Sodium Zirconium Cyclosilicate for Hyperkalaemia: A Single Technology Appraisal

Produced by School of Health and Related Research (ScHARR), The University of Sheffield

Authors Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK

Jean Hamilton, Research Fellow, ScHARR, University of Sheffield, Sheffield, UK

Lesley Uttley, Research Fellow, ScHARR, University of Sheffield, Sheffield, UK

Andrew Rawdin, Research Assistant, ScHARR, University of Sheffield, Sheffield, UK

Mark Clowes, Information Specialist, ScHARR, University of Sheffield, Sheffield, UK

Annette Alfonzo, Consultant Nephrologist, Departments of Renal and Internal Medicine, Victoria Hospital Kirkcaldy, Fife, UK

Correspondence Author Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK

Date completed Date completed (05/09/2018)

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 18/54/08

Declared competing interests of the authors

No author declares a conflict.

Acknowledgements

We would like to thank Becky Pennington, Research Fellow, ScHARR, for providing comments on the draft report and Andrea Shippam, Programme Manager, ScHARR, for providing administrative support and in preparing and formatting the report. We would also like to acknowledge Sean Fenwick, Director of Operations and City Hospitals Sunderland for providing clinical advice.

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:

Stevenson M, Hamilton J, Uttley L, Rawdin A, Clowes M, Alfonso, A. Sodium Zirconium Cyclosilicate for Hyperkalaemia: A Single Technology Appraisal. School of Health and Related Research (ScHARR), 2018.

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

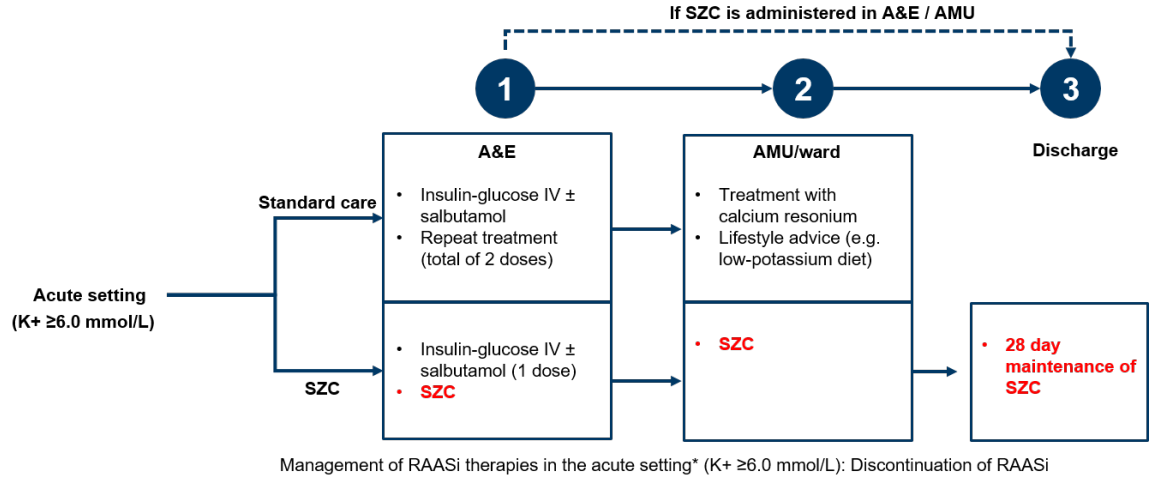
A description of SZC is provided in Section 1.2 of the CS. The intervention is available as either a 5g or 10g powder for oral suspension. During the correction phase of treatment, the recommended dose is 10g three times a day until normokalaemia is achieved. This is typically with 24-48 hours, although 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

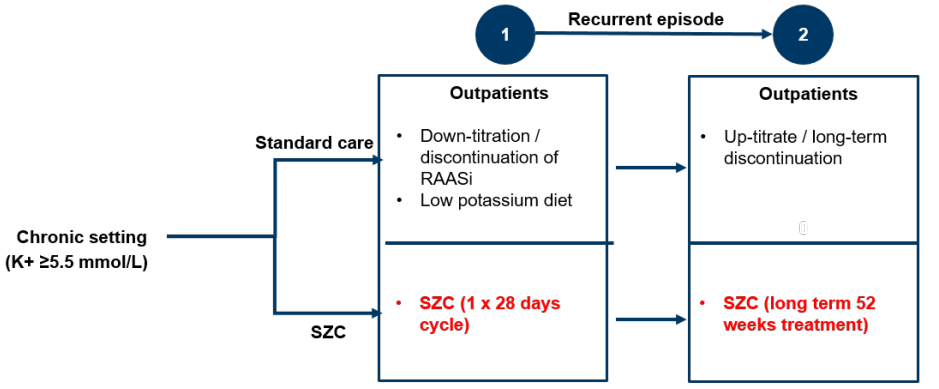
regularly monitored by clinicians in secondary care. Patients identified within the acute setting in the CS are assumed to have S-K levels ≥ 6.0mmol/L and would all be eligible for SZC treatment; patients in the chronic setting would be eligible to receive SZC treatment with S-K levels ≥ 5.5mmol/L, although 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



Management of RAASi therapies in the acute setting* (K+ ≥6.0 mmol/L): Discontinuation of RAASi



Management of RAASi therapies in the chronic setting* (K+ ≥5.5 mmol/L) for 'Standard care' only:
- Initiation of RAASi not recommended if K+ ≥5.0 mmol/L
- Down-titration (80%) / discontinuation (20%) if K+ ≥5.5-5.9 mmol
- Discontinuation of RAASi if K+ ≥6.0 mmol/L

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

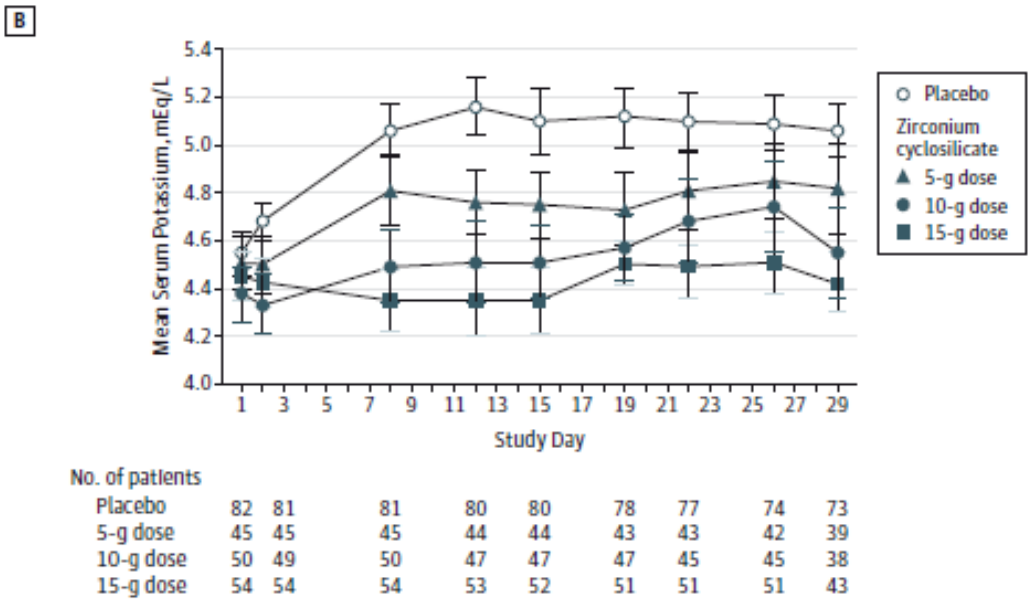
The primary efficacy endpoint was the model-based mean of all available S-K values during maintenance phase study days 8-29 (see Figure 2) Mean S-K levels during days 8-29 in ZS-004[7] were significantly lower for SZC 10 g and 5 g daily dose (4.5 mmol/L and 4.8 mmol/L) than PBO (5.1 mmol/L) ($p<0.0001$). 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)



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

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.

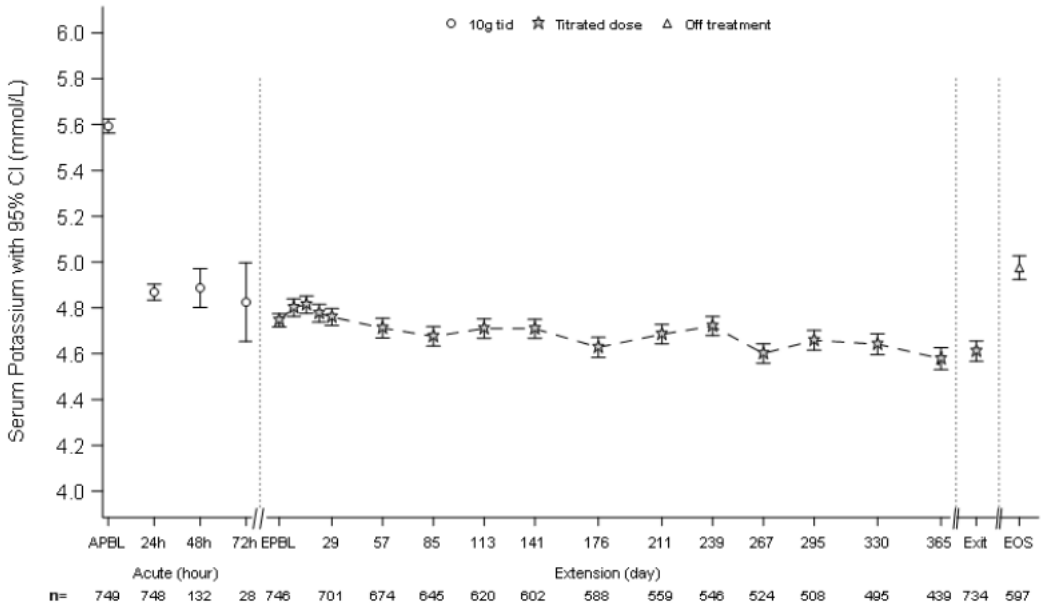
Other outcomes reported but not repeated here included the proportion of patients who achieved normalisation in S-K values at 24 and 48 hours after start of dosing.

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.

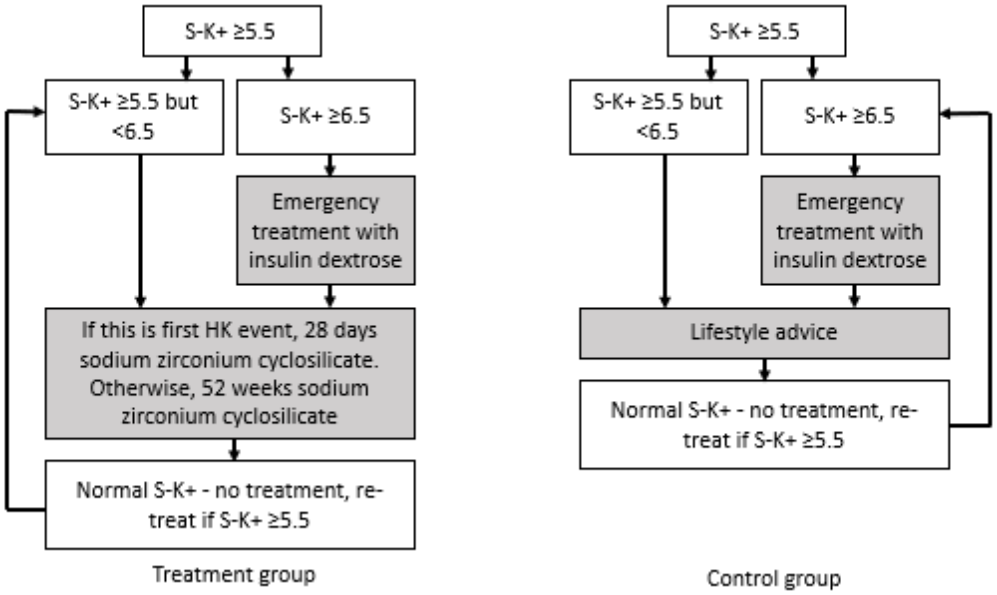
3.2.4 Treatment Pathway and assumed use of RAASi based on clinical setting and treatment

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

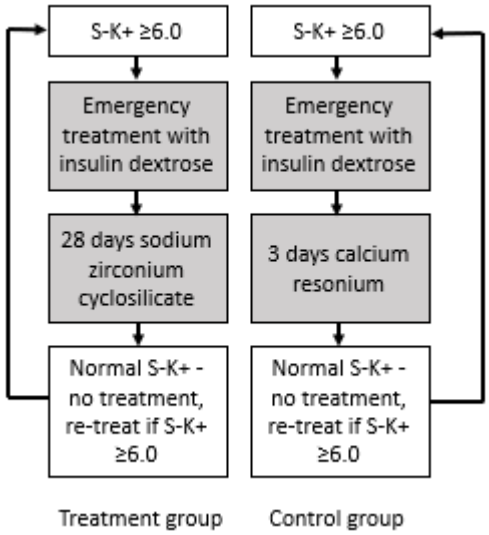
3.2.4.1.2 With SZC being prescribed

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

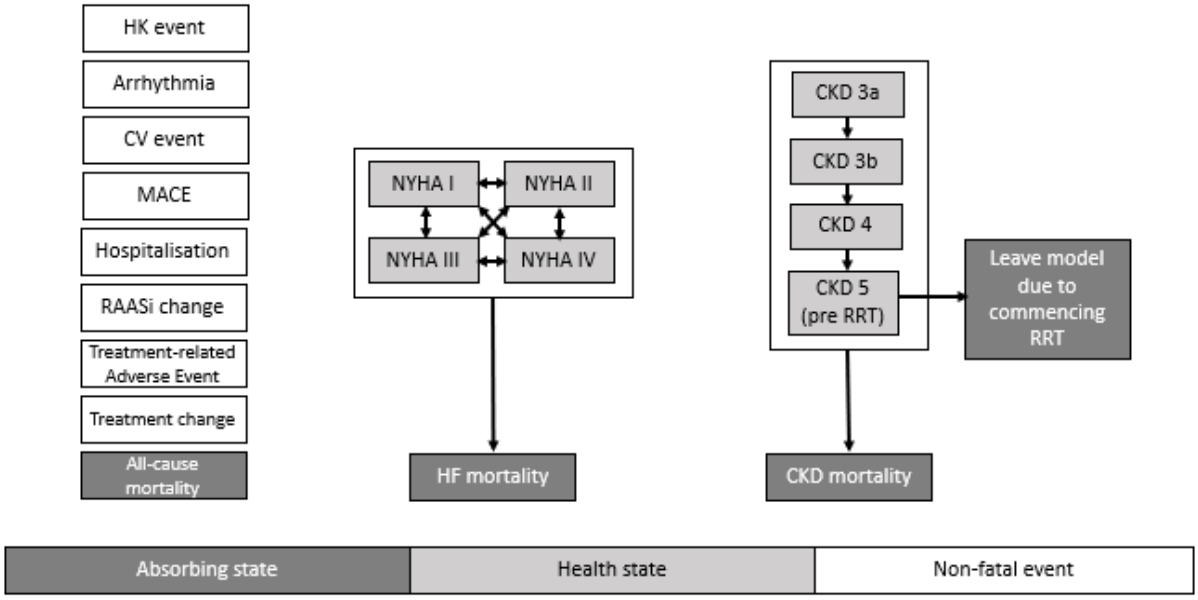
The company anticipate that if SZC was available in the acute setting then patients would be provided with SZC correction treatment for up to 3 days and SZC maintenance treatment for 28 days following their first HK event. For patients who have a second or subsequent HK event, SZC correction and maintenance 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 Figure 7. 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 Figure 7 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

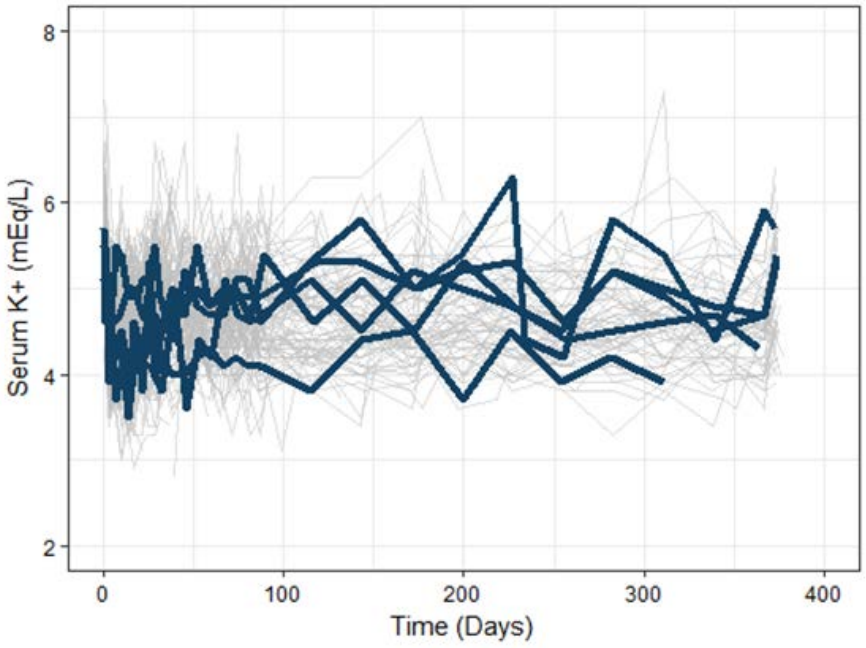
(clarification question B4).[5] The company responded that there was an observed difference between days 4-28 and beyond 29 days in ZS-005,[9] and ran scenario analyses to explore altering this assumption.

[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 8 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 9. 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

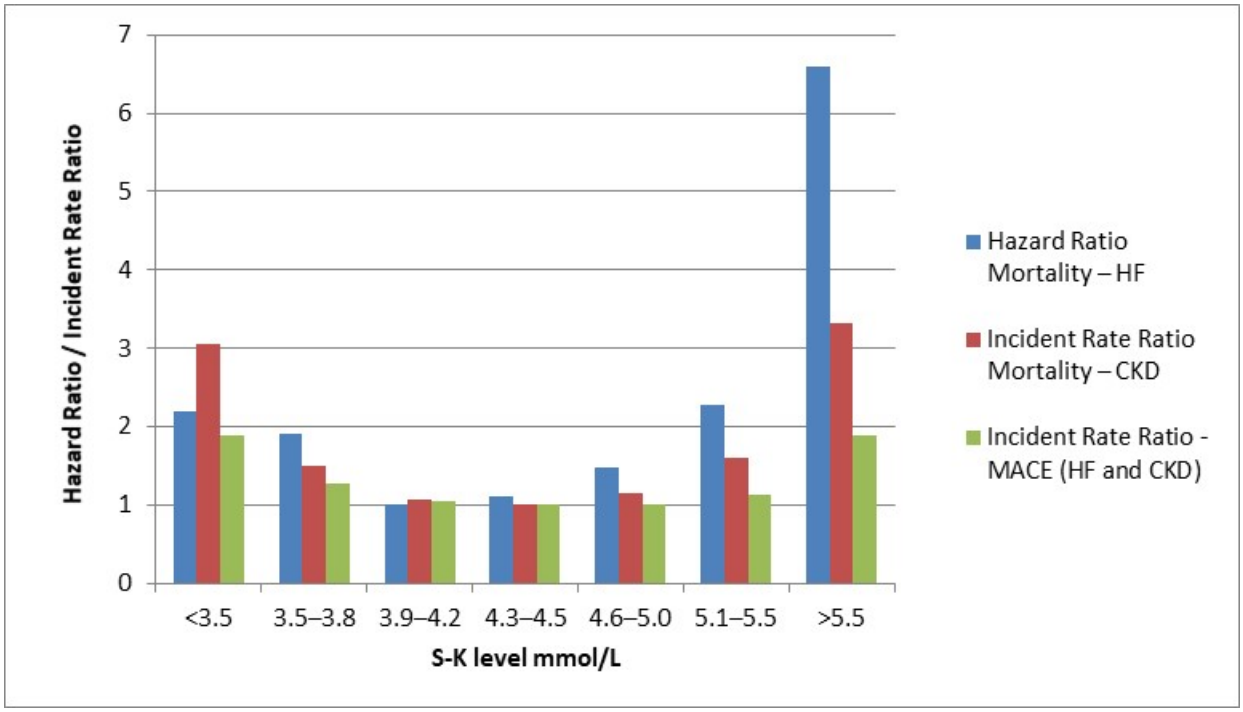


Table 39 of the CS provides data on the incidence risk ratios of hospitalisation that are associated conditional on eGFR level. and on S-K level.[28] Broadly, lower eGFR values are associated with more hospitalisations as are more extreme S-K levels. As with the relationship with S-K levels and mortality 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 9) 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 9. 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.

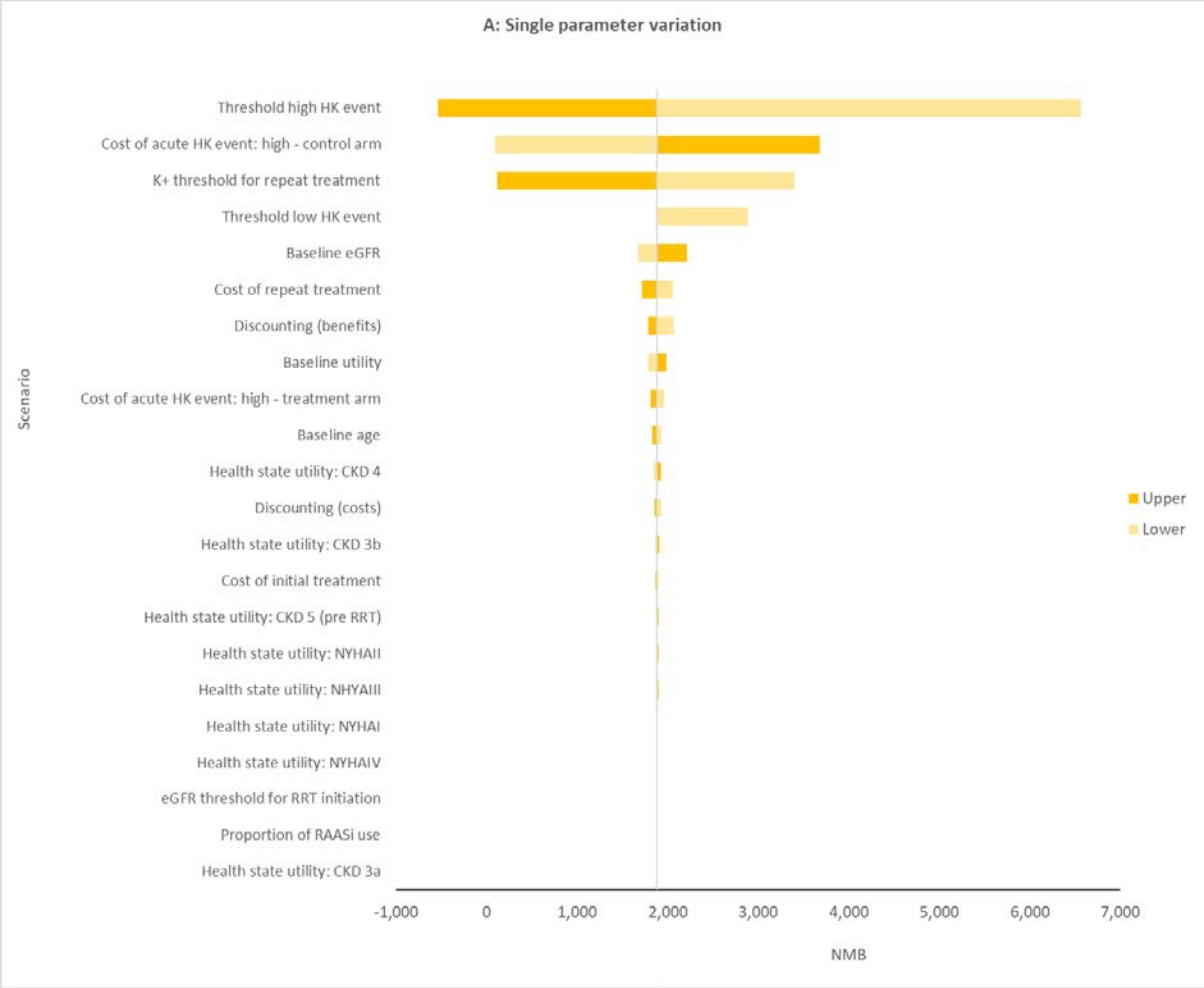
Table 10: The company's all relevant scenarios analysis

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 10. 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 Figure 7 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.

7 REFERENCES

1. AstraZeneca UK Ltd. Sodium Zirconium Cyclosilicate for Hyperkalaemia [ID 1293]. Company evidence submission. 2018.
2. National Institute for Health and Care Excellence. Chronic kidney disease in adults: assessment and management. Clinical Guidelines 182. 2015.
3. National Institute for Health and Care Excellence. Sodium zirconium cyclosilicate for treating hyperkalaemia: Final scope. London: National Institute for Health and Care Excellence; 2018.
4. Palaka E, Leonard S, Buchanan-Hughes A, Bobrowska A, Langford B, Grandy S. Evidence in support of hyperkalaemia management strategies: A systematic literature review. *Int J Clin Pract* 2018;72.
5. AstraZeneca. Sodium zirconium cyclosilicate for treating hyperkalaemia [ID1293] Response to Clarification Letter. 2018.
6. !!! INVALID CITATION !!! 6, 7.
7. NCT02088073. Safety & Efficacy of Zirconium Silicate Dosed for 28 Days in Hyperkalemia. *Journal* 2014. https://clinicaltrials.gov/show/NCT02088073
8. Kosiborod M, Rasmussen HS, Lavin P, Qunibi WY, Spinowitz B, Packham D, *et al.* Effect of Sodium Zirconium Cyclosilicate on Potassium Lowering for 28 Days Among Outpatients With Hyperkalemia. *JAMA* 2014;312:2223.
9. NCT02163499. Open-label Safety and Efficacy of Sodium Zirconium Cyclosilicate for up to 12 Months. *Journal* 2014. https://clinicaltrials.gov/show/NCT02163499
10. NCT01493024. Safety & Efficacy of Zirconium Silicate in Chronic Kidney Disease or Moderate Kidney Dysfunction With Mild Hyperkalemia. *Journal* 2011. https://clinicaltrials.gov/show/NCT01493024
11. NCT01737697. Safety & Efficacy of Zirconium Silicate in Mild to Moderate Hyperkalemia. *Journal* 2012. https://clinicaltrials.gov/show/NCT01737697
12. NCT02107092. Open-label Safety & Efficacy of ZS (Sodium Zirconium Cyclosilicate)10g qd to Extend Study ZS-004 in Hyperkalemia. *Journal* 2014. http://clinicaltrials.gov/show/NCT02107092
13. NCT03337477. A Study to Evaluate a Potassium Normalization Treatment Regimen Including Sodium Zirconium Cyclosilicate (ZS) Among Patients With S-K =6.0 . *Journal* 2017. https://clinicaltrials.gov/show/NCT03337477
14. NCT03303521. A Study to Test Whether ZS (Sodium Zirconium Cyclosilicate) Can Reduce the Incidence of Increased Blood Potassium Levels Among Dialized Patients. *Journal* 2017. https://clinicaltrials.gov/show/NCT03303521
15. Buchanan-Hughes A, Bobrowska A, Langford B, Leonard S. Evidence-based Management of Hyperkalemia. Report of Systematic Literature Review and Feasibility Assessment for Network Meta-analysis: Costello Medical Consulting Ltd,; 2047.
16. Ash SR, Singh B, Lavin PT, Stavros F, Rasmussen HS. A phase 2 study on the treatment of hyperkalemia in patients with chronic kidney disease suggests that the selective potassium trap, ZS-9, is safe and efficient. *Kidney International* 2015;88:404-11.

17. Packham DK, Rasmussen HS, Lavin PT, El-Shahawy MA, Roger SD, Block G, *et al.* Sodium Zirconium Cyclosilicate in Hyperkalemia. *New England Journal of Medicine* 2015;372:222-31.

18. Nasir K, Ahmad A. Treatment of hyperkalemia in patients with chronic kidney disease: a comparison of calcium polystyrene sulphonate and sodium polystyrene sulphonate. *Journal* 2014. http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/604/CN-01110604/frame.html

19. NCT02607085. REal World EVidence for TrEAtment of HyperkaLemia in Emergency Department: Multicenter, Prospective, Observational Study. *Journal* 2015. https://clinicaltrials.gov/show/NCT02607085

20. NCT03283267. A Safety and Pharmacodynamic Study of Healthy Chinese Subjects Administered Sodium Zirconium Cyclosilicate (ZS). *Journal* 2017. https://clinicaltrials.gov/show/NCT03283267

21. NCT03127644. ZS Ph2/3 Dose-response Study in Japan. *Journal* 2017. https://clinicaltrials.gov/show/NCT03127644

22. NCT02875834. A Study to Investigate the Safety and Efficacy of ZS in Patients With Hyperkalemia. *Journal* 2016. https://clinicaltrials.gov/show/NCT02875834

23. NCT03172702. Open-label Safety of Sodium Zirconium Cyclosilicate for up to 12 Months in Japanese Subjects With Hyperkalemia. *Journal* 2017. https://clinicaltrials.gov/show/NCT03172702

24. NCT03528681. A Study to Investigate the Safety and Efficacy of ZS in Patients With Hyperkalemia. *Journal* 2018. https://clinicaltrials.gov/show/NCT03528681

25. Bennett H, Palaka E, Ayoubkhani D, Evans M, Gordon J, Kim K, *et al.* Impact of End-Stage Renal Disease on Health Economic Outcomes of Hyperkalaemia Management In Patients With Chronic Kidney Disease. *Value Health* 2017;20:A490.

26. Bennett H, Palaka E, Ayoubkhani D, Evans M, McEwan P, Bergenheim K, *et al.* A Model To Predict Costs And Outcomes Associated With Hyperkalaemia In Patients With Chronic Kidney Disease Or Heart Failure. *Value Health* 2017;20:A667.

27. Sutherland CS, Braunhofer PG, Vrouchou P, van Stiphout J, Messerli M, Suter K, *et al.* A Cost-Utility Analysis Of Raasi Enabling-Patiromer In Patients With Hyperkalemia. *Value Health* 2017;20:A490.

28. Luo J, Brunelli SM, Jensen DE, Yang A. Association between Serum Potassium and Outcomes in Patients with Reduced Kidney Function. *Clin J Am Soc Nephrol* 2015;11:90-100.

29. National Institute for Health and Care Excellence. Guide to the processes of technology appraisal. London: National Institute for Health and Care Excellence; 2014.

30. Krogager ML, Torp-Pedersen C, Mortensen RN, Køber L, Gislason G, Søgaard P, *et al.* Short-term mortality risk of serum potassium levels in hypertension: a retrospective analysis of nationwide registry data. *European Heart Journal* 2016; 10.1093/eurheartj/ehw129:ehw129.

31. Collins AJ, Pitt B, Reaven N, Funk S, McGaughey K, Wilson D, *et al.* Association of Serum Potassium with All-Cause Mortality in Patients with and without Heart Failure, Chronic Kidney Disease, and/or Diabetes. *American Journal of Nephrology* 2017;46:213-21.

32. Evans M, Bain SC, Hogan S, Bilous RW. Irbesartan delays progression of nephropathy as measured by estimated glomerular filtration rate: post hoc analysis of the Irbesartan Diabetic Nephropathy Trial. *Nephrology Dialysis Transplantation* 2011;27:2255-63.

33. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C-y. Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization. *New England Journal of Medicine* 2004;351:1296-305.

34. Yao G, Freemantle N, Calvert MJ, Bryan S, Daubert JC, Cleland JGF. The long-term cost-effectiveness of cardiac resynchronization therapy with or without an implantable cardioverter-defibrillator. *European Heart Journal* 2006;28:42-51.

35. Ford E, Adams J, Graves N. Development of an economic model to assess the cost-effectiveness of hawthorn extract as an adjunct treatment for heart failure in Australia. *BMJ Open* 2012;2:e001094.

36. Flather MD, Yusuf S, Køber L, Pfeffer M, Hall A, Murray G, *et al.* Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. *The Lancet* 2000;355:1575-81.

37. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JGF, Horowitz JD, Massie BM, *et al.* Comparative Effects of Low and High Doses of the Angiotensin-Converting Enzyme Inhibitor, Lisinopril, on Morbidity and Mortality in Chronic Heart Failure. *Circulation* 1999;100:2312-8.

38. Xie X, Liu Y, Perkovic V, Li X, Ninomiya T, Hou W, *et al.* Renin-Angiotensin System Inhibitors and Kidney and Cardiovascular Outcomes in Patients With CKD: A Bayesian Network Meta-analysis of Randomized Clinical Trials. *American Journal of Kidney Diseases* 2016;67:728-41.

39. Ng KP, Arnold J, Sharif A, Gill P, Townend JN, Ferro CJ. Cardiovascular actions of mineralocorticoid receptor antagonists in patients with chronic kidney disease: A systematic review and meta-analysis of randomized trials. *Journal of the Renin-Angiotensin-Aldosterone System* 2015;16:599-613.

40. Michel A, Martín-Pérez M, Ruigómez A, García Rodríguez LA. Risk factors for hyperkalaemia in a cohort of patients with newly diagnosed heart failure: a nested case-control study in UK general practice. *Eur J Heart Failure* 2015;17:205-13.

41. Horne L, Ashfaq A, MacLachlan S, Sinsakul M, Mukherjee R, Qin L, *et al.* MP370 Incidence and Risk Factors for Hyperkalemia in Adults in the UK. *Nephrology Dialysis Transplantation* 2017;32:iii563-iii.

42. Office for National Statistics. National life tables: United Kingdom. 2016.

43. Szende A, Janssen B, Cabases J. Self-reported population health: an international perspective based on EQ-5D.; 2014.

44. Göhler A, Geisler BP, Manne JM, Kosiborod M, Zhang Z, Weintraub WS, *et al.* Utility Estimates for Decision–Analytic Modeling in Chronic Heart Failure—Health States Based on New York Heart Association Classes and Number of Rehospitalizations. *Value in Health* 2009;12:185-7.

45. Gorodetskaya I, Zenios S, McCulloch CE, Bostrom A, Hsu C-Y, Bindman AB, *et al.* Health-related quality of life and estimates of utility in chronic kidney disease. *Kidney International* 2005;68:2801-8.

46. Lee AJ, Morgan CL, Conway P, Currie CJ. Characterisation and comparison of health-related quality of life for patients with renal failure. *Curr Med Res Opin* 2005;21:1777-83.

47. Curtis L, Burns A. Unit Costs of Health and Social Care 2017. *University of Kent* 2017.

48. Kent S, Briggs A, Eckermann S, Berry C. Are Value of Information Methods Ready for Prime Time? An Application to Alternative Treatment Strategies for Nstemi Patients. *International Journal of Technology Assessment in Health Care* 2013;29:435-42.

49. Colquitt JL, Mendes D, Clegg AJ, Harris P, Cooper K, Picot J, *et al.* Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure: systematic review and economic evaluation. *Health Technology Assessment* 2014;18:1-560.

50. Weir MR, Rolfe M. Potassium homeostasis and renin-angiotensin-aldosterone system inhibitors. *Clin J Am Soc Nephrol* 2010;5:531-48.

51. Aldahl M, Jensen AC, Davidsen L, Eriksen MA, Moller Hansen S, Nielsen BJ, *et al.* Associations of serum potassium levels with mortality in chronic heart failure patients. *Eur Heart J* 2017;38:2890-6.

52. Nakayama Y, Ueda K, Yamagishi SI, Sugiyama M, Yoshida C, Kurokawa Y, *et al.* Compared effects of calcium and sodium polystyrene sulfonate on mineral and bone metabolism and volume overload in pre-dialysis patients with hyperkalemia. *Clin Exp Nephrol* 2018;22:35-44.

53. Arnold R, Pianta TJ, Pussell BA, Kirby A, O'Brien K, Sullivan K, *et al.* Randomized, controlled trial of the effect of dietary potassium restriction on nerve function in CKD. *Clinical Journal of the American Society of Nephrology* 2017;12:1569-77.

54. Allon M, Dunlay R, Copkney C. Nebulized albuterol for acute hyperkalemia in patients on hemodialysis. *Ann Intern Med* 1989;110:426-9.

55. Allon M, Copkney C. Albuterol and insulin for treatment of hyperkalemia in hemodialysis patients. *Kidney International* 1990;38:869-72.

56. Chothia M-Y, Halperin ML, Rensburg MA, Hassan MS, Davids MR. Bolus Administration of Intravenous Glucose in the Treatment of Hyperkalemia: A Randomized Controlled Trial. *Nephron Physiology* 2014;126:1-8.

57. Gruy-Kapral C, Emmett M, Santa Ana CA, Porter JL, Fordtran JS, Fine KD. Effect of single dose resin-cathartic therapy on serum potassium concentration in patients with end-stage renal disease. *Journal of the American Society of Nephrology* 1998;9:1924-30.

58. Lepage L, Dufour AC, Doiron J, Handfield K, Desforges K, Bell R, *et al.* Randomized clinical trial of sodium polystyrene sulfonate for the treatment of mild hyperkalemia in CKD. *Clinical Journal of the American Society of Nephrology* 2015;10:2136-42.

59. Mandelberg A, Krupnik Z, Houri S, al. e. Salbutamol metered-dose inhaler with spacer for hyperkalemia: How fast? How safe? *Chest* 1999;115:617-22.

60. Ngugi N, McLiegeyo S, Kayima J. Treatment of Hyperkalaemia by Altering the Transcellular Gradillnt in Patillnts with Renal Failure: Effect of Various Therapeutic Approaches. *East African Medical Journal* 1997;73:503-9.

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