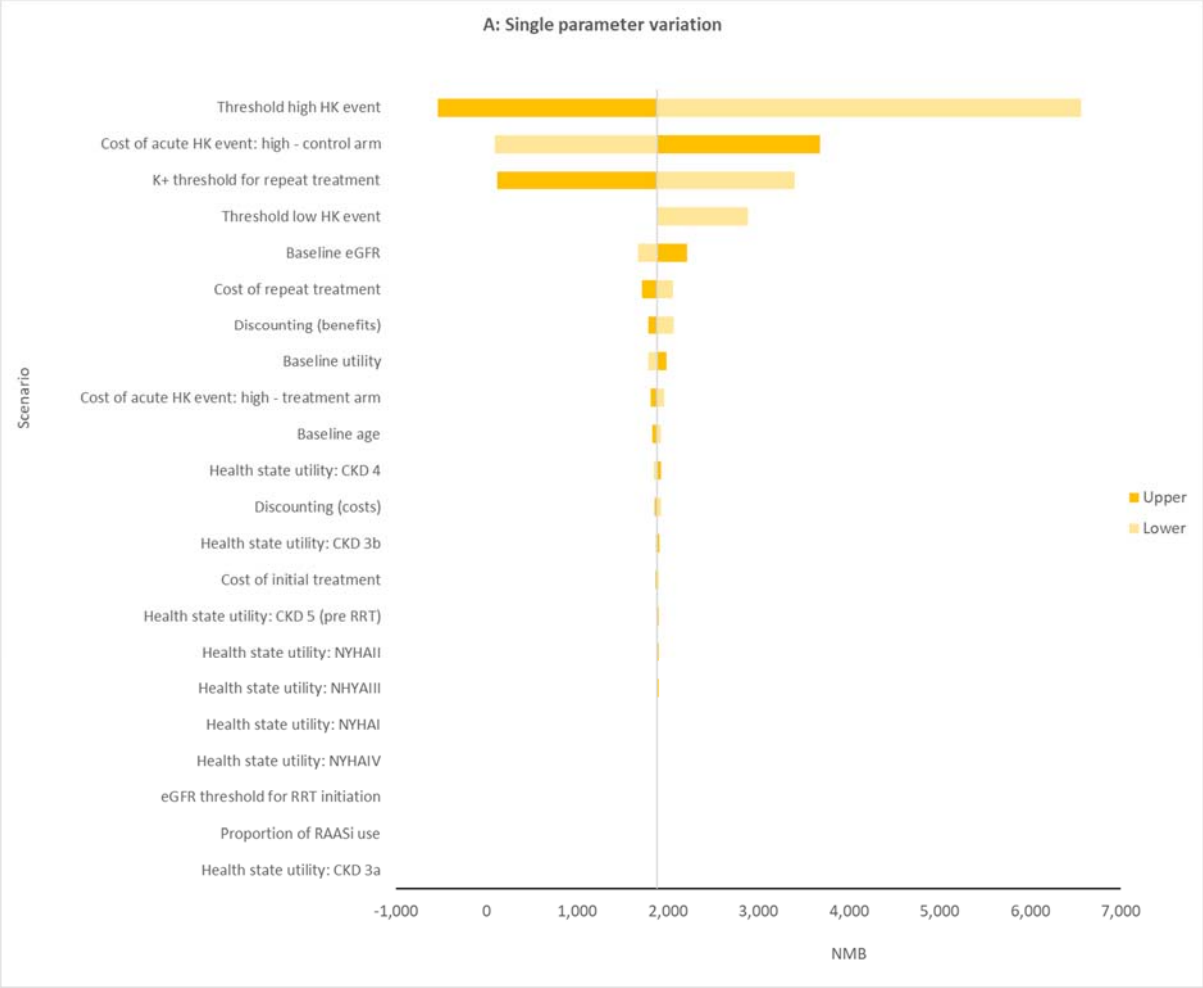
Table 10: The company's all relevant scenarios analysis

Population	Incremental cost of SZC treatment	Incremental QALYs of SZC treatment	Cost per QALY
Chronic Setting			
CKD or HF	[redacted]	[redacted]	£24,575
CKD only	[redacted]	[redacted]	£28,487
HF only	[redacted]	[redacted]	£15,244
Acute Setting			
CKD or HF	[redacted]	[redacted]	Dominating
CKD only	[redacted]	[redacted]	Dominating
HF only	[redacted]	[redacted]	£6022

In addition, the company undertook further sensitivity analyses at the request of the ERG but did not deem these relevant to the results presented in Table 9 and Table 10. These included: using a time horizon of 28 days in the acute setting (clarification question B3,[5] SZC was estimated to be dominant); changing the threshold to investigate measurement error (clarification question B5) where the ICERs changed by approximately £1000 from the base case; altering the assumed eGFR level of patients which changed the ICER in the chronic setting by approximately £1500 (clarification question B17)[5]; and maintaining patients in CKD stage 5 and not assumed to receive RRT (clarification question B21,[5] which increased the ICER by approximately £1000).

Furthermore, the company provided a tornado plot changing model parameters. The results were presented in terms of net monetary benefit, assuming a cost per QALY threshold of £20,000 and £30,000.[5]. The figure using a cost per QALY threshold of £20,000 per QALY is reproduced in Figure 9. To aid interpretation, any net monetary benefit value > 0 would imply that the cost per QALY gained was below £20,000.

Figure 9: The tornado plot provided by the company using net monetary benefit and a cost per QALY threshold of £20,000



4.3 Model validation and face validity check

The company describe the process of model validation on page 158 of the CS. There were no clear face validity errors in the results following the clarification process. However, the ERG highlights what is believed to be a conceptual error in the model in that there is no explicit relationship between RAASi treatment and S-K level. Additionally, there is a lack of consistency between the models fitted within the clinical section and the models used within the economic section. In response to clarification (clarification question A20)[5] the company explained that these differences arose due to differing requirements however details of the model selection and verification procedure were not supplied to allow the ERG to judge whether the most suitable model was used.

The ERG prefers alternative assumptions to those employed in the company base case; these are discussed in Section 5.1.

The ERG does not believe that it is appropriate to combine HF and CKD patients. This is because: these patients are clinically distinct and can be identified; that the relationship between SK levels and adverse outcomes differ; and that the method of pooling does not provide appropriate eGFR levels for either group. As such, the ERG analyses present only results for CKD patients and HF patients separately in the main document. Following a request from NICE results combining the two distinct conditions are contained in Appendix 4 but the ERG caution against putting credence in these results.

5 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

5.1 Exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted the following exploratory and sensitivity analyses for patients within both the chronic and acute setting.

1) Withholding RAASi treatment for 12 weeks for patients in the SZC arm who have an S-K level of > 6.0 mmol/L

This used the functionality of the model supplied by the company following the clarification period.

2) Assuming that RAASi treatment is related to S-K levels

Subsequent to the clarification process the ERG identified that within the model S-K levels were assumed independent of RAASi use, which neither agreed with clinical opinion nor published literature.[39-41]. This company was asked about this omission in an additional clarification question and responded that '*We agree that the relationship between RAASi down-titration or discontinuation with S-K reductions is not currently explicitly modelled. However, due to the methods and data used to model the S-K trajectory in the model, AstraZeneca believe any S-K related benefits from RAASi down-titration or discontinuation to be more than accounted for in the model*'.[5] The company provide a lengthy explanation to try and justify the exclusion of the relationship between RAASi treatment and S-K levels. The ERG does not think that the reasons provided are sufficient to justify the omission of differential S-K levels conditional on RAASi treatment. The ERG acknowledges, however, that the reductions in S-K levels in the SOC arm in the initial three days, and potentially to day 29, is likely to be over-estimated given that within studies ZS-004[7] and ZS-005 these patients received SZC in an open-label acute phase until normokalaemia was reached.

In an attempt to explore the impact of adjusting the S-K levels dependent on RAASi treatment the ERG undertook exploratory analyses. In the first analyses the increase in S-K levels for those on maximum RAASi treatment was assumed to be 0.23, based on the increase associated with mineralocorticoid receptor antagonists, such as spironolactone, reported in Ng *et al*.[39] which was based on 1581 patients. The risk ratio for HK in those using mineralocorticoid receptor antagonists in Ng *et al.*[39] was 1.76 (95% CI 1.20 to 2.57). This does not seem at odds with previously published values, Michel *et al*.[40] report ORs of 3.01 (95% CI 2.61–3.48) for potassium-sparing diuretics and 1.70 (95% CI 1.41–2.04) for ACE inhibitors related to cases of HK based on a nested case-control study of over 19,000 patients, although may underestimate the value as Horne *et al*.[41] report ORs for HK events of 13.63 (95% CI 13.31 to 13.95) for people taking ACE inhibitors, and 15.89 (95% CI 15.27 to 16.54) for people taking angiotensin receptor blockers. The company identified an in-depth narrative review of clinical trials assessing the impact of RAASi on S-K levels. This review concluded that RAASi treatment initiation

and use is associated with an S-K level increase of 0.1–0.3 mmol/L in HF patients and typically ≤0.5 mmol/L (range: 0.06–0.8 mmol/L) in CKD patients.[50]

The ERG performed two exploratory analyses assuming that the increase in S-K level associated with RAASi treatment was i) 0.1 mmol/L and ii) 0.23 mmol/L. The ERG favours the 0.23 value but acknowledges that both may be plausible values and produces two ERG base cases to provide additional information to the committee. In all analyses it was assumed that the S-K increase associated with suboptimal RAASi treatment was half of the maximum treatment increase. For simplicity, it was assumed that the trajectory associated in **Error! Reference source not found.** was associated with people on RAASi treatment and that there would be a decrease in S-K levels were RAASi treatment to be discontinued or down-titrated. The ERG acknowledges that this introduces a potential face validity error within the correction phase where patients on SoC who discontinue RAASi treatment will have a lower S-K level than patients on SZC. However, this limitation was believed to be outweighed by modelling the relationship between RAASi treatment and S-K levels.

3) Using different utility values for CKD than that assumed by the company

Within the company base case, the absolute time trade-off values reported by Gorodetskaya *et al.*[45] were used as multipliers. The ERG believes that this is a limitation for two reasons: i) as the valuation had been undertaken by the patients which is not the method recommended by NICE,[29] and ii) that they values should be adjusted to take into account that these were not multipliers. The Gorodetskaya *et al.* paper[45] also reports values based on the HUI3 which is preference-based. The ERG also note that the utility value for eGFR < 15 mL/min/1.73m^2 and without dialysis is 0.54 which is comparable to the pre-dialysis EQ-5D value of 0.57 reported by Lee *et al.*[46] A comparison of the values assumed by the company and the values assumed by the ERG are presented in Table 11. Note that the ERG values are adjusted so that when multiplied by 0.79 (an ERG-assumed population norm for the patients aged 63 to 65 years) they equal the values reported in Gorodetskaya *et al.*[45]

Table 11: Utility values used in the company's base case and the ERG base cases

CKD Stage	Company base case (SD): TTO values[45]	ERG base cases (SD): HUI-3 values[45]†
3a	0.87 (0.034)	0.848 (0.066)
3b	0.87 (0.034)	0.848 (0.066)
4	0.85 (0.029)	0.696 (0.042)
5 (pre-RRT)	0.85 (0.034)	0.684 (0.068)

† Adjusted. See text for further details.

During the fact check process the company stated that they had identified a study from a systematic literature review which reported EQ-5D values for patients with CKD. The lead author in the study was stated to be Eriksson, although the references state this to be by Giles. The ERG could not identify the paper, and notes that it appears to be a conference abstract rather than a peer-reviewed paper. For this reason, together with the fact that no details were provided on the literature review, and the fact that the CKD5 value were similar between Gorodetskaya et al[45] and Lee et al,[46] the ERG have used the Gorodetskaya et al HUI-3 data in its base case.[45]

4) Using an alternative relationship between S-K levels and HF mortality

The ERG could not verify the values used by the company relating HF mortality to S-K level, that were stated to be based on Krogager *et al*.[30] and further noted that these data related to patients with hypertension only. The clinical advisors to the ERG were aware of a recent abstract that reported the relationship between S-K levels and HF mortality based on 19,549 patients with chronic HF[51] and preferred to use these data.

The differences between the values assumed by the company and those in Aldahl *et al.*[51] are shown in Table 12. The ERG notes that the cut points are slightly misaligned between Krogager *et al.*[30] and Aldahl *et al*., but have for simplicity assumed that the values in Aldahl *et al.* can be assigned to the S-K level that is most similar.

Table 12: S-K to HF mortality used in the company's base case and the ERG base case

S-K level	Company base case[30]	ERG base case[51]†
<3.5	2.19	3.16
3.5 – 3.9	1.91	1.62
3.9 – 4.2	1.00	1.29
4.2 – 4.6	1.10	1.00
4.6 – 5.1	1.47	1.34
5.1 – 5.5	2.28	1.60
>5.5	6.60	3.31

† Adjusted. See text for further details.

5) Assuming a higher level of wastage associated with S-K treatment

Clinical advice to the ERG suggested that it was possible that patients who missed doses of SZC would still collect their next prescription and thus 'waste' the missed doses. The model structure made it easier to inflate costs and thus the ERG assumed one of the scenarios evaluated by the company and assumed that there would be a cost of 30 sachets for every 28 sachets prescribed. This change was implemented

in addition to the wastage assumptions already implemented by the company in response to clarification question B6 (wastage in cycles 2-5).[5]

6) Assuming that the costs associated with RAASi dose changes are lower than assumed by the company

The ERG performed exploratory analyses that assumed that all visits in secondary care to change dosage of RAASi treatment were in outpatient setting rather than an inpatient setting. This reduced the values from £481.48 to £186.48 for discontinuation of RAASi treatment and from £722.22 to £279.72 for a down-titration.

Points 1-6 constitute the ERG base case, although four further analyses were undertaken to assess changes in the company's assumptions.

7) Assuming that SOC has no impact on S-K levels in the correction or maintenance phase iun chronic patients

During the fact check process the company appeared to rescind one of the key assumptions in its model, namely that SOC had the same impact as SZC during the correction phase, and had a benefit in the maintenance period. Instead the company assumed that the underlying S-K level for a patient would remain at a constant value throughout time (subject to the observational component. The ERG comments that this assumption appears not to be based on data, and is likely to represent a highly optimistic scenario for SZC.

8) Assuming that EQ-5D values for CKD patients found after the ERG report are most appropriate

During the fact check process the company stated that it '*identified an alternative source to inform the HSUVs for CKD health states that reports EQ-5D-3L utilities for non-anemic patients. This was identified via an SLR [systematic literature review] of the impact of CKD on patients' quality of life*'. No details of the literature review were provided, so it is unclear if the study is cherry-picked. Furthermore, the paper, that appears to be referenced incorrectly, could not be retrieved by the ERG and appears to be a conference abstract. As such, the ERG does not believe that these values are most appropriate, despite being derived from EQ-5D. The ERG comments that the utility values in CKD stage 3 are very similar to those of Gorodetskaya *et al*.[45] but are higher in CKD stages 4 and 5. As the Gorodetskaya *et al*.value in CKD stage 5 was similar to the EQ-5D value reported by Lee et al.[46] the ERG prefers the Gorodetskaya *et al*. data

9) Assumption of lifetime treatment with SZC

The ERG explored the impact on the ICER of assuming lifelong treatment with SZC. Clinical advice to the ERG suggested that there would be a temptation for clinicians to continue treatment with SZC beyond 52 weeks if it was believed to be efficacious, particularly if the company assumption that S-K levels would return to the no treatment values immediately upon cessation were correct.

10) Assuming that there is no reduction in hospital length of stay associated with SZC treatment

The ERG explored the impact on the ICER of assuming the same length of hospital stay for patients receiving SZC as patients receiving SOC.

For patients in the acute setting the time horizon was reduced to 52 weeks. The ERG believes that patients identified in the acute setting would be followed-up in the chronic setting following multiple episodes. As such, using a short time horizon in the acute setting, and then assuming that the chronic results were generalisable to treatment after 52 weeks was preferred by the ERG. It is likely that the ICERs for patients who were initially assigned to the acute clinical setting may be lower than those in the chronic clinical setting due to a higher S-K threshold level on model entry (≥6.0 mmol/L compared with ≥5.5 mmol/L). However, the potential size of this difference in the ICER is uncertain as it may be that those assigned to the acute clinical setting are not truly differentiable from patients in the chronic clinical setting, but instead were assigned to this group by chance, due to having higher simulated observational components (see Section 3.2.8) than those in the chronic clinical setting. The ERG notes that the trial data on which the model is based is from patients in the chronic setting only. The ERG comment that these observational components change throughout the model and may lessen the difference (in S-K levels) between the two categories of patients used in the company model.

One further change was made in the acute clinical setting.

11) Assuming that patients in the acute clinical setting can continue with RAASi treatment after 12 weeks.

The company assume that in the acute clinical setting that RAASi treatment is discontinued and never restarted. Clinical advice provided to the ERG indicated that this is unlikely to be the case for all patients and would depend on the severity of the episode, the frequency of HK events and the indication of the specific RAASi. It was suggested that if the episode was not life-threatening then resumption of RAASi treatment within 12 weeks would be appropriate and in line with medical practice. However, for patients who have had a life-threatening event, or who has been admitted several times then RAASi treatment may not be restarted. It was assumed in line with the company's base case that all patients on SZC treatment would resume RAASi at 12 weeks but that only 47.9% of patients on SOC would.

Further results were run by the ERG which altered the distribution of patients amongst NYHA Classes and the distribution amongst CKD Stages, but as these did not affect the conclusions they are not presented, although the ERG notes that SZC was more cost-effective in those patients with less severe CKD than those with more severe CKD.

5.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The majority of results were run deterministically with the ERG also running probabilistic analyses for key scenarios. For the deterministic analyses 60,000 individual patients were simulated, whereas for the probabilistic analyses 20,000 patients were run for each of 100 PSA configurations. The probabilistic values were similar to the deterministic ones implying linearity within the model, although the ERG note that key parameters were excluded from the PSA. The ERG's PSA runs were undertaken for an earlier base case and the probabilistic results have not been re-run with the new base cases.

A summary of the exploratory analyses undertaken by the ERG for patients in the chronic setting are presented in Table 13 for HF patients and in Table 14 for CKD patients. Two ERG base cases are provided which are identical except for the assumed level of S-K level mmol/L decrease (0.23 or 0.10) when RAASi treatment in discontinued. The ERG prefers the 0.23 value, but has presented the 0.10 value which is potentially plausible, to provide additional information to the committee.

The ERG comments that the incremental cost-effectiveness ratios (ICERs) are driven by the relative effect of SZC and SOC within the correction and maintenance phase, for which no evidence exists. The ERG base cases are likely to be unfavourable to SZC in the chronic setting as the assumed decrease in S-K levels in the correction phase for SOC is assumed to be that associated with SZC. In the fact check process the company provided further analysis assuming that there would be no change in S-K levels in the SOC arm in the chronic setting apart from changes in RAASi dosage. The ERG believes this is highly optimistic but has evaluated the ICERs using this assumption.

5.2.1 Interpreting the results for HF patients in the chronic setting

The deterministic ICERs for HF patients were below £30,000 in both ERG base cases. Making the hospital length of stay independent of treatment (SZC or SOC) had only a marginal impact on the ICER. Increasing the treatment duration of SZC to lifetime increased the ICERs as to a value greater than £30,000 per QALY in ERG base case 1 but not in ERG base case 2. As stated these ICERs are likely to be unfavourable to SZC. The ERG believes that the ICER in the chronic clinical setting for HF patients is likely to be in the range of £10,000 to £29,000. However, if the surrogate relationship between S-K levels and clinical endpoints do not hold the ICERs are uncertain and likely higher than the quoted range.

5.2.2 Interpreting the results for CKD patients in the chronic setting

The deterministic ICERs for CKD patients were greater than £40,000 in both ERG base cases. Making the hospital length of stay independent of treatment (SZC or SOC) had only a marginal impact on the ICER. Increasing the treatment duration of SZC to lifetime increased the ICER which rose to approximately £53,000 (ERG base case 1) and £46,000 (ERG base case 2). As stated, these ICERs are likely to be unfavourable to SZC; the scenario which the ERG believes to be highly optimistic gave ICERs of £16,000 (assuming a 0.23 decrease in S-K levels when discontinuing RAASi treatment) and £11,000 (a 0.10 decrease). The ERG believes that the ICER in the chronic clinical setting for CKD patients in the chronic clinical setting the ICER is likely to be in the range of £16,000 to £46,000. However, if the surrogate relationship between S-K levels and clinical endpoints do not hold the ICERs are uncertain and likely higher than the quoted range.

A summary of the exploratory analyses undertaken by the ERG for patients in the acute setting are presented in Table 15 for HF patients and in Table 16 for CKD patients.

5.2.3 Interpreting the results for HF patients in the acute setting

The deterministic ICER for HF patients was below £40,000 in ERG base case 2, but was approximately £100,000 in ERG base case 1. However, the ERG comments that these analyses are very unfavourable to SZC which has a life year advantage across the 52-week period which would be expected to result in QALY gains over longer-horizon. Assuming no additional costs, if the survival advantage seen in the remaining lifetime was an additional 0.006 discounted QALYs in ERG base case 1 and an additional 0.001 discounted QALYs in ERG base case 2, then an ICER below £30,000 per QALY would be produced. These values increase to 0.023 and 0.008 if patients can resume RAASi treatment. This is highly plausible. However, if the surrogate relationship between S-K levels and clinical endpoints do not hold the ICERs are uncertain and likely higher than stated with a greater increase in future QALYs required to be cost-effective.

5.2.4 Interpreting the results for CKD patients in the acute setting

The deterministic ICER for CKD patients was below £30,000 in ERG base case 2, but was over £340,000 in ERG base case 1. However, the ERG comments that these analyses are very unfavourable to SZC which has a slight life year advantage across the 52-week period. Assuming no additional costs, if the survival advantage seen in the remaining lifetime was an additional 0.006 discounted QALYs in ERG base case 1 then an ICER below £30,000 per QALY would be produced. This values increases to 0.022 if patients can resume RAASi treatment. For ERG base case 2, an additional 0.003 QALYs would be needed to produce an ICER below £30,000 if patients can resume RAASi treatment This is highly

plausible. However, if the surrogate relationship between S-K levels and clinical endpoints do not hold the ICERs are uncertain and likely higher than stated with a greater increase in future QALYs required to be cost-effective.

Table 13: Exploratory deterministic results for HF patients in the chronic setting*

Analysis	Discounted costs		Discounted QALYs		Life years		ICER
	SZC	SOC	SZC	SOC	SZC	SOC	
Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£13,458**
1) Withdrawing RAASi treatment for twelve weeks when S-K ≥ 6 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,063
2a) Assuming a decrease in S-K levels of 0.23 post-RAASi discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,012
2b) Assuming a decrease in S-K levels of 0.10 post-RAASi discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,333
4) Assuming an alternative relationship between S-K level and HF mortality	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,952
5) Adding in wastage: the cost of 30 sachets assumed over a 28-day period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,329
6) Reducing the costs associated with RAASi changes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,301
7) Assuming no reduction in S-K level due to SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,641
ERG base case 1 (1, 2a, 4, 5 and 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£29,239**
ERG base case 1 with lifetime SZC treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,668
ERG base case 1 with hospitalisation stay independent of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,257
ERG base case 1 with no effect of SOC on S-K levels	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8817
ERG base case 2 (1, 2b 4, 5 and 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£23,296**
ERG base case 2 with lifetime SZC treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,056
ERG base case 2 with hospitalisation stay independent of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,313
ERG base case 2 with no effect of SOC on S-K levels	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6949

*Note that ERG exploratory analysis 3 relates to CKD utilities and does not change the HF results.

Table 14: Exploratory deterministic results for CKD patients in the chronic setting

Analysis	Discounted costs		Discounted QALYs		Life years		ICER
	SZC	SOC	SZC	SOC	SZC	SOC	
Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£25,363**
1) Withdrawing RAASi treatment for twelve weeks when S-K ≥ 6 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,056
2a) Assuming a decrease in S-K levels of 0.23 post-RAASi discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,200
2b) Assuming a decrease in S-K levels of 0.10 post-RAASi discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,851
3) Using HUI3 utilities rather than TTO utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,537
5) Adding in wastage: the cost of 30 sachets assumed over a 28-day period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,882
6) Reducing the costs associated with RAASi changes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,683
7) Assuming no reduction in S-K level due to SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,532
8) Using EQ-5D values identified by the company	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,928
ERG base case 1 (1, 2a, 3, 5 and 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£46,936**
ERG base case 1 with lifetime SZC treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£53,685
ERG base case 1 with hospitalisation stay independent of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,965
ERG base case 1 with no effect of SOC on S-K levels	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,877
ERG base case 2 (1, 2b, 3, 5 and 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£40,731**
ERG base case 2 with lifetime SZC treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,135
ERG base case 2 with hospitalisation stay independent of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,761
ERG base case 2 with no effect of SOC on S-K levels	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,173

*Note that ERG exploratory analysis 4 relates to HF and does not change the CKD results.

Table 15: Exploratory deterministic results for HF patients in the acute setting (52-week analysis)*

Analysis	Discounted costs		Discounted QALYs		Life years		ICER
	SZC	SOC	SZC	SOC	SZC	SOC	
Company base case (lifetime)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£7,380**
Company base case (52-weeks)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£10,263**
1) Withdrawing RAASi treatment for twelve weeks when S-K ≥ 6 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,263†
2a) Assuming a decrease in S-K levels of 0.23 post-RAASi discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,652
2b) Assuming a decrease in S-K levels of 0.10 post-RAASi discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,223
4) Assuming an alternative relationship between S-K level and HF mortality	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
5) Adding in wastage: the cost of 30 sachets assumed over a 28-day period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,098
6) Reducing the costs associated with RAASi changes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,263†
ERG base case 1 (1,2a, 4, 5 and 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£100,093**
ERG base case 1 plus restarting on RAASi treatment at 12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£196,049
ERG base case 2 (1,2b, 4, 5 and 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£37,097**
ERG base case 2 plus restarting on RAASi treatment at 12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£72,109

*Note that ERG exploratory analyses 3 and 8 relates to CKD utilities and do not change the HF results. Analysis 7 applies only in the chronic setting.
†This does not affect the ICER as the company models assumes that all patients in the acute setting discontinue RAASi treatment and never have RAASi treatment restarted

Table 16: Exploratory deterministic results for CKD patients in the acute setting (52-week analysis)

Analysis	Discounted costs		Discounted QALYs		Life years		ICER
	SZC	SOC	SZC	SOC	SZC	SOC	
Company base case (lifetime)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominating**
Company base case (52-weeks)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominating**
1) Withdrawing RAASi treatment for twelve weeks when S-K ≥ 6 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating†
2a) Assuming a decrease in S-K levels of 0.23 post-RAASi discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£289,171
2b) Assuming a decrease in S-K levels of 0.10 post-RAASi discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9627
3) Using HUI3 utilities rather than TTO utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
5) Adding in wastage: the cost of 30 sachets assumed over a 28-day period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
6) Reducing the costs associated with RAASi changes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating†
8) Using EQ-5D values identified by the company	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
ERG base case 1 (1, 2a, 3, 5 and 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£346,485**
ERG base case 1 plus restarting on RAASi treatment at 12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£140,264
ERG base case 2 (1, 2b, 3, 5 and 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£28,760**
ERG base case 2 plus restarting on RAASi treatment at 12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,566

*Note that ERG exploratory analysis 4 relates to HF and does not change the CKD results. Analysis 7 applies only in the chronic setting.
†This does not affect the ICER as the company models assumes that all patients in the acute setting discontinue RAASi treatment and never have RAASi treatment restarted

5.3 Conclusions of the cost effectiveness section

The ERG prefers alternative assumptions to some of those used by the company. The relative efficacy of SZC and SOC in the correction phase and maintenance phase is unknown and has a big impact on the ICER. Assuming that the surrogate relationships between S-K levels and clinical endpoints hold the ERG believes that the ICER in the chronic clinical setting for HF patients is likely to be in the range of £10,000 to £29,000; for CKD patients in the chronic clinical setting the ICER is likely to be in the range of £16,000 to £46,000. If, however, the surrogate relationships do not hold then the ICERs for all analyses are uncertain and likely to be higher than the ranges quoted.

For patients in the acute clinical setting, it is highly plausible, assuming that the surrogate relationships hold, that the ICERs are below £30,000 per QALY gained when the reduced mortality within the 52-week period is extrapolated to longer time horizons. However, there remains uncertainty in the ICERs within the acute clinical setting due to the robustness of the surrogate relationships when S-K levels are changed with SZC and also because there are no data on these specific patients. These data will be produced in the ENERGIZE[13] and DIALIZE[14] studies.

Clinical advice to the ERG stated that decline in eGFR would be more rapid in patients with CKD with heavy proteinuria and uncontrolled hypertension, and that there would be more benefit in these patients but ICERs for this population were not presented by the company.

6 END OF LIFE

The company does not make a claim that the end of life criteria are met within the appraisal of SZC. The ERG agrees with this position and notes that the short-life expectancy criterion is not met, with patients living on average considerably longer than two years.

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8 APPENDICES

Appendix 1: Records of identified and excluded trials from the CS

Table 17: RCTs excluded from CS systematic literature review following quality appraisal. Modified from clarification response to question A13 (c)

Trial Population	Comparator, dose, duration	Reason for exclusion
Nakayama, 2018[52] 20 pre-dialysis CKD 4–5 outpatients with hyperkalaemia (S-K>5 mmol/l) not treated with polystyrene sulfonate	CPS, 5g powder after each meal, 4 weeks SPS, 5g powder after each meal, 4 weeks After 4 weeks, the patients swapped cohort without a washout period so 8 weeks total	The dose of CPS used in UK clinical practice is 15g, 3 or 4 times a day SPS is not used in UK clinical practice
Arnold, 2017[53] 47 patients with CKD 3-4	Dietary potassium restriction group: low potassium diet, 60-75 mmol/d potassium intake for 24 months. If S-K>4.5mmol/L for 2 consecutive readings, a 15g-30g daily dose of SPS was given until S-K levels <4.5mmol/L Control group: N/A, 24 month-duration. SPS administered if S-K>6.0	It was a study to determine whether dietary restriction of potassium intake may be a neuroprotective factor in CKD. SPS is not commonly used in UK clinical practice
Allon 1989[54] Patients on haemodialysis with S-K>5.0 mmol/L	Albuterol, 20 mg, Albuterol, 10 mg, placebo	Albuterol (also known as salbutamol) is an adjuvant therapy given alongside temporising agents. As such it is not a relevant comparator as it is administered earlier in the treatment pathway to shift potassium into the cells.
Allon 1990[55] Patients on haemodialysis with S-K>5.0 mmol/L	Albuterol, 20 mg, Insulin 10U + glucose 50 ml, 50%	Temporising agents such as insulin + glucose and adjuvant therapy such as albuterol are not relevant comparators as they are administered earlier in the treatment pathway to shift potassium into the cells
Chothia 2014[56] Patients on haemodialysis with S-K>5.0 mmol/L	Glucose 100 ml 50%, Insulin 10U + glucose 100 ml 50%	Temporising agents such as insulin + glucose are not relevant comparators as they are administered earlier in the treatment pathway to shift potassium into the cells
Gruy-Kapral 1998[57] Patients with chronic renal failure maintained on haemodialysis	SPS, 30g, 12 hours Phenolphtalein-docusate, 8 tablets, 12 hours Phenolphtalein-docusate 8 tablets + 30g SPS, 12 hours Sorbitol + 30g SPS, 12 hours Placebo, 12 hours	SPS is not commonly used in UK clinical practice Only 6 patients were included in the study

Trial **Population**	**Comparator, dose, duration**	**Reason for exclusion**
Lepage 2015 (SKIP)[58] Patients with CKD and S-K 5.0-5.9 mmol/L	Sodium polystyrene sulfonate 30 g QD, 7 days Placebo QD, 7 days	SPS is not commonly used in UK clinical practice
Mandelberg 1999[59] Patients with severe renal failure and S-K>5.0 mmol/L	Salbutamol, 1.2 mg, Placebo	Salbutamol is not a relevant comparator as it is administered as an adjuvant therapy earlier in the treatment pathway to shift potassium into the cells
Nasir 2014[18] Patients with CKD and hyperkalemia (S-K>5.2 mmol/L)	SPS, 5g TID, 3 days CPS, 5g TID, 3 days	The dose of CPS used in clinical practice is 15g, 3 or 4 times a day SPS is not commonly used in UK clinical practice
Ngugi 1997[60] Patients with acute or chronic renal failure with S-K>5.0 mmol/L	Insulin 10U + glucose 50 ml 50%, Salbutamol 0.5 mg, 8.4% sodium bicarbonate	Temporising agents such as insulin + glucose and adjuvant therapy such as albuterol are not relevant comparators as they are administered earlier in the treatment pathway to shift potassium into the cells

Abbreviations: CKD, chronic kidney disease; CPS, calcium polystyrene sulfonate; S-K, serum potassium; QD, once daily; TID, three times daily

Appendix 2: Results of efficacy analyses

Table 18: ZS-004 results of longitudinal modelling of S-K values during maintenance phase. Adapted from company response to clarification (Question A15, Table 6)

covariate	category	Estimate	95% CI		p-value
			lower	upper	
Intercept		[redacted]	[redacted]	[redacted]	[redacted]
Treatment	**Placebo**	reference	[redacted]	[redacted]	[redacted]
	5 g ZS	[redacted]	[redacted]	[redacted]	[redacted]
	10 g ZS	[redacted]	[redacted]	[redacted]	[redacted]
	15 g ZS	[redacted]	[redacted]	[redacted]	[redacted]
Acute Phase Baseline eGFR		[redacted]	[redacted]	[redacted]	[redacted]
Acute Phase Baseline S-K		[redacted]	[redacted]	[redacted]	[redacted]
Maintenance Phase Baseline S-K		[redacted]	[redacted]	[redacted]	[redacted]
Age	**<55**	reference	[redacted]	[redacted]	[redacted]
	55-64	[redacted]	[redacted]	[redacted]	[redacted]
	>=65	[redacted]	[redacted]	[redacted]	[redacted]
RAASi Use	**No**	reference			
	Yes	[redacted]	[redacted]	[redacted]	[redacted]
CKD	**No**	reference			
	Yes	[redacted]	[redacted]	[redacted]	[redacted]
CHF	**No**	reference			
	Yes	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes	**No**	reference			
	No	[redacted]	[redacted]	[redacted]	[redacted]

Table 19: ZS-005 results of longitudinal modelling of S-K values during maintenance phase. Adapted from company response to clarification (Question A17, Table 11)

covariate	category	Estimate	95% CI		p-value
			lower	upper	
Intercept		[redacted]	[redacted]	[redacted]	[redacted]
Acute Phase Baseline eGFR		[redacted]	[redacted]	[redacted]	[redacted]
Acute Phase Baseline S-K		[redacted]	[redacted]	[redacted]	[redacted]
Extended Phase Baseline S-K		[redacted]	[redacted]	[redacted]	[redacted]
Age	**<55**	[redacted]	[redacted]	[redacted]	[redacted]
	55-64	[redacted]	[redacted]	[redacted]	[redacted]
	>=65	[redacted]	[redacted]	[redacted]	[redacted]
RAASi Use	**No**	[redacted]	[redacted]	[redacted]	[redacted]
	Yes	[redacted]	[redacted]	[redacted]	[redacted]
CKD	**No**	[redacted]	[redacted]	[redacted]	[redacted]
	Yes	[redacted]	[redacted]	[redacted]	[redacted]
CHF	**No**	[redacted]	[redacted]	[redacted]	[redacted]
	Yes	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes	**No**	[redacted]	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]	[redacted]

Appendix 3: Results of longitudinal model fitting to pooled ZS-004 and ZS-005 data

Table 20: ZS-004 and ZS-004 results of longitudinal modelling of S-K values during acute phase days 0-3. Adapted from company response to clarification (Question A20, Table 15)

Parameter	Estimate	95% CI	P-value
Intercept	[redacted]	[redacted]	[redacted]
Day	[redacted]	[redacted]	[redacted]
Patient component (SD)	[redacted]	[redacted]	[redacted]
Observation component (SD)	[redacted]	[redacted]	[redacted]

Table 21: ZS-004 and ZS-005 results of longitudinal modelling of S-K values in SZC arm during maintenance phase days 4 onwards. Adapted from company response to clarification (Question A20, Table 16)

Parameter	category	Estimate	95% CI	P-value
Intercept		[redacted]	[redacted]	[redacted]
Day>28	no	reference		
	yes	[redacted]	[redacted]	[redacted]
Patient component (SD)		[redacted]	[redacted]	[redacted]
Observation component (SD)		[redacted]	[redacted]	[redacted]

Table 22: ZS-004 results of longitudinal modelling of S-K values in SOC arm during maintenance phase days 4 onwards. Adapted from company response to clarification (Question A20, Table 17)

Parameter	category	Estimate	95% CI	P-value
Intercept		[redacted]	[redacted]	[redacted]
Day>14	no	reference		
	yes	[redacted]	[redacted]	[redacted]
Patient component (SD)		[redacted]	[redacted]	[redacted]
Observation component (SD)		[redacted]	[redacted]	[redacted]

Appendix 4: Exploratory analyses conducted by the ERG using the combined HF and CKD populations

Table 23: Exploratory deterministic results for combined HF and CKD patients in the chronic setting

Analysis	Discounted costs		Discounted QALYs		Life years		ICER
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£21,849**
1) Withdrawing RAASi treatment for twelve weeks when S-K ≥ 6 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,105
2a) Assuming a decrease in S-K levels of 0.23 post-RAASi discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,048
2b) Assuming a decrease in S-K levels of 0.10 post-RAASi discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		£24,786
3) Using HUI3 utilities rather than TTO utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,210
4) Assuming an alternative relationship between S-K level and HF mortality	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,009
5) Adding in wastage: the cost of 30 sachets assumed over a 28-day period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,194
6) Reducing the costs associated with RAASi changes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,806
7) Assuming no reduction in S-K level due to SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5377
8) Using EQ-5D values identified by the company	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,407
ERG base case 1 (1, 2a, 3, 4, 5 and 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£37,983**
ERG base case 1 with lifetime SZC treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,207
ERG base case 1 with hospitalisation stay independent of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,004
ERG base case 1 with no effect of SOC on S-K levels	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,846
ERG base case 2 (1, 2b, 3 4, 5 and 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£32,255**
ERG base case 2 with lifetime SZC treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,940

ERG base case 2 with hospitalisation stay independent of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,276
ERG base case 2 with no effect of SOC on S-K levels	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,255

Table 24: Exploratory deterministic results for combined HF and CKD patients in the acute setting

Analysis	Discounted costs		Discounted QALYs		Life years		ICER
	SZC	SOC	SZC	SOC	SZC	SOC	
Company base case (52-weeks)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominating**
1) Withdrawing RAASi treatment for twelve weeks when S-K ≥ 6 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating[†]
2a) Assuming a decrease in S-K levels of 0.23 post-RAASi discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£95,047
2b) Assuming a decrease in S-K levels of 0.10 post-RAASi discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,756
3) Using HUI3 utilities rather than TTO utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
4) Assuming an alternative relationship between S-K level and HF mortality	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
5) Adding in wastage: the cost of 30 sachets assumed over a 28-day period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
6) Reducing the costs associated with RAASi changes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
8) Using EQ-5D values identified by the company	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
ERG base case 1 (1,2a, 4, 5 and 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£159,616**
ERG base case 1 plus restarting on RAASi treatment at 12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£411,038
ERG base case 2 (1,2b, 4, 5 and 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£39,457**
ERG base case 2 plus restarting on RAASi treatment at 12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£129,460

Analysis 7 applies only in the chronic setting.
[†]This does not affect the ICER as the company models assumes that all patients in the acute setting discontinue RAASi treatment and never have RAASi treatment restarted

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Sodium zirconium cyclosilicate for treating hyperkalaemia [ID1293]

You are asked to check the ERG report from School of Health and Related Research (ScHARR) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **6pm on 14 September 2018** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

In addition to the Fact Check issues highlighted by the company the ERG has also made amendments to the report, most noticably in Section 3.2.9 which relates to the surrogate relationship between S-K levels and clinical endpoints. This additional level of uncertainty has been detailed in Section 3.2.9 and in the interpretation of the results throughout the report.

KEY CLINICAL ISSUES

AstraZeneca believe there are three key clinical issues relating to positioning and populations to be assessed for SZC.

Issue 1 Acute setting positioning

Description of problem	Description of proposed amendment	Justification for amendment	
Page 27 Clinical advice to the ERG is that patients in the "acute" phase in the included studies are not representative of real-world patients with acute HK, as the CS included trials were conducted in an outpatient setting, excluding acutely unwell patients, dialysis patients,	Clinical advice to the ERG is that patients in the "acute" phase in the included studies are not fully representative of real-world patients with acute HK, as the CS included trials were conducted in an outpatient setting, excluding acutely unwell patients, and dialysis patients~~, and patients with high arrhythmic risk (e.g.~~	It is important to highlight that the marketing authorisation for SZC is across all settings of use and was granted on the evidence base presented in the CS, including the data for ZS-004 and ZS-005 which was used as a pooled efficacy dataset in both the acute and chronic settings. Furthermore, ZS-004 included patients with S-K ≥5.1 mmol/L with no upper bound, and ZS-005 included patients with S-K ≥5.1 and ≤6.5 mmol/L and therefore enrolled patients with a S-K level of clinical relevance to an acute/A&E setting. Additionally, ZS-003 included patients with S-K levels ≤6.5 mmol/L. Specifically, the EMA did not raise concerns in the EPAR that the clinical effectiveness of SZC in different settings of care would differ to that demonstrated in the clinical trials.[1]	Text amended by changing "not representative" to "not fully representative". The suggested deletion has been made. The additional analysis conducted by the company is assumed to have little impact on the cost-effectiveness results as these reduced quality of life will apply in both arms and will only change the ICER if there are differential deaths during this period. As such, this has not been

<table>
<tr>
<td>and patients with high arrhythmic risk (e.g. S-K > 6.0 mmol/L; high risk ECG abnormalities).</td>
<td><s>S-K > 6.0 mmol/L; high risk ECG abnormalities)</s>. However, it should be noted that ZS-004 included patients with S-K ≥5.1 mmol/L with no upper bound, and ZS-005 included patients with S-K ≥5.1 and ≤6.5 mmol/L and therefore enrolled patients with a S-K level of clinical relevance to an acute/A&E setting. In addition, as SZC has a marketing authorisation for the treatment of HK (which is not restricted by clinical setting) the company have indicated that SZC would be used in the acute setting. This positioning was confirmed by clinical advice from 7 specialists interviewed by the company.</td>
<td>AstraZeneca interviewed 7 specialists in HK across England and Wales including 2 cardiologists, 3 nephrologists and 2 A&E physicians.[2] All 7 specialists confirmed that SZC would be used in the acute clinical setting as presented in Figure 1 of the ERG report.

As such, there appears to be no concern from interviewed specialists in England and Wales on the evidence base for its use in the acute setting.

Therefore, to ensure NICE evaluate SZC within its licence and for where it would be used in clinical practice, AstraZeneca believe the evidence base presented to and accepted by the EMA is sufficient for NICE to evaluate SZC in the acute setting. In particular, the clinical advice to the ERG received from 1 nephrologist in Scotland and 1 operations director (also a nephrologist) in England, should be balanced with the marketing authorisation for SZC and the clinical advice reported in the CS.[2]

Nevertheless, AstraZeneca does acknowledge that the cost-effectiveness model does not currently account for acutely unwell patients. Therefore, a sensitivity analysis has been conducted which applies a range of disutilities from 0.1 to 0.3 to patients at baseline and through the in-hospital period to reflect the disutilities associated with acute illness. This sensitivity analysis represents the potential effect of acute illnesses such as pneumonia and sepsis on the ICER.

<table>
<tr><th colspan="4">ICER – Acute setting</th></tr>
<tr><th></th><th>Disutility = 0.1</th><th>Disutility = 0.2</th><th>Disutility = 0.3</th></tr>
</table>
</td>
<td>commented on further, or included in the ERG report.</td>
</tr>
</table>

		CKD or HF	Dominating	Dominating	Dominating	
		CKD	Dominating	Dominating	Dominating	
		HF	Dominating	Dominating	Dominating	
		As one can observe, SZC remains dominant even when the disutilities of acute illness are taken into account.				

Issue 2 Chronic setting positioning

Description of problem	**Description of proposed amendment**	**Justification for amendment**	
Page 26 Clinical advice to the ERG stated that discontinuation of SZC could lead to potentially dangerous clinical scenarios if SZC approval encourages clinicians to use extra RAAS drugs and the goal of SZC	Clinical advice to the ERG stated that discontinuation of SZC could lead to potentially dangerous clinical scenarios if SZC approval encourages clinicians to use optimised RAASi drugs and the goal of SZC treatment is to protect patients from the risks	This correction is necessary to clarify that whilst discontinuation of SZC may elevate the risk of HK when the dose of RAASi is increased, the down-titration or discontinuation of RAASi drugs may elevate the risk of mortality, disease progression and MACE. Clinicians currently face this dilemma, without SZC available.	Not a factual error.

treatment is to protect patients from the risks associated with potassium-increasing drugs for serious conditions, such as those for HF.	associated with potassium-increasing drugs for serious conditions, such as those for HF. However, the alternative of down-titrating or discontinuing RAASi drugs may also be considered potentially dangerous as it increases the risks of mortality, disease progression, hospitalization and MACE. In addition, it is not aligned with guidelines and consensus statements, including NICE, European Society of Cardiology – Heart Failure (ESC-HF) and British Society for Heart Failure which recommend the use of RAASi drugs in patients with CKD and HF due to their cardiorenal protective effects.[3-5]		

Page 26 Both clinical advisors highlighted that it is preferable to attempt dietary interventions or at least to provide brief diet information before considering drugs such as SZC as patients may not welcome dietary advice later in their treatment pathway than earlier.	Both clinical advisors to the ERG highlighted that it is preferable to attempt dietary interventions or at least to provide brief diet information before considering drugs such as SZC as patients may not welcome dietary advice later in their treatment pathway than earlier. However, in line with NICE final scope, clinical advice from 7 specialists interviewed by the company suggested that SZC would be used instead of low potassium diet. Literature presented in the CS and clinical advice to the company highlighted that when a low-potassium diet is advised, adherence is low, and quality of life is negatively affected [2].	The NICE final scope states that the comparator for the submission is: *"Standard care. This includes a low potassium (K^+) diet with or without agents that reduce levels of potassium in the body"* Therefore, this statement should be made in the context of the NICE scope. In addition, AstraZeneca interviewed 7 specialists in HK across England and Wales including 2 cardiologists, 3 nephrologists and 2 A&E physicians [2]. All 7 specialists confirmed that SZC would be used instead of low potassium diet in the acute clinical setting as presented in Figure 1 of the ERG report. Literature and clinical advice from the 7 specialists have demonstrated that adherence to the low potassium diet is low and quality of life is negatively affected. In particular, the clinical advice to the ERG received from 1 nephrologist in Scotland and 1 operations director (also a nephrologist) in England, should be balanced with the evidence presented in the CS and NICE's final scope.	Not a factual error.

Issue 3 Pooled CKD or HF population

Description of problem	Description of proposed amendment	Justification for amendment	
Page 38 There are health states related to the level of severity of a hypothetical individual's HF or CKD (the schematic does not show that there are effectively additional health states for no HF and for no CKD).	There are health states related to the level of severity of a hypothetical individual's HF or CKD. The HF health states and the CKD health states are mutually exclusive, i.e. patients cannot occupy a HF health state at the same time as a CKD health state.	This correction is necessary for clarity. No additional health states for "no HF" and "no CKD" are needed, as only patients with HF or patients with CKD are modelled. The CKD and HF health states are mutually exclusive.	Text changed
Page 50 The ERG does not believe that it is appropriate to combine HF and CKD patients. This is because: these patients are clinically distinct and can be identified; that the relationship between SK levels and adverse outcomes differ; and that the method of pooling	The ERG does not believe that it is appropriate to combine HF and CKD patients. This is because: these patients are clinically distinct and can be identified; that the relationship between SK levels and adverse outcomes differ; and that the method of pooling does not provide appropriate eGFR levels for either group. However, it should be noted that SZC has a marketing authorisation for the treatment of HK, which primarily comprises both CKD and HF patients.	It is important to highlight that the marketing authorisation for SZC is for treatment of HK and was based on the evidence base presented in the CS, including the data for ZS-004 and ZS-005 which comprised of 64.3% of CKD patients and 35.7% of HF patients. Subgroup analyses presented in Appendix E of the CS showed that the effect of SZC was consistent across comorbid conditions of HF and CKD, justifying the use of all trial data rather than individual subgroups. Additionally, HK occurs predominantly in patients with an underlying degree of CKD or HF. Due to the nature of the cardio-renal	Not a factual error However, following a request from NICE combined results are included in an appendix. The ERG still believes that these results should not be considered by the committee.

does not provide appropriate eGFR levels for either group.		system, CKD patients tend to have a degree of heart disfunction while those with HF have a degree of kidney dysfunction. Therefore, it is relevant to consider CKD and HF patients as one population with a continuum of disease characteristics. Whilst we acknowledge the ERG's view, it is important to highlight the definition of the marketing authorisation, which is the scope of evaluation for the NICE STA. Whilst the cost-effectiveness of subgroups may be of interest, this should only be considered if the licenced population is not considered cost-effective. It is therefore relevant to present ICERs for the pooled CKD and HF population as the base case to align with the marketing authorisation.	

KEY ECONOMIC ISSUES:

AstraZeneca believe there are four key economic issues relating to assumptions and errors implemented in the ERG model. The impact of amending these issues is summarised in the Table 1. Revised company base case for the acute setting

	CKD or HF (revised company's base-case)	CKD only	HF only
Revised company base-case, including assumptions recommended by the ERG - Time horizon = 52 weeks (ERG base case 1)	Dominating	Dominating	Dominating

- Assuming a decrease in S-K levels of 0.23 post-RAASi discontinuation, and 0.115 post RAASi down-titration (ERG base case 1) - Assuming an alternative relationship between S-K level and HF mortality (ERG base case 1) - Reducing the costs associated with RAASi changes (ERG base case 1) **And addressing four key issues identified by AstraZeneca** **1.** Removing effect of SZC from the standard care arm **2.** Using EQ-5D utilities for the CKD population **3.** Assuming wastage only for the first 28 days, no wastage assumed for continuous use **4.** Model error corrections			
Scenarios analyses			
Adding in wastage: the cost of 30 sachets assumed over a 28-day period	Dominating	Dominating	Dominating
Using HUI3 utilities rather than EQ5D utilities	Dominating	Dominating	Dominating
Lifetime time horizon	Dominating	Dominating	Dominating
Hospitalisation stay independent of treatment	Dominating	Dominating	Dominating

Table 2 and Table 1 below. We ask that the ERG reconsider their base case, scenarios and conclusions in light of the response below.

Table 1. Revised company base case for the acute setting

	CKD or HF (revised company's base-case)	**CKD only**	**HF only**
Revised company base-case, including assumptions recommended by the ERG - Time horizon = 52 weeks (ERG base case 1)	Dominating	Dominating	Dominating

- Assuming a decrease in S-K levels of 0.23 post-RAASi discontinuation, and 0.115 post RAASi down-titration (ERG base case 1) - Assuming an alternative relationship between S-K level and HF mortality (ERG base case 1) - Reducing the costs associated with RAASi changes (ERG base case 1) **And addressing four key issues identified by AstraZeneca** **5.** Removing effect of SZC from the standard care arm **6.** Using EQ-5D utilities for the CKD population **7.** Assuming wastage only for the first 28 days, no wastage assumed for continuous use **8.** Model error corrections			
Scenarios analyses			
Adding in wastage: the cost of 30 sachets assumed over a 28-day period	Dominating	Dominating	Dominating
Using HUI3 utilities rather than EQ5D utilities	Dominating	Dominating	Dominating
Lifetime time horizon	Dominating	Dominating	Dominating
Hospitalisation stay independent of treatment	Dominating	Dominating	Dominating

Table 2. Revised company base case for the chronic setting

	CKD or HF (revised company's base-case)	**CKD only (revised company's base-case)**	**HF only (revised company's base-case)**
Revised company base-case, including assumptions recommended by the ERG - Withdrawal of RAASi for 12 weeks in SZC when S-K ≥6.0mmol/L* (ERG base case 1)	£11,474	£13,054	£8,134

- Assuming a decrease in S-K levels of 0.23 post-RAASi discontinuation, and 0.115 post RAASi down-titration (ERG base case 1) - Assuming an alternative relationship between S-K level and HF mortality (ERG base case 1) - Reducing the costs associated with RAASi changes (ERG base case 1) **And addressing four key issues identified by AstraZeneca** **1.** Removing effect of SZC from the standard care arm **2.** Using EQ-5D utilities for the CKD population **3.** Assuming wastage only for the first 28 days, no wastage assumed for continuous use **4.** Model error corrections			
Scenarios analyses			
Adding in wastage: the cost of 30 sachets assumed over a 28-day period	£12,368	£14,024	£8,817
Using HUI3 utilities rather than EQ5D utilities	£11,918	£14,779	£8,134
Lifetime SZC treatment	£14,505	£16,639	£10,607
Hospitalisation stay independent of treatment	£11,484	£13,066	£8,141

*This change is in the chronic setting only as this withdrawal is already implemented in the acute setting

Issue 4 S-K and RAASi relationship

Description of problem	Description of proposed amendment	Justification for amendment	
Page 6 The company model did not model the relationship between renin-angiotensin-aldosterone system inhibitor (RAASi) treatment and serum potassium (S-K) levels.	The company model did not explicitly model the relationship between renin-angiotensin-aldosterone system inhibitor (RAASi) treatment and serum potassium (S-K) levels. However, a decrease in S-K levels in the SOC arm was inherently assumed as clinical effectiveness was based on the placebo arm of ZS-004. These patients were only randomised to placebo after having received SZC for the first three days and once normalisation of S-K levels was achieved.	AstraZeneca acknowledge the ERG's concern that the relationship between RAASi and S-K levels is not explicitly modelled. We also appreciate that the ERG acknowledged a reduction in S-K levels is likely to be over-estimated in the SOC arm: *"The ERG acknowledges, however, that the reductions in S-K levels in the SOC arm in the initial three days, and potentially to day 29, is likely to be over-estimated given that within study ZS-004[6] these patients received SZC in an open-label acute phase until normokalaemia was reached" [Page 51, ERG Report: Sodium Zirconium Cyclosilicate for Hyperkalaemia: A Single Technology Appraisal]* The assumptions applied by the ERG to model the relationship between S-K levels and RAASi discontinuation / down-titration have the largest impact on the ICER. AstraZeneca strongly feel that the ERG's discussion of this limitation should be balanced with the fact that the SOC clinical effectiveness is over-estimated in the original CS model. As discussed in the response to clarification questions (B16), the over-estimation of clinical effectiveness in the SOC arm as a consequence of placebo patients receiving SZC for the first three days until normokalaemia was reached, more than accounts for the clinical effectiveness estimated by	Not a factual error, as stated a comment is provided on p51. The relative impact of SZC vs other treatments is unknown due to the lack of comparative data in the correction phase. The assumption in the CS that SOC produces the same decrease in the correction phase as SZC has been stated more prominently to be unfavourable to SZC.
Page 46	The ERG comments that the use of RAASi, or not, is excluded from the estimated S-K levels.		See above

<table>
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<td>The ERG comments that the use of RAASi, or not, is excluded from the estimated S-K levels.</td>
<td>However, a significant decrease in S-K levels is modelled in the SOC arm, above that expected by the discontinuation of RAASi drugs alone, based on the placebo arm of ZS-004. These patients were only randomised to placebo after having received SZC for the first three days and once normalisation of S-K levels was achieved.</td>
<td>reducing or discontinuing RAASi as demonstrated below:
<table>
<tr><th></th><th>SOC S-K level reduction Day1-4 (mmol/L)</th><th>SOC S-K level reduction Day4+ (mmol/L)</th></tr>
<tr><td>Company base case:
Three days SZC until normokalaemia is reached followed by placebo</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Effect of RAASi discontinuation as recommend by the ERG</td><td>-0.23</td><td>-0.23</td></tr>
<tr><td>ERG base case 1:
Three days SZC until normokalaemia is reached followed by placebo + Effect of RAASi discontinuation</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Effect of RAASi down-titration</td><td>-0.115</td><td>-0.115</td></tr>
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<td>Page 50:
The company describe the process of model validation on page 158 of the CS. There were no clear face validity errors in the results following the clarification process. However, the ERG highlights what is believed to be a conceptual error in the model in that there is no explicit relationship between RAASi treatment and S-K level.</td>
<td>The company describe the process of model validation on page 158 of the CS. There were no clear face validity errors in the results following the clarification process. However, the ERG highlights what is believed to be a conceptual error in the model in that there is no explicit relationship between RAASi treatment and S-K level. However, a decrease in S-K levels in the SOC arm was inherently assumed as clinical effectiveness was based on the placebo arm of ZS-004 whereby placebo patients receiving SZC in the initial three days until normokalaemia was reached.</td>
<td>See above</td>
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<tr>
<td>Page 51:
Subsequent to the clarification process the ERG identified that within the model S-K levels were assumed independent of RAASi use, which neither agreed with clinical</td>
<td>Subsequent to the clarification process the ERG identified that within the model S-K levels were assumed independent of RAASi use, which neither agreed with clinical opinion nor published literature. However, a decrease in S-K levels in the SOC arm was inherently assumed as clinical effectiveness was based on the placebo arm of ZS-004 whereby placebo</td>
<td>See above</td>
</tr>
</table>

opinion nor published literature.	patients receiving SZC in the initial three days until normokalaemia was reached.			
Page 52: For simplicity, it was assumed that the trajectory associated in **Error! Reference source not found.** was associated with people on RAASi treatment and that there would be a decrease in S-K levels were RAASi treatment to be discontinued or down-titrated.	The company has suggested an alternative method, viewed by the company as more clinically appropriate, for estimating the S-K trajectory in the SOC arm. This method assumes a decrease in S-K levels of 0.1 or 0.23 mmol/L from baseline upon RAASi discontinuation, or a decrease of 0.05 or 0.115 mmol/L from baseline upon RAASi down-titration to suboptimal doses. The mean population S-K trajectories for patients who discontinue RAASi and for patients who down-titrate RAASi based on the method proposed by the company are plotted in Figures A and B. [redacted] [redacted]	ERG base case 1: Three days SZC until normokalaemia is reached followed by placebo + Effect of RAASi down-titration	[redacted]	[redacted]
		In clinical practice, no pharmacological interventions are given in the first three days to SOC patients and the only options available to clinicians are to discontinue or down-titrate RAASi, which the ERG assert is associated with a reduction in S-K level of 0.115-0.23. Following this, low-potassium diet may be given, but this is associated with low compliance, poor quality of life and a systematic literature search has found no evidence of effect on S-K levels. Therefore, in assuming a reduction of [redacted] in Days 1-4 followed by a reduction of [redacted] in Day 4+ the company base case is highly conservative, compared to just assuming a reduction based on RAASi discontinuation or down-titration of 0.115-0.23. AstraZeneca believe there is a fundamental error in the approach proposed by the ERG to incorporate RAASi discontinuation and down-titration effects in the ERG model; in the current ERG report, the effects of RAASi discontinuation and down-titration are included in addition to the effect of SZC, during the first three days of the placebo arm in study ZS-004. To be aligned with clinical practice, the effect of S-K normalisation in the SZC arm, must be removed prior to introducing the reductions in S-K associated		The ERG believes that the company are referring to the chronic clinical setting when it is stated that no pharmaceutical interventions are given. The ERG notes that there are no comparative data relating to SZC in the correction phase and that assuming that there is no impact on S-K levels apart from change in RAASi dose is likely to be optimistic: short-term compliance with a low potassium diet is likely to be greater when S-K levels are higher; there

[redacted]

[redacted]

with RAASi discontinuation or down-titration. The current approach applied by the ERG combines the effects of SZC plus RAASi discontinuation or down-titration, which is not representative of a placebo arm. The clinical implausibility of this method is illustrated in Appendix 2, Figure C, which shows that SOC RAASi discontinuers have a larger decrease in S-K during the first 3 days than SZC, and have the same decrease in S-K during the subsequent 11 days as SZC. This finding is not in line with results from the ZS-004 clinical trial.

If the relationship between S-K levels and RAASi discontinuation and down-titration is incorporated as per the ERG report, then the effect of SZC in the placebo arm of ZS-004 should be removed to reflect clinical practice as current SOC patients would not be treated with SZC first. As such, AstraZeneca would propose an amend to the ERG's base case such that no reduction in S-K is assumed, other than 0.23 mmol/L from baseline or 0.115 mmol/L from baseline upon RAASi discontinuation or down-titrated, respectively.

The company's revised base case (see Table 1 and Table 2) where the SZC effect has been removed from the SOC arm, and a scenario where the SZC effect has not been removed from the SOC arm (as in the ERG base case) can be seen below:

	ICER - Chronic setting	**ICER – Acute setting**
Revised company base case		
CKD or HF	£11,474	Dominating

may also be factors that would reduce S-K levels in the SOC arm in addition to changing RAASi treatment.

The ERG comments that the limitations within the submitted model in terms of: i) not explicitly modelling the impact of RAASi discontinuation / down-titration and ii) assuming that the correction phase of the SOC arm is equal to that of SZC were decisions that were made by the company.

The ERG acknowledges that in the absence of any trial evidence there is

			CKD only	£13,054	Dominating	considerable uncertainty in the relative decreases between SZC and SOC in the correction phase, and in the resultant S-K levels for SZC and SOC after the correction phase. The ERG agrees that it is unlikely that S-K levels in SOC patients would be lower the SZC patients in the correction phase. However, the ERG believes that for the model to reflect clinical reality that patients not on RAASi treatment should have lower S-K levels than those on
			HF only	£8,134	Dominating	
			Revised company base case with ERG's method for incorporating RAASi effect on S-K (i.e. not removing SZC effect)			
			CKD or HF	£34,709	£153,296	
			CKD only	£39,136	£300,704	
			HF only	£27,453	£96,794	

			RAASi treatment and has added text to this effect. The ERG acknowledges that the current approach is likely pessimistic to SZC and has added words to this effect within the document and has presented results using the scenario suggested by the ERG.
Page 51 Contrastingly, the company identified a study[7] that reported the increases in S-K levels due to RAASi reported in clinical trials (n=39). These values were typically below 0.3 mmol/L for patients with	Similarly, the company identified an in-depth narrative review of clinical trials assessing the impact of RAASi on S-K levels. This review concluded that RAASi treatment initiation and use is associated with an S-K level increase of 0.1–0.3 mmol/L in HF patients and typically ≤0.5 mmol/L (range: 0.06–0.8 mmol/L) in CKD patients.[50]	This correction is necessary for factual accuracy in the reported numbers, and for factual accuracy regarding the type of publication (literature review) by Weir and Rolfe 2010.	Change accepted. Although 'Similarly' is omitted.

CKD and between 0.1 and 0.3 mmol/L for patients with HF.			

Issue 5 Utility values

Description of problem	Description of proposed amendment	Justification for amendment	
Page 33 The utilities for CKD are from time trade-off (TTO) exercises valued by US patients rather than a representative sample of the UK population.	The utilities for CKD are from time trade-off (TTO) exercises valued by US patients rather than a representative sample of the UK population. However, following the initial submission, the company has identified an alternative source based on EQ-5D-3L, which aligns with NICE's reference case.	AstraZeneca acknowledge the ERG's preference to use a preference-based measure as opposed to TTO valuation. Following the initial NICE SZC submission, AstraZeneca has identified an alternative source to inform the HSUVs for CKD health states that reports EQ-5D-3L utilities for non-anemic patients. This was identified via an SLR of the impact of CKD on patients' quality of life.[8] This aligns with NICE's preferred methods for the measuring and valuation of health effects.[9] We appreciate this study was not made aware to the ERG during the CS or response to clarification questions, but thought it would be useful to highlight in response to the ERG report and help inform the upcoming committee meeting. The company's revised base case (see Table 1 and Table 2), using this alternative source for CKD	It is unclear if the new study Eriksson (or Giles as stated in the reference list) was found during the literature review performed for the CS or not. If it was, then it is unclear why it was not used earlier; if it was not, then there has been no description of the review and the ERG cannot rule out that the study has been cherry-picked.
Page 52 The ERG also note that the utility value for eGFR < 15 mL/min/1.73m^2 and without dialysis is 0.54 which is comparable to the pre-dialysis EQ-5D value of 0.57 reported by Lee et al.[10] A comparison of the values assumed by the company and the values	The ERG also note that the utility value for eGFR < 15 mL/min/1.73m^2 and without dialysis is 0.54 which is comparable to the pre-dialysis EQ-5D value of 0.57 reported by Lee et al.[10] Following the initial submission, the company identified an alternative source, Eriksson et al., which reports EQ-5D-3L utilities by CKD stage for non-anemic patients. A comparison of the values assumed by the company and the values assumed by the ERG are presented in **Error! Reference source not found.**. Note that the ERG values are adjusted so that when multiplied by 0.79 (an ERG-assumed population norm for		

assumed by the ERG are presented in **Error! Reference source not found.**. Note that the ERG values are adjusted so that when multiplied by 0.79 (an ERG-assumed population norm for the patients aged 63 to 65 years) they equal the values reported in Gorodetska et al.[11]

the patients aged 63 to 65 years) they equal the values reported in Gorodetskaya et al.[11]

utilities, and the company's revised base case using the ERG's source for utilities can be seen below:

	ICER - Chronic setting	**ICER – Acute setting**
Revised company base case		
CKD or HF	£11,474	Dominating
CKD only	£13,054	Dominating
HF only	£8,134	Dominating
Revised company base case with ERG's source for utilities using HUI3		
CKD or HF	£11,918	Dominating
CKD only	£14,779	Dominating
HF only	£8,134	Dominating

The ERG comments that there is similarity between the HUI3 value reported by Gorodetskaya et al in CKD5 and the EQ-5D value in CKD5 reported by Lee et al whilst the new value is higher. The Eriksson/Giles paper could not be identified by the ERG but appears to be conference proceedings. As such, the HUI3 data from Gorodetskava et al is preferred.

For completeness, the values using Giles/ Eriksson are also presented.

Page 52

Table 11. Utility values used in the company's base case and the ERG base cases

CKD Stage	**Company base case (SD): TTO Gorodetskaya et al. 2005 (N=269)**	**ERG base cases (SD): HUI-3 Gorodetskaya et al. 2005 † (N=269)**	**Company alternative source (SD) EQ-5D-3L Eriksson et al. 2016 * (N=313)**
3a	0.87 (0.034)	0.848 (0.066)	0.85 (0.21)
3b	0.87 (0.034)	0.848 (0.066)	0.85 (0.21)
4	0.85 (0.029)	0.696 (0.042)	0.81 (0.22)
5 (pre-RRT)	0.85 (0.034)	0.684 (0.068)	0.74 (0.29) (CKD stage 5, dialysis patients used a proxy)

† Adjusted so that the health state utility value equals the value reported in the literature after multiplying with 0.79 (the population age-band specific utility value for 63-65 year olds)

	*Not adjusted by 0.79, the ERG-assumed population norm for the patients aged 63 to 65 years because the adjustment would lead to values capped to 1		

Issue 6 Wastage assumption

Description of problem	Description of proposed amendment	Justification for amendment	
Page 53 Clinical advice to the ERG suggested that it was possible that patients who missed doses of SZC would still collect their next prescription and thus 'waste' the missed doses. Whilst this would impact more on the effectiveness the model structure made it easier to inflate costs and thus the ERG assumed one of the scenarios evaluated by the company and assumed that there would be a cost of 30 sachets for every 28 sachets prescribed.	Clinical advice to the ERG suggested that it was possible that patients who missed doses of SZC would still collect their next prescription and thus 'waste' the missed doses. The model structure made it easier to inflate costs and thus the ERG assumed one of the scenarios evaluated by the company and assumed that there would be a cost of 30 sachets for every 28 sachets prescribed. This change was implemented in addition to the wastage assumptions already implemented by the company in response to clarification question B6 (wastage in cycles 2-5).	The effectiveness implemented in the model is based on the pooled data from ZS-004 and ZS-005 trials and is associated to the use of SZC as observed in the trials. This accounts for missed doses during the trials. In addition, it should be highlighted by the ERG that the base case presented by AstraZeneca following clarification questions (B6) implemented wastage assumptions in cycles 2-5 during the correction phase and first month of maintenance phase. AstraZeneca would highlight that it is highly pessimistic to assume that 2 sachets are wasted for every 30 sachets, when a patient is on continuous treatment with SZC. There is no basis for this assumption, as sachets would be stored at home and prescribed again once they have been consumed. The company's revised base case (see Table 1 and Table 2) without wastage during the maintenance phase, and the company's revised	Text added relating to wastage in cycles 2-5.

base case using the ERG's wastage assumption can be seen below:

	ICER - Chronic setting	ICER – Acute setting
Revised company base case		
CKD or HF	£11,474	Dominating
CKD only	£13,054	Dominating
HF only	£8,134	Dominating
Revised company base case with ERG's method for wastage (i.e. patients waste 2 sachets for every prescription whilst on continuous treatment)		
CKD or HF	£12,368	Dominating
CKD only	£14,024	Dominating
HF only	£8,817	Dominating

Issue 7 Model error corrections

Description of problem	Description of proposed amendment	Justification for amendment	
Inputs sheet S93, S94 =IF(SZCWithdrawal=1,12, IF(frontend_DownTitrationforZS = "Acute",0,1))	=IF(SZCWithdrawal=1,12,IF(frontend_DownTitrationforZS="Acute",0,**12**))	The code relates to the implementation of "1) Withholding RAASi treatment for 12 weeks for patients in the SZC arm who have an S-K level of > 6.0 mmol/L". Based on clinical expert input, the time to RAASi resumption from discontinuation or down titration should be 12 weeks for standard care in the chronic setting.	Change made. The ERG comments that this did not impact the results unless patients are also allowed to restart RAASi treatment.
VBA – mod_simulation Code after ERG changes: If blnpatientflag_ontreatment = True Then dbl_arrCostTreatment(cycle) = dbl_arrCostTreatment(cycle) + **(dbl_cTreat_4weekly)** Original code in company's model:	VBA – mod_simulation Search for "f47" in corrected model If blnpatientflag_ontreatment = True **And Worksheets("Front End").Range("F47").Value = 0 Then** dbl_arrCostTreatment(cycle) = dbl_arrCostTreatment(cycle) + **(dbl_cTreat_4weekly * 30 / 28)** ElseIf blnpatientflag_ontreatment = True **And Worksheets("Front End").Range("F47").Value = 1** Then dbl_arrCostTreatment(cycle) = dbl_arrCostTreatment(cycle) + **(dbl_cTreat_4weekly)**	While implementing the scenario "5) Assuming a higher level of wastage associated with S-K treatment", a part of the VBA code that was originally in the model was deleted. The original code modelled a pack of 30 sachets being costed for at the beginning of cycle 4, to account for any wastage (B6 of clarification questions). Once deleted, the code applied costs for a pack of 28 sachets rather than 30 for cycle 4 when the wastage scenario was not being run. The deleted code should have been reinserted when running the non-wastage scenarios. The proposed amendment to the code ensures that a pack of 30 is costed in cycle 4 regardless of the scenario being run, as per B6 of clarification questions.	Change accepted

If blnpatientflag_ontreatment = True Then dbl_arrCostTreatment(cycle) = dbl_arrCostTreatment(cycle) + **(dbl_cTreat_4weekly * 30 / 28**)		The deletion of the code caused a difference between the company base case reported in Tables 1-4 and 13-16 of the ERG report and the base care results supplied by AstraZeneca in response to the clarification questions (Table 9, page 48).	
Tables 1-4 and 13-16	Tables 1-4 and 13-16 have been corrected and are presented in Appendix 1.	Analyses have been re-run following the implementation of the corrections described above.	Changes accepted

Issue 8 Other issues

Description of problem	**Description of proposed amendment**	**Justification for amendment**	
Page 6: The company base case model did not withdraw RAASi treatment for patients receiving SZC despite having S-K levels of ≥6.0 mmol/L. The ERG believes that this is not aligned with NICE guidance, and prefer a sensitivity analysis conducted by the company.	The company base case model did not withdraw RAASi treatment for patients receiving SZC in the chronic setting, despite having S-K levels of ≥6.0 mmol/L. The ERG believes that this is not aligned with NICE guidance, and prefer a sensitivity analysis conducted by the company. Although, clinical advice from 7 clinicians interviewed by the company suggests that SZC may negate the need to withdraw RAASi.	In the acute setting, all patients receiving SZC and standard care withdraw RAASi treatment when S-K levels are ≥6.0 mmol/L. In the chronic setting, the company base case model did not withdraw RAASi treatment for patients receiving SZC with S-K levels of ≥6.0 mmol/L. Although AstraZeneca acknowledges that NICE guidance indicates that RAASi drugs should be stopped for patients with S-K levels of ≥6.0 mmol/L, this guidance predates new therapies such as SZC and AstraZeneca believe that the majority of SZC patients would not discontinue RAASi.	Not a factual error.

<table>
<tr>
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<td>The impact on the company's revised base case (see Table 1 and Table 2) of removing the assumption of RAASi withdrawal for patients receiving SZC having S-K levels of ≥6.0 mmol/L., can be seen below:
<table>
<tr><th></th><th>ICER - Chronic setting</th><th>ICER – Acute setting</th></tr>
<tr><td colspan="3">Revised company base case</td></tr>
<tr><td>CKD or HF</td><td>£11,474</td><td>Dominating</td></tr>
<tr><td>CKD only</td><td>£13,054</td><td>Dominating</td></tr>
<tr><td>HF only</td><td>£8,134</td><td>Dominating</td></tr>
<tr><td colspan="3">Revised company base case, but with removal of the withdrawal of RAASi assumption for patients receiving SZC having S-K levels of ≥6.0 mmol/L</td></tr>
<tr><td>CKD or HF</td><td>£11,342</td><td>Dominating</td></tr>
<tr><td>CKD only</td><td>£12,912</td><td>Dominating</td></tr>
<tr><td>HF only</td><td>£7,992</td><td>Dominating</td></tr>
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<td>Page 19

73 references relating to 13 RCTs were identified as relevant to the review question. Trials of patiromer were appropriately excluded as</td>
<td>73 references were considered for extraction. Two trials of patiromer were appropriately excluded as it is not a comparator in the decision problem. The remaining 71 references related to 13 RCTs that were identified as relevant to the review question.</td>
<td>Clarifying that 71 references (13 RCTs) were identified as relevant to the review question, following the exclusion of two references for patiromer.</td>
<td>Text amended</td>
</tr>
</table>

it is not a comparator in the decision problem.			
Page 24 Secondary outcomes reported but not repeated here included: the number of normokalaemic days during the maintenance phase inclusive of days 8-29 and change and percent change from acute phase baseline to each maintenance phase follow-up time point.	Secondary outcomes reported but not repeated here included: the number of normokalaemic days during the maintenance phase inclusive of days 8-29, change and percent change from acute phase baseline to each maintenance phase follow-up time point, the proportion of patients who achieved normalisation in S-K values at Day 29 of the maintenance phase, and the time to hyperkalaemia.	Including the two other secondary endpoints for completeness.	Text amended
Page 26 Other secondary and additional outcomes reported but not repeated here included: the mean S-K levels at each visit; the mean change and mean percent change from acute phase baseline in S-K; time to first recurrent HK ≥5.6 mmol/L; and proportions using RAASi at the extended phase baseline and at quarterly intervals.	Other secondary and additional outcomes reported but not repeated here included: the mean S-K levels at each visit; the mean change and mean percent change from acute phase baseline in S-K; nominal and percent change from the acute phase baseline in bicarbonate levels at each visit; proportion of subjects with normal bicarbonate values at acute phase day 1 and each extended phase visit.”	List of secondary endpoints corrected.	Text amended
Page 27:	In clinical practice patients in the correction phase in the acute setting are treated with	This amendment is necessary for clarity.	Text amended

In clinical practice patients in the correction phase are treated with temporising agents such as insulin dextrose and SZC to stabilise S-K levels within 48 hours but as patients in the study population were chronic and stable (not acute HK patients), insulin dextrose was not administered.	temporising agents such as insulin dextrose and SZC to stabilise S-K levels within 48 hours but as patients in the study population were chronic and stable (not acute HK patients), insulin dextrose was not administered.		
Page 30/31: The CS provides evidence that SZC lowers S-K levels in the study population of chronic, stable patients versus PBO. It does not provide direct evidence for: • SZC as plausible alternative for dietary modification or versus any active comparator (no narrative or formal data synthesis in the systematic review to compare SZC versus anything)	The CS provides evidence that SZC lowers S-K levels in the study population of chronic, stable patients versus PBO. It does not provide direct evidence for: • ~~SZC as plausible alternative for dietary modification or versus any active comparator (no narrative or formal data synthesis in the systematic review to compare SZC versus anything)~~ • SZC efficacy or safety in acutely unwell patients ~~SZC efficacy or safety in patients taking concomitant or combined treatments which may interact with SZC such as ACE inhibitors, or spironolactone.~~	Patients in the key clinical trials that informed the cost-effectiveness model were allowed to be on potassium lowering diets, as there were no diet restrictions in the trials. As such, the cost-effectiveness model compares SZC against a placebo group, where a proportion of the patients received dietary modification. Therefore, cost-effectiveness model should be considered to provide evidence for SZC as an alternative to dietary modification. In the correction phase and maintenance phase of ZS-005, [redacted] and [redacted]%, respectively, of patients were treated with RAASi. Similarly, patients in ZS-004 were also allowed to take concomitant RAASi therapy. As such, the efficacy and safety data of SCZ from ZS-005 and ZS-004 should be considered to provide evidence for SZC in patients who take concomitant RAASi medication.	Text Amended to "SZC as plausible alternative for protocol mandated dietary modification or versus any comparator in the correction phase" The following text has been deleted: "SZC efficacy or safety in patients taking concomitant or combined treatments which may interact with SZC such as

• SZC efficacy or safety in acutely unwell patients SZC efficacy or safety in patients taking concomitant or combined treatments which may interact with SZC such as ACE inhibitors, or spironolactone.			ACE inhibitors, or spironolactone.”
Page 32 These are summarised in Table 23 of the CS and were all Markov models.	These are summarised in Table 23 of the CS and of the three studies, one was a Markov model[12] and two were patient level simulation models.[13, 14]	Information presented is incorrect.	Text amended (including table ref, which should have been Table 22)
Page 34 Patients that are sampled with an S-K level <5.5 mmol/L in the chronic setting are assumed, and <6.0 mmol/L in the acute setting are discarded.	Patients that are sampled with an S-K level <5.5 mmol/L in the chronic setting, and those with an SK level <6.0 mmol/L in the acute setting are resampled.	Wording amended for clarification. Patients are not discarded as the total number of patients entering the model sum to the size of the cohort (60,000).	Text changed to “discarded and resampled”
Page 34 Patients with CKD were assumed to have an eGFR of 44.66 mL/min/1.73m^2 as detailed in Table 69 of the CS. This differs from the value of 31.63 mL/min/1.73m^e for CKD	The CKD and HF population mean baseline eGFR value was 44.66 mL/min/1.73m^2 as detailed in Table 69 of the CS and is based on the weighted average eGFR between CKD and HF patients (64.3% CKD, 35.7% HF). Patients with HF have an eGFR of 68.14 mL/min/1.73m^e and patients with CKD have an eGFR of 31.63 mL/min/1.73m^2.	This correction is necessary for factual accuracy and consistency with the CS and the model.	Text amended

patients and of 68.14 mL/min/1.73m^{e} reported in Table 28 of the CS.			
Page 36/37: The model assumes that currently, in the acute setting all patients will discontinue RAASi if their S-K levels are equal to, or greater than, 6.0 mmol/L. In contrast, only 20% of patients with an S-K level equal or greater than 5.5 mmol/L, but less than 6.0 mmol/L would discontinue RAASi, with the remaining 80% intended to down-titrate their RAASi dose. Patients who have discontinued, or down-titrated their RAASi dose have a 49.7% chance per cycle, based on Luo *et al*.[15] of returning to maximum RAASI dose.	The model assumes in the acute setting all patients will discontinue RAASi if their S-K levels are equal to, or greater than, 6.0 mmol/L, in line with NICE guidance CG182 and expert clinical input from clinicians in England and Wales [2, 3]. Patients with an S-K level equal or greater than 5.5 mmol/L, but less than 6.0 mmol/L, are not treated in the acute setting of the model, i.e. there is no RAASi down-titration or discontinuation in this group of patients. Patients are not allowed to re-initiate RAASi treatment in the acute setting of the model.	This correction is necessary for factual accuracy and consistency with the CS and the model. Based on clinical experts' opinion and local guidelines, patients' management is different in the acute and chronic settings.	Text amended
Page 37 The company anticipate that if SZC was available in the acute setting then patients would be provided with SZC for 28 days following their first	The company anticipate that if SZC was available in the acute setting then patients would be provided with SZC correction treatment for up to 3 days and SZC maintenance treatment for 28 days following their first HK event. For patients who have a second or subsequent HK event, SZC correction and maintenance treatment would	This correction is necessary for clarity.	Text Amended

HK event. For patients who have a second or subsequent HK event, SZC treatment would be prescribed also for a period of 28 days.	be prescribed also for a period of 3 days and 28 days, respectively.		
Page 41 The trajectory for each treatment is provided in **Error! Reference source not found.**.	The mean trajectory for each treatment is provided in **Error! Reference source not found.**.	This correction is necessary for clarity. The S-K profiles are modelled to be patient specific with the individual patients S-K values scattered around the central mean trajectory	Text amended
Page 41 Note that the use of separate models does not maintain the correlation of serial measurements within an individual over time.	Note that the use of separate models does not maintain the correlation of serial measurements within an individual over time, although the modelling of a patient-component in the mixed-effect model corrects for this.	This correction is necessary for clarity.	Not a factual error and we believe that the company's proposed amendment is not entirely accurate. This is discussed later in the ERG report
Page 41 The time component is treated as a continuous variable for the acute phase model but applies only after a certain time point for the maintenance phase models, resulting in	A potassium gradient is modelled in the acute phase. From day 4 onwards, potassium is sampled around a mean with no gradient.	This correction is necessary to clarify that there is no time component in the mixed-effect model from day 4 onwards.	The description relates to equation (2) in the ERG report. "*time*" is the same as X_ij in the equations supplied by the company in response to A20

piecewise constant trajectories after day 3.			which apply after 28 days in the SZC arm and 14 in SoC. Text amended to clarify
Page 42 The relative magnitude of the standard deviation of the observational component was large ([redacted] for patients treated with SZC; [redacted] for patients treated with SOC) and could result in large changes in the patient's S-K level as the width of the 95% CI will be in the region of [redacted] mmol/L. It is possible that some of this variation could have been explained by the inclusion of additional patient level covariates as was implemented in the clinical effectiveness modelling.	The relative magnitude of the standard deviation of the observational component was large [redacted] for patients treated with SZC; [redacted] for patients treated with SOC) and could result in large changes in the patient's S-K level as the width of the 95% CI will be in the region of [redacted] mmol/L. Based on the company's analyses, the inclusion of additional covariates resulted in no significant improvement in the predictive power of the mixed-effect model.	Correction to reflect the methodology used to generate the mixed-effect model: In deriving statistical models describing the time-dependent trajectory of K+ in the model a number of candidate fixed effects covariates were considered for inclusion to act as control variables (all at baseline): age, sex, presence of diabetes (yes/no), RAASi usage (yes/no), cohort (CKD only / CHD only / both CKD and CHD). With an intercept and a time trend variable included each time, all possible models involving all 33 combinations of covariates were fitted to the trial data. Once a time trend is included in the models, no combination of the other considered covariates results in a significantly smaller MSE; these additional variables therefore do not contribute to out-of-sample predictive power, over and above the time trend. Based on these results, the mixed effects models include only a time trend and fixed/random intercepts, without further adjustment for baseline covariates.	The last sentence has been deleted. The ERG does not have any evidence to support the company's proposed additional text which has therefore not been accepted.
Page 47 The threshold for severe events was an S-K level	In the acute setting, the threshold for both a severe and less severe HK event was 6.0 mmol/L and in the chronic setting, the	Information presented is incorrect.	Text Amended

of > 6.0 mmol/L in the acute setting and an S-K level > 5.5 mmol/L in the chronic setting	threshold for the severe event was 6.5 mmol/L and 5.5 mmol/L for the less severe HK event.		
Page 47 A large number of parameters was not included meaning that the uncertainty in the answers is likely to be underestimated.	A large number of parameters were not included due to difficulties in statistically correcting for multi-variable correlations. All parameters that could have been probabilistically varied were included to estimate uncertainty in the results.	All parameters that could have been appropriately varied in the probabilistic analysis were included. The omitted parameters were excluded due to difficulties in statistically correcting for multi-variable correlations.	Not a factual error.
Page 50 Additionally, there is a lack of consistency between the models fitted within the clinical section and the models used within the economic section.	This statement should be removed.	This statement should be removed because it is misleading and (incorrectly) implies an error. The differences in model specification arose because the models have different purposes; the models used in the clinical effectiveness analysis were intended to provide estimates for the ZS-004 and ZS-005 study endpoints, while those used to estimate potassium trajectories were required to provide specific inputs to the economic model and utilized pooled data. This was clarified in response to the clarification question A20.	Not a factual error. Text amended to reflect company's response to clarification.
Page 54: The ERG comment that these observational components change throughout the model and may lesson the difference (in S-K levels) between the two categories of	The ERG comment that these observational components change throughout the model and may **increase or decrease** the difference (in S-K levels) between the two categories of patients used in the company model.	Continual variation of S-K levels causes the difference in S-K levels between the acute population and chronic population to increase or decrease throughout the duration of the model.	Not a factual error

patients used in the company model.			
Page 54: The company assume that in the acute clinical setting that RAASi treatment is discontinued and never restarted. Clinical advice provided to the ERG indicated that this is unlikely to be the case for all patients and would depend on the severity of the episode, the frequency of HK events and the indication of the specific RAASi. It was suggested that if the episode was not life-threatening then resumption of RAASi treatment within 12 weeks would be appropriate and in line with medical practice. However, for patients who have had a life-threatening event, or who has been admitted several times then RAASi treatment may not be restarted. It was assumed in line with the company's base case that all patients on SZC treatment would	The company assume that in the acute clinical setting that RAASi treatment is discontinued and never restarted. This assumption was based on feedback from clinicians working within A&E/AMU England and Wales who stated that if the local protocol for the management of patients with HK is initiated, then all patients would discontinue RAASi and RAASi would be marked as an allergy in the patient's summary of care record (as there is no other place to mark the RAASi discontinuation), and therefore it is very unlikely that RAASi would be re-initiated by GPs following discharge. Clinical advice provided to the ERG indicated it is unlikely that patients never restart RAASi, as RAASi re-initiation would depend on the severity of the episode, the frequency of HK events and the indication of the specific RAASi. It was suggested that if the episode was not life-threatening then resumption of RAASi treatment within 12 weeks would be appropriate and in line with medical practice. However, for patients who have had a life-threatening event, or who has been admitted several times then RAASi treatment may not be restarted. It was assumed in line with the company's base case that all patients on SZC treatment would resume RAASi at 12 weeks but that only 47.9% of patients on SOC would.	Management of RAASi in the acute setting differs from that in the chronic setting. Because RAASi discontinuation is marked as an allergy in patients' summary of care records (due to lack of any other fields of this information), it is unlikely that GPs would subsequently re-initiate RAASi therapy. This view is based on feedback from clinicians working with in A&E/AMU in England and Wales.	Not a factual error

resume RAASi at 12 weeks but that only 47.9% of patients on SOC would.			
Page 55 The probabilistic values were similar to the deterministic ones implying linearity within the model, although the ERG note that key parameters were excluded from the PSA.	The probabilistic values were similar to the deterministic ones implying linearity within the model, although the ERG note that some parameters were excluded from the PSA due to difficulties in statistically correcting correlations between variables.	This correction is needed for clarification	Not a factual error
Page 55 Increasing the treatment duration of SZC to lifetime increased the ICERs as to a value greater than £30,000 per QALY in ERG base case 1 but not in ERG base case 2.	Increasing the treatment duration of SZC to lifetime increased the ICERs as to a value **just** greater than £30,000 per QALY in ERG base case 1 but not in ERG base case 2.	This clarification is needed as the ICER is only increased by £600.	Not a factual error
Page 55 The deterministic ICERs for CKD patients were greater than £45,000 in both ERG base cases.	The deterministic ICERs for CKD patients were greater than **£40,000** in both ERG base cases.	Base case 2 has an ICER of £40,731.	Text Amended

Issue 9 Typographical errors

Page 23 Mean S-K levels during days 8-29 in ZS-004 were significantly lower for SZC 10 g and 5 g daily dose (4.8 mmol/L and 4.5 mmol/L) than PBO (5.1 mmol/L) (p<0.001).	Mean S-K levels during days 8-29 in ZS-004 were significantly lower for SZC 10 g and 5 g daily dose (**4.5** mmol/L and **4.8** mmol/L) than PBO (5.1 mmol/L) (p<0.0001).	Consistency to present results for the associated cohort and the reported p-value in literature.[16]	Text Amended
Page 34 It was assumed within the model that the population are 63% female and 37% male, pooled from studies ZS-004[6] and ZS-005.[17]	It was assumed within the model that the population are **63% male** and **37% female**, pooled from studies ZS-004[6] and ZS-005.[17]	Information presented is incorrect.	Text Amended
Page 40/41 As stated, following the clarification process,5 the company provided an analyses where patients remained in the CKD5 health state and were assumed to not have RRT (question B25).	As stated, following the clarification process,5 the company provided an **analysis** where patients remained in the CKD5 health state and were assumed to not have RRT (question **B21**).	Typographical error The number of the clarification question is incorrect.	Text Amended
Page 41 For both SZC and lifestyle advice it was assumed that there was a fixed	For both SZC and **standard of care** it was assumed that there was a fixed trajectory of S-K level for the average patient.	This correction is necessary to have consistency in the use of the ‘standard of care’ terminology.	Text Amended

trajectory of S-K level for the average patient.			
Page 47 The company assume that the costs of maximum dose RAASi is £46 for CKD patients and £50 for HF patients. These costs are reduced to £25 (CKD patients) and £29 (HF patients) where there is sub-optimal dosing.	The company assume that the costs of maximum dose RAASi is £46 for CKD patients and **£58** for HF patients. These costs are reduced to £25 (CKD patients) and **£36** (HF patients) where there is sub-optimal dosing.	Information presented is incorrect	Text Amended
Page 51 The ERG acknowledges, however, that the reductions in S-K levels in the SOC arm in the initial three days, and potentially to day 29, is likely to be over-estimated given that within study ZS-004[6] these patients received SZC in an open-label acute	The ERG acknowledges, however, that the reductions in S-K levels in the SOC arm in the initial three days, and potentially to day 29, is likely to be over-estimated given that within **studies** ZS-004[6] and **ZS-005** these patients received SZC in an open-label acute	Information presented was not complete	Text Amended
Page 52 Within the company base case, the absolute time trade-off values reported by Gorodetska *et al.*[11] were used as multipliers. The ERG believes that	Within the company base case, the absolute time trade-off values reported by **Gorodetskaya** *et al.*[11] were used as multipliers. The ERG believes that this is a limitation for two reasons: i) as the valuation had been undertaken by the patients which is not the method recommended by NICE,[18]	Typographical error	Text Amended

this is a limitation for two reasons: i) as the valuation had been undertaken by the patients which is not the method recommended by NICE,[18] and ii) that they values should be adjusted to take into account that these were not multipliers. The Gorodetska *et al.* paper[11] also reports values based on the HUI3 which is preference-based. The ERG also note that the utility value for eGFR < 15 mL/min/1.73m^2 and without dialysis is 0.54 which is comparable to the pre-dialysis EQ-5D value of 0.57 reported by Lee *et al.[10]* A comparison of the values assumed by the company and the values assumed by the ERG are presented in **Error! Reference source not found.**. Note that the ERG values are adjusted so that when multiplied by 0.79 (an ERG-assumed population norm for the patients aged 63 to 65 years) they equal	and ii) that they values should be adjusted to take into account that these were not multipliers. The **Gorodetskaya** *et al.* paper[11] also reports values based on the HUI3 which is preference-based. The ERG also note that the utility value for eGFR < 15 mL/min/1.73m^2 and without dialysis is 0.54 which is comparable to the pre-dialysis EQ-5D value of 0.57 reported by Lee *et al.[10]* A comparison of the values assumed by the company and the values assumed by the ERG are presented in **Error! Reference source not found.**. Note that the ERG values are adjusted so that when multiplied by 0.79 (an ERG-assumed population norm for the patients aged 63 to 65 years) they equal the values reported in **Gorodetskaya** *et al*.[11]		

the values reported in Gorodetska *et al*.[11]			
Page 54 The ERG comment that these observational components change throughout the model and may lesson the difference (in S-K levels) between the two categories of patients used in the company model.	The ERG comment that these observational components change throughout the model and may less**e**n the difference (in S-K levels) between the two categories of patients used in the company model.	Typographical error	Text Amended
Page 48, Table 9 £7,340	£7,380	Typographical error	Text Amended
Page 53 This reduced the values from £481.48 to £286.48 for discontinuation of RAASi treatment and from £722.22 to £279.72 for a down-titration	This reduced the values from £481.48 to **£186.48** for discontinuation of RAASi treatment and from £722.22 to £279.72 for a down-titration	Typographical error	Text Amended
Page 54 Clinical advice to the ERG suggested that there would be a temptation for clinicians to continue treatment with SZC beyond 52 if it was believed to be efficacious,	Clinical advice to the ERG suggested that there would be a temptation for clinicians to continue treatment with SZC beyond 52 **weeks** if it was believed to be efficacious, particularly if the company assumption that S-K levels would return to the no treatment values immediately upon cessation were correct	Typographical error	Text Amended

particularly if the company assumption that S-K levels would return to the no treatment values immediately upon cessation were correct			
Page 56 The deterministic ICERs for HF patients was below £40,000 in ERG base case 2, but were approximately £100,000 in ERG base case 1	The deterministic **ICER** for HF patients was below £40,000 in ERG base case 2, but **was** approximately £100,000 in ERG base case 1	Typographical error	Text Amended
Page 56 The deterministic ICERs for HF patients was below £30,000 in ERG base case 2, but was over £340,000 in ERG base case 1	The deterministic **ICER** for **CKD** patients was below £30,000 in ERG base case 2, but was over £340,000 in ERG base case 1	Typographical errors	Text Amended
Page 56 Assuming no additional costs, if the survival advantage observed at 52 weeks produced [redacted] discounted QALYs (ERG base case 1) and [redacted] discounted QALYs (ERG base case 2) in the remaining lifetime to produce an ICER of	Assuming no additional costs, if the survival advantage seen in the remaining lifetime was an additional [redacted] discounted QALYs in ERG base case 1 and an additional [redacted] discounted QALYs in ERG base case 2, then an ICER below £30,000 per QALY would be produced. These values increase to [redacted] and [redacted] if patients can resume RAASi treatment	Corrections have been made for clarity and to correct typographical errors	Text Amended

£30,000 per QALY. These values increase to [redacted] and [redacted] if patients can resume RAASi treatment			
Page 56 Assuming no additional costs, if the survival advantage observed at 52 weeks produced [redacted] discounted QALYs (ERG base case 1) and [redacted] discounted QALYs (ERG base case 2) in the remaining lifetime to produce an ICER of £30,000 per QALY. These values increase to [redacted] and [redacted] if patients can resume RAASi treatment	Assuming no additional costs, if the survival advantage seen in the remaining lifetime was an additional [redacted] discounted QALYs in ERG base case 1, then an ICER below £30,000 per QALY would be produced. This value increases to [redacted] if patients can resume RAASi treatment. For ERG base case 2, an additional [redacted] QALYs would be needed to produce an ICER below £30,000 if patients can resume RAASi treatment	Corrections have been made for clarity and to correct typographical errors	Text Amended
Page 61 The ERG prefers alternative assumptions to some of those used by the committee.”	The ERG prefers alternative assumptions to some of those used by the **company**	Typographical error	Text Amended
Appendices. Page 68, Table 18 5 g ZS p-value: p=0.000	**p=0.0001**	Typographical error	Text Amended
Appendices. Page 68, Table 18	**-**0.085	Typographical error	Text Amended

10 g ZS upper 95% CI: 0.085			
Appendices. Page 68, Table 18 15 g ZS upper 95% CI: 0.116	**-**0.116	Typographical error	Text Amended
Appendices. Page 69, Table 21 Observation component estimate: 0.404	**0.405**	Typographical error	Text Amended

APPENDIX 1 - Corrected Tables 1-4 and 14-16

As Table 1 is identical to Table 13, Table 2 is identical to Table 14, Table 3 is identical to Table 15 and Table 4 is identical to Table 16, only Tables 1-4 are presented below.

Table 1. Exploratory deterministic results for HF patients in the chronic setting*

Analysis	Discounted costs		Discounted QALYs		Undiscounted Life years		ICER
	SZC	SOC	SZC	SOC	SZC	SOC	
Company base case (as per response to clarification questions)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	~~£13,432~~ **£13,458**
1) Withdrawing RAASi treatment for twelve weeks when S-K ≥ 6 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	~~£14,035~~ **£14,063**
2a) Assuming a decrease in S-K levels of 0.23 post-RAASi discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	~~£18,972~~ **£19,012**
2b) Assuming a decrease in S-K levels of 0.10 post-RAASi discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	~~£15,302~~ **£15,333**
4) Assuming an alternative relationship between S-K level and HF mortality	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	~~£16,924~~ **£16,952**
5) Adding in wastage: the cost of 30 sachets assumed over a 28-day period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£14,329**
6) Reducing the costs associated with RAASi changes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	~~£14,274~~ **£14,301**
ERG base case 1 (1, 2a, 4, 5 and 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£29,239**
ERG base case 1 with lifetime SZC treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£30,668**

ERG base case 1 with hospitalisation stay independent of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£29,257**
ERG base case 2 (1, 2b 4, 5 and 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£23,296**
ERG base case 2 with lifetime SZC treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£25,056**
ERG base case 2 with hospitalisation stay independent of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£23,313**

*Note that ERG exploratory analysis 3 relates to CKD utilities and does not change the HF results.

Table 2. Exploratory deterministic results for CKD patients in the chronic setting

Analysis	Discounted costs		Discounted QALYs		Undiscounted life years		ICER
	SZC	SOC	SZC	SOC	SZC	SOC	
Company base case (as per response to clarification questions)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	~~**£25,329**~~ **£25,363**
1) Withdrawing RAASi treatment for twelve weeks when S-K ≥ 6 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	~~£27,020~~ £27,056
2a) Assuming a decrease in S-K levels of 0.23 post-RAASi discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	~~£33,157~~ £33,200
2b) Assuming a decrease in S-K levels of 0.10 post-RAASi discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	~~£28,813~~ £28,851
3) Using HUI3 utilities rather than TTO utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	~~£30,496~~ £30,537
5) Adding in wastage: the cost of 30 sachets assumed over a 28-day period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,882

6) Reducing the costs associated with RAASi changes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	~~£26,649~~ £26,683
ERG base case 1 (1, 2a, 3, 5 and 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£46,936**
ERG base case 1 with lifetime SZC treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£53,685
ERG base case 1 with hospitalisation stay independent of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,965
ERG base case 2 (1, 2b, 3, 5 and 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£40,731**
ERG base case 2 with lifetime SZC treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,135
ERG base case 2 with hospitalisation stay independent of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,761

*Note that ERG exploratory analysis 4 relates to the relationship between S-K levels and HF mortality and does not change the CKD results.

Table 3. Exploratory deterministic results for HF patients in the acute setting (52-week analysis)*

Analysis	Discounted costs		Discounted QALYs		Life years		ICER
	SZC	SOC	SZC	SOC	SZC	SOC	
Company base case (as per response to clarification questions) (Lifetime)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£7,380**
Company base case (as per response to clarification questions) (52-weeks)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**~~£8,096~~ £10,263**
1) Withdrawing RAASi treatment for twelve weeks when S-K ≥ 6 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	~~£8,096~~† £10,263†

2a) Assuming a decrease in S-K levels of 0.23 post-RAASi discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	~~£48,229~~ £51,652
2b) Assuming a decrease in S-K levels of 0.10 post-RAASi discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	~~£25,616~~ £28,223
4) Assuming an alternative relationship between S-K level and HF mortality	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
5) Adding in wastage: the cost of 30 sachets assumed over a 28-day period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,098
6) Reducing the costs associated with RAASi changes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	~~£8,096~~† £10,263†
ERG base case 1 (1,2a, 4, 5 and 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£100,093**
ERG base case 1 plus restarting on RAASi treatment at 12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£196,049
ERG base case 2 (1,2b, 4, 5 and 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£37,097**
ERG base case 2 plus restarting on RAASi treatment at 12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£72,109

*Note that ERG exploratory analysis 3 relates to CKD utilities and does not change the HF results.
** New scenario added
†This does not affect the ICER as the company models assumes that all patients in the acute setting discontinue RAASi treatment and never have RAASi treatment restarted

Table 4. Exploratory deterministic results for CKD patients in the acute setting (52-week analysis)

Analysis	Discounted costs		Discounted QALYs		Life years		ICER
	SZC	SOC	SZC	SOC	SZC	SOC	
Company base case (as per response to clarification questions) (Lifetime) **	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominating**

Company base case (as per response to clarification questions) (52-weeks)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominating**
1) Withdrawing RAASi treatment for twelve weeks when S-K ≥ 6 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating†
2a) Assuming a decrease in S-K levels of 0.23 post-RAASi discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	~~£260,611~~ £289,171
2b) Assuming a decrease in S-K levels of 0.10 post-RAASi discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	~~Dominating~~ £9,627
3) Using HUI3 utilities rather than TTO utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
5) Adding in wastage: the cost of 30 sachets assumed over a 28-day period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
6) Reducing the costs associated with RAASi changes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating†
ERG base case 1 (1, 2a, 3, 5 and 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£346,485**
ERG base case 1 plus restarting on RAASi treatment at 12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£140,264
ERG base case 2 (1, 2b, 3, 5 and 6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£28,760**
ERG base case 2 plus restarting on RAASi treatment at 12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,566

†This does not affect the ICER as the company models assumes that all patients in the acute setting discontinue RAASi treatment and never have RAASi treatment restarted
** New scenario added

APPENDIX 2 – Mean population S-K trajectory for patients

[redacted]

A 0.23 mmol/L reduction in S-K levels, as recommended by the ERG, is assumed from Day 1 onwards in SOC patients who discontinue RAASi. In this revised company base case, this decrease in S-K level is from the baseline S-K level.

[redacted]

A 0.115 mmol/L reduction in S-K level, as recommended by the ERG, is assumed from Day 1 onwards in SOC patients who down-titrate RAASi. In this revised company base case, this decrease in S-K level is from the baseline S-K level.

[redacted]

The ERG base case (blue) assumes a 0.23 mmol/L reduction in the S-K level of patients in the SOC arm who discontinue RAASi. In this ERG base case, the reduction is applied to the SOC S-K trajectory modelled by in the original company base case (as submitted following clarification questions, grey). The resulting ERG base case SOC S-K trajectory is not representative of the S-K trajectory expected in clinical practice from SOC patients.

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