Single Technology Appraisal

Sodium zirconium cyclosilicate for the treatment of persistent hyperkalaemia with a serum potassium level between 5.5 mmol/litre and 5.9 mmol/litre (partial review of TA599) [ID6439]

Committee Papers

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SINGLE TECHNOLOGY APPRAISAL

Sodium zirconium cyclosilicate for treating hyperkalaemia (partial review of TA599) [ID6439]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from AstraZeneca :**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. UK Kidney Association (UKKA)

4. **Expert personal perspectives** from:
   a. Professor James Burton, Professor of Renal Medicine – clinical expert, nominated by AstraZeneca
   b. Dr Aaron Wong, Consultant Cardiologist and General Physician – clinical expert, nominated by AstraZeneca

5. **External Assessment Report** prepared by the Liverpool Reviews and Implementation Group (LRiG)

6. **External Assessment Report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Single technology appraisal

Sodium Zirconium Cyclosilicate for the First Line Treatment of Hyperkalaemia [ID6439]

Document B

Company evidence submission

January 2025

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Abbreviations

ACEi	Angiotensin-converting-enzyme inhibitor
AE	Adverse event
A&E	Accident and Emergency
AHA	American Heart Association
AKI	Acute kidney injury
AMU	Acute Medical Unit
ARB	Angiotensin II receptor blocker
ARNi	Angiotensin receptor-neprilysin inhibitor
BICD	Biventricular implantable cardioverter defibrillator
BMI	Body mass index
BNF	British National Formulary
BP	Blood pressure
BSH	British Society of Heart Failure
CC	Complications and comorbidities
CHF	Congestive heart failure
CI	Confidence interval
CKD	Chronic kidney disease
CPD	Chronic pulmonary disease
CPRD	Clinical Practice Research Datalink
CSR	Clinical study report
DASH	Dietary approaches to stop hypertension
DNPR	Danish National Patient Registry
DSP	Disease specific programme
eGFR	Estimated glomerular filtration rate
eMIT	Electronic Market Information Tool
ECG	Electrocardiogram
ESC	European Society of Cardiology
ESH	European Society of Hypertension
ESKD	End-stage kidney disease
ESRD	End-stage renal disease
GEE	Generalised estimating equations
GI	Gastrointestinal
GP	General practitioner
Hb	Haemoglobin
HCRU	Healthcare resource use
HES	Hospital episode statistics
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
HK	Hyperkalaemia
HR	Hazard ratio
HRQoL	Health-related quality of life
ICD	Implantable cardioverter defibrillator
ICER	Incremental cost-effectiveness ratio
IQR	Interquartile range
IRR	Incidence rate ratio
ISN	International Society of Nephrology
ITT	Intent-to-treat
K^+	Potassium cation
KDIGO	Kidney Disease: Improving Global Outcomes
LoS	Length of study
LVEF	Left ventricular ejection fraction
LS	Least-squares
MACE	Major adverse cardiac event
MedDRA	Medical Dictionary of Regulatory Activities
MRA	Mineralocorticoid-receptor antagonists
NICE	National Institute for Health and Care Excellence

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NHS	National Health Service
NYHA	New York Heart Association
OD	Once daily (dosing)
ONS	Office for National Statistics
OR	Odds ratio
PS	Propensity score
PSS	Personal Social Services
PVD	Peripheral vascular disease
PY	Patient-years
QALY	Quality-adjusted life-year
QoL	Quality of life
RAASi	Renin-angiotensin-aldosterone system inhibitor
RR	Relative risk
RRT	Renal replacement therapy
RWE	Real-world evidence
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SGLT-2	Sodium-glucose cotransporter 2
SHFM	Seattle Heart Failure Model
S–K	Serum potassium
SMD	Standardised mean difference
SZC	Sodium zirconium cyclosilicate
TEAE	Treatment-emergent adverse event
TID	Three times daily (dosing)
TRAE	Treatment-related adverse event
UKKA	UK Kidney Association
VAS	Visual Analogue Scale

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

B.1.1 *Decision problem*

The submission covers a subgroup of eligible patients for the technology's full marketing authorisation for this indication.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with persistent hyperkalaemia (HK) and a serum potassium (S–K) level between 5.5 to 6.0 mmol/L • People with persistent HK who need dialysis	Adults with persistent HK that have a serum potassium concentration (S–K) level between ≥5.5–<6.0 mmol/L The decision problem addressed in this submission focuses specifically on the comorbid patient population comprising patients with HK and chronic kidney disease (CKD; stage 3b–5) or heart failure (HF). HK occurs more commonly in patients with CKD or HF due to disease pathophysiology and the wide use of cardio-renal protective medicines, such as renin–angiotensin–aldosterone system inhibitors (RAASi), which significantly increase the risk of developing HK due to their mechanism of action.[1, 2] People with persistent HK who need haemodialysis are not considered in this submission.	The patient population addressed in this submission is narrower than the population specified in the NICE final scope and the full licensed population. The population has been aligned to that already recommended by NICE in TA599, that is those with persistent hyperkalaemia and chronic kidney disease stage 3b to 5 or heart failure and because of hyperkalaemia, are not taking an optimised dosage of renin-angiotensin-aldosterone system (RAAS) inhibitor. Therefore, this partial update focuses specifically on expanding the existing NICE guidance for those with persistent HK and S–K level ≥6.0 mmol/L to also those include those between ≥5.5–<6.0 mmol/L. Whilst there is evidence demonstrating sodium zirconium cyclosilicate (SZC) is a safe and effective treatment for those on haemodialysis there is currently insufficient evidence for robust economic modelling. As such, this population is not addressed in the

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			decision problem addressed within this submission (section B.1.3.8).
Intervention	SZC	As per scope	N/A
Comparator(s)	Standard care.	Standard care: No therapy administered.[3] Patients with HK with an S–K of ≥5.5–<6.0 mmol/L are managed with lifestyle interventions to maintain normokalaemia. This includes modification of concomitant medications, such as RAASi.[4]	Cost and impacts of dietary intervention have not been included. Evidence presented shows that this is a clinically ineffective treatment and is expected to be associated with a HRQoL decrement. Therefore, exclusion is expected to benefit standard of care.

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	The outcome measures to be considered include: • S–K level • Use of RAASi therapy • Mortality • Time to S–K normalisation • Use of sodium-glucose cotransporter 2 (SGLT-2) inhibitors • Adverse effects of treatment • Major adverse cardiac events (MACE) • Health-related quality of life (HRQoL)	Outcomes included in the submission, include: • S–K level • Use of RAASi therapy • Mortality • Time to S–K normalisation • Adverse effects of treatment • MACE • Hospitalisation	HRQoL and use of SGLT-2 therapy were not collected in the clinical trial programme nor any follow up observational studies for SZC. Given that HK is known to be detrimental to HRQoL, it is expected that the decrease in S–K associated with SZC treatment would have a positive impact on the patient HRQoL. Additionally, SGLT-2 inhibitors are treatments that can be prescribed to CKD and HF patients in addition to RAASi therapies to lower the risk of MACE and slow the progression of kidney disease, and it had been demonstrated that treatment with SZC can increase the proportion of patients receiving treatment. As such, the omission of these outcomes from the economic modelling due to lack of suitable data is likely to result in a conservative estimate of the ICER.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY). If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal	As per scope.	N/A

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	guidance for the same indication, a cost comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.		
Subgroups to be considered	If the evidence allows, the following subgroups will be considered • People with CKD • People with HF	As per scope.	N/A
Special considerations including issues related to equity or equality	None	N/A	SZC is licenced in patients who are receiving chronic haemodialysis.[5] There are a paucity of data for SZC reporting on longer term outcomes suitable for economic modelling, and as such, dialysis patients are not included in the decision problem assessed in this submission. However, SZC has shown

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			it is safe and effective in this population.[6] Restricting access to SZC in this population after previously allowing access in NG160 on the basis of insufficient data to demonstrate cost-effectiveness would preclude the small number of patients from having the option of a safe and effective treatment if it is clinically appropriate for them to have it and would result in inequitable access across the full group of people for which SZC has marketing authorisation (Section B.1.3.8).

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

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B.1.2 *Description of the technology being appraised*

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

Table 2. Technology being appraised

UK approved name and brand name	Sodium zirconium cyclosilicate (Lokelma)
Mechanism of action	SZC is a non-absorbed, non-polymer inorganic powder with a uniform micropore structure that preferentially captures potassium ions (K^+) in exchange for hydrogen and sodium cations. SZC is highly selective for potassium ions, even in the presence of other cations such as calcium and magnesium, in vitro. SZC captures potassium throughout the entire gastrointestinal (GI) tract and reduces the concentration of free potassium in the GI lumen, thereby lowering serum potassium (S–K) levels and increasing faecal potassium excretion to resolve HK.[7-9] (Appendix C)
Marketing authorisation/CE mark status	SZC received marketing authorisation from the MHRA on 22 March 2018 and was subsequently revised on 28 April 2020 to extend indication for the treatment of patients receiving chronic haemodialysis via the EMA centralised procedure.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	SZC is indicated for the treatment of HK in adult patients.
Method of administration and dosage	SZC is a 5 g or 10 g powder for oral suspension. The entire contents of the sachet should be emptied into a drinking glass containing approximately 45 mL of water and stirred well. It should be drunk while still cloudy. The suspension can be taken with or without food and does not require separation from other medications. **Correction phase** The recommended starting dose of SZC is 10 g, administered three times a day orally (TID). Typically, normokalaemia is achieved within 24–48 hours. If patients are still hyperkalaemic after 48 hours, the same regimen can be continued for an additional 24 hours. If normokalaemia is not achieved after 72 hours of treatment, other treatment approaches should be considered. **Maintenance phase** When normokalaemia is achieved, the maintenance regimen should be followed. A starting dose of 5 g once-daily (OD) is recommended with possible titration up to 10 g OD or down to 5 g once every other day, as needed, to maintain a normal potassium level. No more than 10 g OD should be used for maintenance therapy in patients not in receipt of chronic haemodialysis. **Patients on chronic haemodialysis** For patients on dialysis SZC should only be dosed on non-dialysis days. The recommended starting dose is 5 g OD. To establish normokalaemia (4.0–5.0 mmol/L), the dose may be titrated up or down weekly based on the pre-dialysis S–K value after the long inter-dialytic interval (LIDI). The dose could be adjusted at intervals of one week in increments of 5 g up to 15 g OD on non-dialysis days. It is recommended to monitor S–K weekly while the dose is adjusted; once normokalaemia is established, S–K should be monitored regularly (e.g. monthly,

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UK approved name and brand name	Sodium zirconium cyclosilicate (Lokelma)
	or more frequently based on clinical judgement including changes in dietary potassium or medication affecting S–K).
Additional tests or investigations	S–K levels should be monitored when clinically indicated, including after changes are made to medicinal products that affect the S–K concentration, e.g. RAASi or diuretics, and after the SZC dose is titrated. Monitoring frequency will depend upon a variety of factors including other medicinal products, progression of chronic kidney disease and dietary potassium intake.
List price and average cost of a course of treatment	List price: SZC 5 g = £5.20; SZC 10 g = £10.40 Treatment cost in persistent HK: Cost for a full course of SZC = [redacted] (no wastage assumption), [redacted] (with wastage assumption of 2 days per 28 days)*
Patient access scheme (if applicable)	N/A

Footnotes: *Note that the marketing authorisation does not specify treatment duration and the cost given here is that used to inform the cost-effectiveness model.[5, 10] The cost of a full course of treatment is made up of the correction phase, and the maintenance phase of three four-week cycles. The micro-costing approach is summarised in Section B.3.5.4.
Abbreviations: GI: gastrointestinal; GIT: gastrointestinal tract; HK: hyperkalaemia; OD: once-daily; RAASi: renin-angiotensin-aldosterone system inhibitors; S–K: serum potassium; SZC: sodium zirconium cyclosilicate; TID: three times a day.

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

Hyperkalaemia

Hyperkalaemia (HK) is a debilitating and potentially life-threatening condition characterised by elevated serum potassium (S–K) levels. There is no universally accepted definition of the threshold for HK and variation exists between clinical guidelines as to when treatment should commence.[1-11] The UK Kidney Association (UKKA) NICE accredited Clinical Practice Guidelines define HK as an S–K level exceeding 5.5 mmol/L,[12] a threshold also acknowledged by the British Society of Heart Failure (BSH) and international guidelines such as the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[13]

HK can present as either an emergency event, posing an immediate risk to life and requiring urgent medical treatment, or as persistent HK where S–K levels remain elevated over time. Persistent HK can have a direct impact on health due to the effects of elevated S–K and poses challenges for the optimal management of other medical conditions such as CKD and HF, where the use of RAASi therapy is associated with increasing S–K.

Current Management

In UK clinical practice, patients with HK may be managed in emergency or non-emergency primary care, or secondary care settings, dependent on their S–K level and whether their HK is acute or persistent in nature. Patients with S–K levels <6.0 mmol/L or persistent HK are often managed in non-emergency or primary care settings.[12] NICE guidelines and current technology appraisal guidance currently does not recommend initiation of treatment for HK until S–K reaches ≥6.0 mmol/L in the chronic setting.[3, 4, 14]

Current NICE recommended treatment options for patients with persistent HK and an S–K of ≥5.5–<6.0 mmol/L are limited to non-pharmaceutical interventions, most commonly down-titration/discontinuation of RAASi therapy.[3, 15] Additionally patients with persistent HK may be

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unable to achieve optimal RAASi dosage. In patients with CKD and/or HF, down-titration, discontinuation, or non-optimal dosing of RAASi therapy is associated with worsened long-term health outcomes compared with patients that are able to reach and maintain optimal RAASi usage.[2, 16, 17] Low K^+ diets have also historically been used, but are now considered not to be clinically effective and are associated with decreased patient quality of life (QoL).[18-19, 20]

Patients with acute or persistent HK with S–K levels of ≥6.0 mmol/L may be treated with the potassium (K^+) binders SZC or patiromer as per NICE recommendations.[3, 15]

Changes since the 2019 TA599 NICE Evaluation

Prior to TA599, lifestyle interventions were previously the only available treatment for patients with HK.[3, 15] In the original appraisal of SZC, TA599, it was accepted that the clinical evidence package sufficiently demonstrated that SZC normalises S–K.[3] However, uncertainties were raised by NICE and the EAG which meant that the cost-effectiveness of SZC in the treatment of patients with persistent HK was only established for those with an S–K ≥6.0 mmol/L.[3] SZC is currently recommended by NICE (TA599) as an option for use in patients:[3]

- In emergency care for acute life-threatening HK alongside standard care, or;
- With persistent HK and chronic kidney disease (CKD) stage 3b to 5 or heart failure (HF), if they:
    - Have a confirmed S–K level of at least 6.0 mmol/L and
    - Because of HK, are not taking an optimised dosage of renin-angiotensin aldosterone system inhibitors (RAASi) drugs
    - Are not on dialysis

Since the TA599 recommendation for SZC, patiromer has also received positive NICE recommendation in the same population as SZC.[3, 15] As such, pharmaceutical interventions are now available for patients with HK and an S–K of ≥6.0 mmol/L.[3, 15] However, no pharmaceutical interventions are available for those with persistent HK and an S–K of ≥5.5–<6.0 mmol/L and recommended treatment options remain limited to down-titration/discontinuation of RAASi therapy and the implementation of a low K^+ diet.

Since 2019 multiple clinical guidelines have been released including the UK Kidney Association (UKKA) NICE accredited Clinical Practice Guidelines,[12] and international guidelines such as the European Society of Cardiology (ESC) clinical practice guideline,[21] American Heart Association (AHA) HF guideline,[22] and Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[13] These all recommend RAASi as the first-line therapy to delay disease progression and stress the importance of maximising RAASi dose. They recommend the use of K^+ binders as the preferred option to manage persistent HK instead of RAASi down-titration or discontinuation.

According to interviews conducted with UK clinical experts for the management of CKD to support the partial reappraisal of TA599, in the absence of K^+ binders, clinicians would begin down-titrating RAASi therapy in patients with an S–K of ≥5.5–<6.0 mmol/L.[4] However, even in the absence of formal NICE guidance within this population, clinical experts report treating these patients with K^+ binders, because HF and CKD clinicians recognise the value of optimising and maximising RAASi treatment, more so today than in 2019, and therefore actively look to treat patients in alignment with ESC guidelines.[23] Furthermore, in patients with S–K ≥5.5–<6.0 mmol/L clinicians report proactive use of K^+ binders to facilitate the up-titration/optimisation of RAASi treatment.[23]

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B.1.3.1 *Definition of hyperkalaemia*

Hyperkalaemia (HK) is a debilitating and potentially life-threatening condition that occurs when the serum potassium (S–K) concentration increases above normal levels. There is no universally accepted definition of the S–K level at which HK begins, or when management should be initiated, and variation exists between treatment guidelines.[1-11] The NICE accredited UK Kidney Association Clinical Practice (UKKA) Guidelines define HK as an S–K of >5.5, and state that treatment should be initiated once this threshold is reached; this threshold is also recognised in the British Society of Heart Failure (BSH) position statement for HK,[12-24] as well as international guidelines such as the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[13] Although, other international guidelines such as the European Society of Cardiology (ESC),[25] the European Society of Hypertension (ESH)[21] and the International Society of Nephrology (ISN)[26] guidelines define HK as an S–K of 5.0 mmol/L.

Persistent HK (also referred to as chronic HK) generally refers to persistent mild-moderate HK in clinically well patients in the community. There is no consensus on the magnitude, duration and frequency of elevated potassium ion (K^+) levels that define persistency, and persistent hyperkalaemia is clinically important as it can interfere with the management of many medical conditions.[12] This differs from acute HK in which patients present as a medical emergency requiring immediate treatment.

B.1.3.2 *Current treatment of hyperkalaemia*

In UK clinical practice, patients with HK may have either an emergency HK event or have persistent HK. An emergency HK event is an immediately life-threatening event that is normally managed in secondary care within accident and emergency (A&E). Persistent hyperkalaemia may be managed in primary care (general practitioner [GP] surgery) or secondary care (outpatient clinic) settings. Persistent HK with S–K <6.0 mmol/L is more likely to be managed in a primary care setting, whereas S–K levels ≥6.0 mmol/L are more likely to be managed in A&E within a secondary care setting.[12] NICE guidelines currently do not recommend initiation of treatment for HK until S–K reaches ≥6.0 mmol/L in the chronic setting.[3, 4, 14] Compared to NHS clinical practice, recent international guidelines are more proactive in managing HK. For example, the ESC heart failure guidelines recommend initiating K^+ binders as soon as S–K exceeds 5.0 mmol/L and note that K^+ binders enable continuation of RAASi treatment.[25]

B.1.3.2.1 Current management of patients with S–K of ≥6.0 mmol/L

Prior to 2019, patients in England with acute or persistent HK were managed primarily with down-titration/discontinuation of RAASi therapy and potentially a low K^+ diet. Since 2019, those with acute or persistent HK with S–K levels of ≥6.0 mmol/L may be treated with K^+ binders as per NICE recommendations.[3, 15] K^+ binders such as SZC and patiromer are orally administered, non-absorbed compounds that capture K^+ throughout the GI tract and in the colon, respectively, and reduce the concentration of K^+ in the GI lumen, thereby increasing faecal K^+ excretion and lowering S–K to resolve HK.[5, 27] Both SZC and patiromer have received positive NICE recommendations in the same population.[3, 15]

SZC is currently recommended by NICE (TA599) as an option for use in patients:[3]

- In emergency care for acute life-threatening HK alongside standard care, or;
- With persistent HK and chronic kidney disease (CKD) stage 3b to 5 or heart failure (HF), if they:

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- Have a confirmed S–K level of at least 6.0 mmol/L and
- Because of HK, are not taking an optimised dosage of renin-angiotensin aldosterone system inhibitors (RAASi) drugs
- Are not on dialysis

B.1.3.2.2 Current treatment for persistent hyperkalaemia for patients S–K of ≥5.5–<6.0 mmol/L

NICE has not made a positive recommendation for SZC or patiromer for those with persistent HK and an S–K of ≥5.5–<6.0 and current treatment options for these patients remain limited to non-pharmaceutical interventions, most commonly down-titration/discontinuation of RAASi therapy.[3, 15]

In patients with comorbid CKD or HF, down-titration/ discontinuation of RAASi therapy is associated with worsened long-term health outcomes compared with patients that maintain RAASi usage.[2, 16, 17] Since 2019, international guidelines recommend the use of K^+ binders as the preferred option to manage persistent HK instead of RAASi down-titration or discontinuation.[13, 21, 22] Low K^+ diets have also historically been used, but are now considered not to be clinically effective and are associated with decreased patient quality of life (QoL).[18-19, 20, 23]

In the original appraisal of SZC (TA599) it was accepted that the clinical evidence package sufficiently demonstrates that SZC normalises S–K.[3] However, uncertainties were raised by NICE and the EAG which meant that the cost-effectiveness of SZC in the treatment of patients with persistent HK and an S–K of ≥5.5–<6.0 mmol/L could not be established.[3] The key uncertainties include:

- There was a paucity of clinical data linking S–K levels and long-term clinical outcomes (mortality, hospitalisations, MACE).
- Clinical evidence did not adequately demonstrate that SZC usage allows reinitiation, up-titration or maintenance/optimisation of RAASi dosage.
- Clinical evidence did not adequately demonstrate the relationship between RAASi dosage and long-term clinical outcomes.

An overview of the evidence presented in this submission to address these evidence gaps is summarised in Table 4.

As such, this submission will be a targeted review of TA599 to address these uncertainties with the intention of expanding the reimbursement of SZC to those with persistent HK with an S–K level of ≥5.5–<6.0 mmol/L, ensuring these patients also have access to clinically effective licensed K^+ binder therapies.

B.1.3.3 *Symptoms, causes and risk factors for hyperkalaemia overview*

Symptoms of HK are often absent or non-specific. Thus, HK is often detected incidentally by diagnostic tests conducted as part of routine care.[28] Reported symptoms typically include diarrhoea, nausea and vomiting, difficulty breathing, abdominal pains, muscle pain, weakness and paralysis, and generally increase in severity as S–K levels increase. Persistent HK can be a serious health concern due to its effects on the heart and muscles. The recent ESC HF guideline notes that S–K levels have a U-shaped relation with mortality, with the lowest risk of death within a relatively narrow range of 4–5 mmol/L.[21] Further evidence has shown that those with an S–K level of ≥5.5–<6.0 mmol/L are at greater risk of a range of adverse clinical outcomes, including hospitalisation, mortality and MACE than those with normokalaemia.[29-34] Persistent HK can also have an indirect impact on health due to sub-optimal use of RAASi therapy to manage HK.[2, 35-40]

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When HK is left untreated, patients' S–K often continues to rise, potentially resulting in an emergency HK event with life threatening consequences, including respiratory failure, cardiac arrhythmia, cardiac arrest, and sudden death.[28, 41-43] For this reason, early identification of HK and timely, appropriate treatment is vital to restore normokalaemia is critically important to prevent serious complications of disease.

B.1.3.3.1 Risk factors: Chronic kidney disease or heart failure

S–K is regulated by a number of mechanisms, including the transport of K^+ between extracellular and intracellular spaces and the rate of excretion of K^+ via the kidneys.[44] The increase in S–K leading to HK can be the result of increased K^+ intake, disrupted intracellular redistribution of K^+, impaired K^+ excretion, or a combination of these causes.

Therefore, people with underlying cardiorenal conditions such as CKD or HF, as well as people of advancing age, are at an increased risk of developing HK, typically due to decreasing renal function and capacity for renal excretion. Of these, reduced renal function is the strongest independent predictor for HK.[1, 30, 45]

B.1.3.3.2 Risk factors: Renin-angiotensin aldosterone system inhibitors

Renin-angiotensin-aldosterone system inhibitor (RAASi) treatments are mainstay medications used in the management of CKD or HF, as recommended in international treatment guidelines such as those from ESH,[21] ESC,[46] KDIGO,[13] the ISN,[26] and local guidelines such as those from the BSH,[47] UKKA,[48] and NICE.[4, 49] RAASi therapies include angiotensin-converting-enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), mineralocorticoid-receptor antagonists (MRAs), and angiotensin receptor-neprilysin inhibitor (ARNi).[50, 51] Since 2019, international treatment guidelines emphasise the importance of optimised RAASi dosages to delay disease progression. These guidelines recommend the use of K^+ binders as the preferred option for management of persistent HK, to avoid RAASi down-titration or discontinuation.[13, 21, 22] The effectiveness of RAASi treatment is supported by multinational RCT data. For example, the ATLAS and HEAAL multinational RCTs, which enrolled 3,164 and 3,846 patients with HF, respectively, found that higher RAASi doses offer greater cardiorenal protective benefits than lower doses.[52-54] The studies concluded that clinicians should strive to obtain target doses as specified in the guidelines.[52-54] This is supported by further real-world observational studies that demonstrate that the down-titration or discontinuation of RAASi therapy is typically associated with an increased risk of adverse cardiorenal outcomes, including death, compared with patients who maintain RAASi dose.[1, 2, 17, 39, 55-59]

Use of RAASi therapy is linked with increased S–K

Despite the vital cardiorenal protective effects provided by RAASi therapies, these medicines increase S–K levels by reducing renal excretion of K^+ which can lead to HK. A meta-analysis of 21 trials demonstrated that the use of MRAs was associated with a statistically significant increase in S–K levels (mean difference in S–K MRA vs control: 0.23; 95% confidence interval [CI]: 0.13–0.30; p<0.001) and an increased relative risk (RR) for HK of 1.76 (95% CI: 1.20–2.57; p=0.004).[60] This has been further supported by UK studies.[61-63] Michel *et al.* in a nested control study which analysed medical records using the health improvement network (THIN®) database (n=19,194). This study determined that the use of ACE inhibitors is correlated to an increased risk of HK with an odds ratio (OR) of 1.41 (95% CI: 1.11–1.79).[62] Horne *et al.* in an analysis of the Clinical Practice Research Database (CPRD) (n=195,178) which determined that the use of RAASi is strongly linked to recurrent HK, with an OR of 1.27 (95% CI: 1.23–1.31) and 1.74 (95% CI: 1.64–1.85) for ACEi and MRA use, respectively.[61-63]

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Risk of HK can lead to sub-optimal usage of RAASi therapy

As use of RAASi therapies is known to increase S–K, patients with persistent HK are often unable to receive an optimised RAASi dose due to concerns that an increase in RAASi dose will result in a severe HK event.[35, 38-40] Furthermore, clinicians may have no choice but to down-titrate or discontinue their patient's RAASi medication due to HK.[35, 38]

For example, in a retrospective observational cohort study of CPRD, investigating the relationship between S–K and guideline RAASi usage in patients with HF (n=23,541), Qin *et al.* found that at baseline, 44.6% and 66.0% of patients receiving ACEi and ARBs, respectively, achieved <50% of the recommended target dose for these therapies.[38] Sub-optimal dosing of RAASi is further exacerbated by HK, with patients who have an S–K of ≥5.5–<6.0 mmol/L discontinuing RAASi treatment with an incident rate ratio (IRR) of 1.30 (95% CI: 1.13–1.50) compared with the reference value of 4.5–5.0 mmol/L according to the analysis by Qin *et al*.[38]

In another CPRD analysis conducted by Linde *et al.* which investigated the association between RAASi dosage and HK in patients with CKD (n=100,572) and HF (n=13,113), it was found that patients with an S–K of ≥5.0 mmol/L had higher risk of RAASi down-titration, with ORs of 1.79 (95% CI: 1.64–1.96) and 1.33 (95% CI: 1.08–1.62), for CKD and HF patients respectively.[35] In the same study, the mean duration of RAASi discontinuation was greater than 2.4 years and 1.9 years in CKD and HF patients, respectively.[35] This highlights the extended duration of time which patients remain without RAASi treatment following a discontinuation, and emphasises the need for treatments that effectively control HK to allow patients to receive optimised guideline dosages of RAASi treatment and ensure optimal disease management.

Sub-optimal RAASi therapy is linked to poor long-term outcomes

The sub-optimal dosing of RAASi due to HK is associated with an increased risk of adverse cardiorenal outcomes, including MACE and death, compared with patients in receipt of guideline directed RAASi therapy.[2, 16, 17] Since 2019, international treatment guidelines have emphasised the importance of patients receiving optimised RAASi dosages to delay disease progression. These guidelines recommend the use of K^+ binders as the preferred option for management of persistent HK, to avoid the need for RAASi down-titration or discontinuation unless other treatment options have been attempted.[13, 21, 22]

In a retrospective cohort analysis of CPRD (n=434,027) investigating the relationship between RAASi interruption/ cessation and adverse clinical outcomes, Humphrey *et al.* found that the risk of all-cause mortality, HF, cardiac arrythmia and cardiac arrest was reduced by 75.0%, 28.0%, 22.0% and 44.0%, respectively for patients receiving continued RAASi treatment compared with those experiencing interruptions or cessations.[2] This aligns with the findings from the CPRD analysis conducted by Linde *et al.* (described above), which found increased risk of mortality (57.74 versus 7.17 deaths per 1,000 patient-years [PY] [IRR: 5.60; 95% CI: 5.29–5.93]) for the CKD population and 141.74 versus 12.53 death per 1,000 PY [IRR: 7.34; 95% CI: 6.35–8.48] for the HF population) amongst patients receiving <50% of the guideline recommended RAASi dose compared with those on ≥50%.[35] This study also identified an increased risk of MACE for the CKD population (130.38 versus 72.95 events per 1,000 PY [IRR: 1.60; 95% CI: 1.55–1.66]) and for the HF population (290.35 versus 148.49 events per 1,000 PY [IRR: 1.85; 95% CI: 1.71–1.99]) observed amongst patients receiving <50% of the guideline recommended RAASi dose compared with those on ≥50%.[35]

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In another retrospective observational study of the CPRD investigating the link between S–K and long-term outcomes, RAASi usage was found to be linked to a decreased risk of mortality based on risk equations fitted to data from adult CKD patients (n=191,964) and HF patients (n=21,334).[36, 37] The predicted mortality rates of patients (per 1,000 PY) as a function of S–K level and disaggregated by RAASi usage is presented in Figure 1.[36, 37] A meta-analysis conducted by Sun *et al*. evaluated target RAASi (specifically ACEi/ARBs) dose (defined as 50–99% of guideline-recommended dose) versus sub-target RAASi doses in elderly patients (>60 years) with heart failure with reduced ejection fraction (HFrEF) and reported significantly lower rates of all-cause mortality among patients receiving the target RAASi dose (HR: 0.92;95% CI: 0.87–0.98).[64] A further meta-analysis reported significantly lower odds of all-cause mortality with high-dose (mean daily dose ≥200 mg) versus low-dose (mean daily dose <200 mg) sacubritril/valsartan for patients with left ventricular ejection fraction (LVEF) <40% (OR: 0.23; 95% CI: 0.11–0.47).[65]

Internationally, in an observational study investigating the clinical impact of suboptimal RAASi therapy following an episode of HK in patients with CKD and/or HF currently receiving RAASi therapy who experienced an index HK episode, Kanda *et al.* analysed the medical records of 15,488 and 6,020 patients in the US and Japan, respectively.[39] It was found that patients who discontinued or down-titrated RAASi treatment dosages following an HK event had a higher risk of cardiorenal events, measured using a composite outcome (HF emergency visit, HF hospitalisation, or progression to end-stage renal disease [ESRD]), compared with patients who maintained or up-titrated RAASi treatment dosages.[39] In the US, the risk at 6-months was 17.5% (95% CI: 16.1–18.8%) in those who discontinued, 18.2% (95% CI: 15.1–21.3%) in those who down-titrated, and 10.6% (95% CI: 9.8–11.4%) in those who maintained or up-titrated RAASi treatment dosages (p<0.001). In Japan, the corresponding risks were 19.7% (95% CI: 17.7–21.6%), 20.0% (95% CI: 15.3–24.4%), and 15.1% (95% CI: 13.8–16.4%) in who discontinued, down-titrated, or maintained/ up-titrated RAASi treatment dosages (p<0.001), respectively. This study suggests that down-titration and discontinuation of RAASi therapy leads to similar levels of adverse outcomes.

In a retrospective cohort study investigating the risk of RAASi discontinuation in patients with HK, Johnson *et al.* analysed the medical data of 82,732 US patients with cardiometabolic disease (defined as coronary artery disease, HF, diabetes mellitus or CKD).[57] Among the study patients, 7,729 (9.34%) developed HK, and were more likely (34.4%) to discontinue/ down-titrate RAASi therapy, than patients without HK (29.2%, p<0.001). Overall, the five-year cumulative risk of a composite end point of cardiovascular (CV) events, renal dysfunction, and all-cause mortality, was higher in patients who down-titrated RAASi dosages (50.4%; 95% CI: 48.5–52.4%) or discontinued RAASi (49.3%; 95% CI: 48.5–50.1%), compared with patients who continued optimum dosages of RAASi therapy (36.1%; 95% CI: 25.7–36.5%) following HK;[57] supporting that both down-titration and discontinuation of RAASi are associated with similar risks of adverse outcomes. In those who developed HK, the five-year cumulative risk of composite outcomes was higher (63.9%; 95% CI: 62.8%–65.1%) compared with those who did not develop HK (37.2%; 95% CI: 36.8%–37.6%); highlighting the interlink between HK, RAASi down-titration/discontinuation and increased incidence of adverse outcomes.

Considering patients with HF, an RCT (HF-ACTION) reported that among 1,999 ambulatory patients with chronic HFrEF, discontinuation of RAASi treatment resulted in a statistically significant increase in all-cause mortality (HR: 1.86; 95% CI: 1.28–2.68). This study also demonstrated that patients discontinuing RAASi were at a numerically increased risk of CV mortality or HF hospitalisation, although after adjusting for baseline characteristics this result was not statistically significant.[66] Among patients with CKD, a meta-analysis conducted by Tang *et al*. found that discontinuation of

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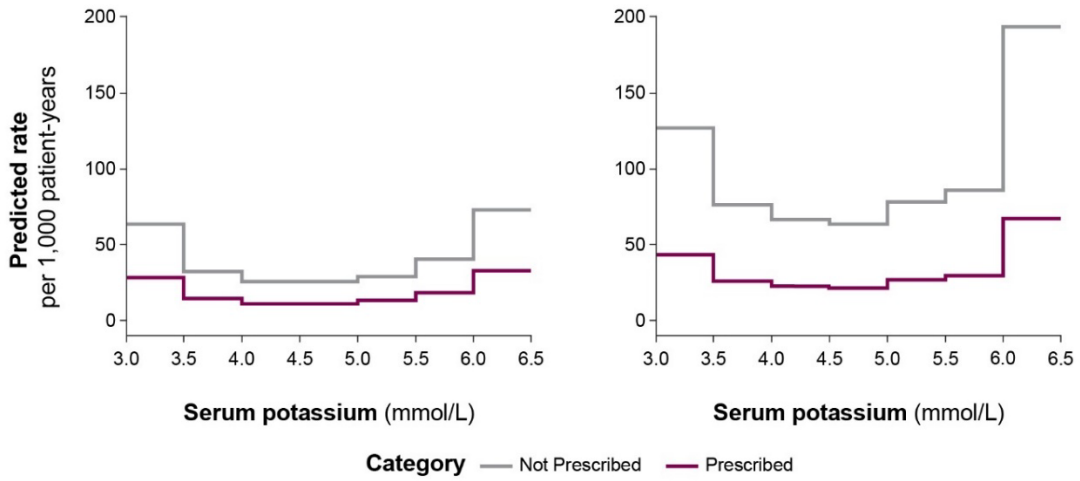
RAASi was shown to significantly increase the risk of CV events (HR: 1.25; 95% CI: 1.17–1.32) and mortality (HR: 1.42; 95% CI: 1.23–1.63). In patients who discontinue RAASi specifically due to HK, there was also a statistically significant increased risk of mortality (HR: 1.48; 95% CI: 1.29–1.70).[67] Similarly, a meta-analysis conducted by Nakayama *et al*. found that discontinuation of RAASi among patients with CKD was shown to significantly increase the risk of mortality (HR: 1.41; 95% CI: 1.23–1.63) and MACE (HR: 1.20; 95% CI: 1.15–1.25).[68]

Figure 1: Predicted incidence rates of mortality, disaggregated by RAASi prescriptions and S–K, in patients with CKD and HF



Footnotes: Left panel represents patients with CKD, right panel represents patients with HF.
Abbreviations: CKD: chronic kidney disease; HF: heart failure; RAASi: renin-angiotensin-aldosterone system inhibitor.
Source: Adapted from Furuland *et al.* 2018 [36] and Linde *et al.* 2019 [37]

In summary, these studies demonstrate that the down-titration or discontinuation of RAASi therapies due to HK, in HF and CKD patients, leads to worsened morbidity and mortality. Down-titration and discontinuation of RAASi therapies are associated with increased risk of cardiorenal outcomes, highlighting the importance of receiving guideline directed RAASi therapy.[39, 57] International guidelines recommend that HK should be proactively managed with appropriate interventions that facilitate the maintenance and optimisation of RAASi therapies to minimise risk to patients.[13, 21, 22]

B.1.3.3.3 Incidence and prevalence

Given the varying S–K thresholds used to define HK, the difficulty in quantifying HK between the acute and chronic settings, and the broad causes of HK (ranging from acute kidney injury to drug-induced), estimating the number of people suffering from HK is complex. As many patients with persistent HK are incidentally diagnosed, the majority of patients with HK diagnosed within secondary care are not coded appropriately, and therefore hospital episode statistics (HES) data are likely to be unreliable and present a conservative estimate. The UKKA estimates that between 1–10% of hospital inpatients have experienced HK,[12] and in a National Kidney Foundation survey conducted among patients with CKD, it was found that at least two-thirds of CKD patients have experienced HK, with one-in-five currently experiencing HK at the time of survey.[69] As outlined above and in Section B.1.3.3, HK generally occurs frequently in patients with CKD and/or HF, themselves highly prevalent diseases. In a recently conducted observational study of CPRD (see Section B.2.3.1), it was found that the incidence of CKD and HF are both 0.1 per 1,000 person-years in 2019 in the UK, and the prevalence is 1.79 and 1.27 per 1,000 person-years for CKD and HF, respectively.[29]

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The incidence and prevalence of HK

In the UK population, the strongest predictors of an incident HK event is the concomitant use of MRAs, ACEi and ARBs.[61] Recent studies in Europe have revealed that the incidence of HK increases as CKD severity increases.[70, 71] A population-based cohort study conducted by Thomsen *et al.* in Northern Denmark studied the incidence rate of HK in all newly diagnosed CKD patients (eGFR <60 mL/min/1.73 m^2 or hospital diagnosis).[70] Of 157,766 patients with CKD, 27.5% experienced HK (S–K of >5.0 mmol/L) with an overall incidence rate of 7.0 per 100 person-years. Incidence rate increases with CKD severity, with the incidence rate increasing to 11.9, 23.9, and 33.3 per 100 person-years, respectively in stage 3b, 4, and 5 CKD patients. Within the first year of diagnosis, 18.4%, 31.4% and 42.4% of patients experience HK, in stage 3b, 4, and 5 CKD patients, respectively.[70] Thomsen *et al.* also investigated the incidence rate of HK in the HF population in Northern Denmark. It was found that among 31,649 patients with HF, 25.2% experienced HK, with an overall incidence rate of 17.8 per 100 person-years.[33] In an observational study conducted on patient laboratory data in Sweden, Nilsson *et al.* also found that among CKD stage 1–4 patients, incidence of HK (S–K of >5.5 mmol/L) increased with disease severity, with an adjusted incidence rate of 0.6 per 100 person-years in patients with CKD stage 1–2 increasing to 4.3 and 41.9 per 100 person-years in patients with CKD stage 3 and 4+, respectively.[71] Together, these studies demonstrate that patients with CKD and HF are at increased risk of HK compared with the general population.

Most recently, the SPARK study identified the incidence rate of HK, stratified by S–K level (Table 3). The SPARK study is a UK-specific, retrospective, observational, longitudinal study conducted by AstraZeneca using secondary data extracted from the CPRD and linked datasets (See Section B.2.3.1).

Overall, it is clear that HK is a highly frequent disease globally in patients with CKD and/or HF, with a greater incidence reported among those with underlying cardiorenal comorbidities compared with the general population.

Table 3: Summary of hyperkalaemia 2019 incidence rates from SPARK

Publication and data source	Country	Definition of hyperkalaemia	Incidence rate (per 100 person-years)
AstraZeneca Data on File: SPARK[29]	England	S–K ≥5.0–<5.5 mmol/L	[redacted]
		S–K ≥5.5–<6.0 mmol/L	[redacted]
		S–K ≥5.5 mmol/L	[redacted]
		S–K ≥6.0 mmol/L	[redacted]

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

As with incidence rates, HK prevalence rates vary considerably based on the population of interest, with a number of studies reporting a higher prevalence of HK among patients with cardiorenal comorbidities, such as CKD, HF, or diabetes/insulin resistance, compared with those without these conditions.[72,73, 74]

The prevalence of HK globally has been estimated by a 2022 systematic literature review (SLR).[1] Across 221 studies, the pooled mean prevalence of HK (defined as those with a measured S–K of ≥5.5 mmol/L) amongst all adult studies was 5.9% (95% CI: 3.5–10.0), with a higher prevalence observed in patients with comorbidities such as non-dialysis CKD (8.9%), HF (8.0%), and end-stage kidney disease (ESKD) (23%) as well as patients using RAASi therapy (7.9%), compared with the general population (defined as the patient population without specific reporting of comorbidities or K^+ management therapies).[1] Kyriakou *et al.* conducted a prospective cohort study in Greek patients

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in the nephrology outpatient setting and found the prevalence of HK (S–K of ≥5.5 mmol/L) to be 11.2% in patients with CKD stage 3–4.[75] A review carried out by Kovesdy *et al.* reported that the prevalence of HK (any threshold) can be as high as 40–50% in patients with advanced CKD, diabetes, kidney transplant recipients, and patients treated with RAASi.[76] In the UK, Sarafidis *et al.* found that in 238 patients under regular follow-up in an advanced kidney care facility, 31.5% of patients had an S–K level of ≥5.5 mmol/L. This further demonstrates that HK is highly prevalent in patients with CKD.[77]

B.1.3.3.4 Recurrence of hyperkalaemia

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

Recurrence of HK has been reported in a number of real-world, observational studies conducted in Europe. SCREAM and LABKA are observational studies analysing records of routine laboratory test results in Stockholm (n=364,955) and Denmark (n=157,766), respectively.[71, 78] These studies found that after a first event of HK (S–K of ≥5.0 mmol/L), 35.7% (follow-up: 3 years) and 43.5% (median follow up: 2.27 years) of patients, had a second event of HK in the SCREAM study (CKD or HF patients) and LABKA study (CKD patients), respectively.[71, 78] Recurrence of HK has also been reported by Rossignol *et al.* as part of a prospective registry study conducted in France within patients receiving chronic haemodialysis.[79] In patients with an initial HK event (S–K of ≥5.5 mmol/L) at any time during a 2-year study follow-up period (n=305), the proportion of patients experiencing a recurring event of HK within 3 months was 59.7%.[79] The persistent and recurrent nature of HK in patients with cardiorenal comorbidities highlights the importance of pre-emptive and proactive approaches for monitoring and managing HK, that facilitates the maintenance of cardiorenal protective RAASi therapies.

RAASi therapies are known to increase S–K levels by reducing renal excretion of K^+ which can lead to HK. Clinicians have historically needed to consider the risk of recurrence of HK with the cardiorenal protective effects provided by RAASi therapies. A retrospective review of HF patients with recurrent HK (83.4% with two HK events and 16.6% with ≥3 events) in France, Italy, Spain, Germany and the UK (n=1,457), demonstrated that at the second HK event, RAASi and loop diuretics use were significantly decreased compared to the first event. Hospitalisations were commonly reported (307 patients, 326 hospitalisations) and were attributed to HK or cardiorenal events.[79, 80] Since 2019 and the availability of selective K^+ binders, international guidelines place a greater emphasis on optimising and maintaining RAASi dose rather than decreasing the dose or stopping RAASi immediately.[13, 21]

In summary, recurrence of HK is high in patients comorbid with CKD and HF, multiple comorbidities and those taking RAASi therapy. Typically, down-titration or discontinuation of RAASi and MRA therapy is common in response to an HK event (see Section B.1.3.2), and the fear of recurrent HK prevents clinicians from achieving or maintaining an optimised RAASi dosage among patients. This is contrary to the most recent international guidelines and signals an unmet need for NHS patients to ensure appropriate monitoring, a longer-term, proactive control of S–K levels and maintenance of their critical disease-modifying RAASi therapy.

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B.1.3.4 *Burden to patients, carers and society*

Overview

There is significant burden of disease associated with persistent HK both in terms of increased patient morbidity and mortality. Across different patient groups, such as those patients with CKD or HF, the risk of adverse clinical outcomes, such as hospitalisations, MACE, and mortality, increases with elevated S–K levels.[30, 31, 34, 81, 82] Patients with persistent HK receiving RAASi therapy are often unable to reach or maintain guideline directed dosages and are therefore unable to benefit from the cardiorenal protective effect of RAASi therapy, compounding the already increased risk of potentially life-threatening outcomes from both HK and underlying cardiorenal comorbidities.[59]

These studies will be discussed in the following Sections B.1.3.4.1 and B.1.3.4.2.

Morbidity and mortality burden

Untreated persistent HK is associated with an increased risk all-cause mortality, hospitalisations and MACE,[30, 31, 34, 70, 78, 81-86] As reported in TA599, multiple studies have shown a 'U-shaped' association between S–K levels and the risk of death for CKD or HF patients.[30, 31, 34, 81, 82, 86] Such an association has also been observed in studies of hospitalised patients, and patients with other comorbidities, such as hypertension and diabetes.[83, 84, 86-88] As such, international guidelines now recognise the importance of this association, and guidance has transitioned to become more proactive in the management of persistent HK using K^+ binders, even amongst those with milder disease.[13, 21, 22]

HK is a significant cause of patient morbidity, with an increased risk of CV events reported in studies of patients with CKD or HF.[33, 34, 70, 81, 82, 89] The associated risk of adverse clinical outcomes with elevated S–K levels has been shown, with increasing severity of HK being associated with increasing morbidity risk.

In the assessment of TA599, NICE raised concerns relating to the evidence presented to demonstrate the association between persistent HK and adverse clinical outcomes, as these studies did not adjust for RAASi usage or adjust for unmeasured confounders, and thus the independence of the relationship between S–K and long-term outcomes could not be reliably established.[3] To address these concerns, AstraZeneca have conducted the SPARK study. The IRRs obtained from the SPARK study demonstrate the relationship between S–K and hospitalisation, MACE, and mortality, as stratified by S–K levels and eGFR, and adjusted by an additional 30+ confounders than the studies used to inform TA599, including co-medications, comorbidities and RAASi usage.[29] In addition, e-values were calculated to quantify the strength of the unmeasured confounder needed to reverse the observed relationships (see Section B.2.3.1).[29]

B.1.3.4.1 Hyperkalaemia in CKD

Several studies have confirmed an association between elevated S–K levels, hospitalisations, MACE, and mortality in CKD patients, specifically.[30-32, 78, 81, 84, 86]

The evidence presented in TA599 demonstrated that an S–K level of ≥5.5–<6.0 mmol/L was associated with statistically significant increases in hospitalisations, MACE, and RAASi discontinuation in CKD patients across 59 studies,[30] An S–K of ≥5.5–<6.0 mmol/L was also associated with an increased risk of all-cause mortality, and patients with CKD had an HR of 1.69 (95% CI: 1.65–1.74) compared with those without CKD.[30] This relationship is further supported by analyses of CKD and HF patients by Qin *et al.* and Thomsen *et al.* using UK CPRD and Danish medical records, respectively.[31, 70, 78, 82] Qin *et al.* found that for CKD patients the adjusted IRR for

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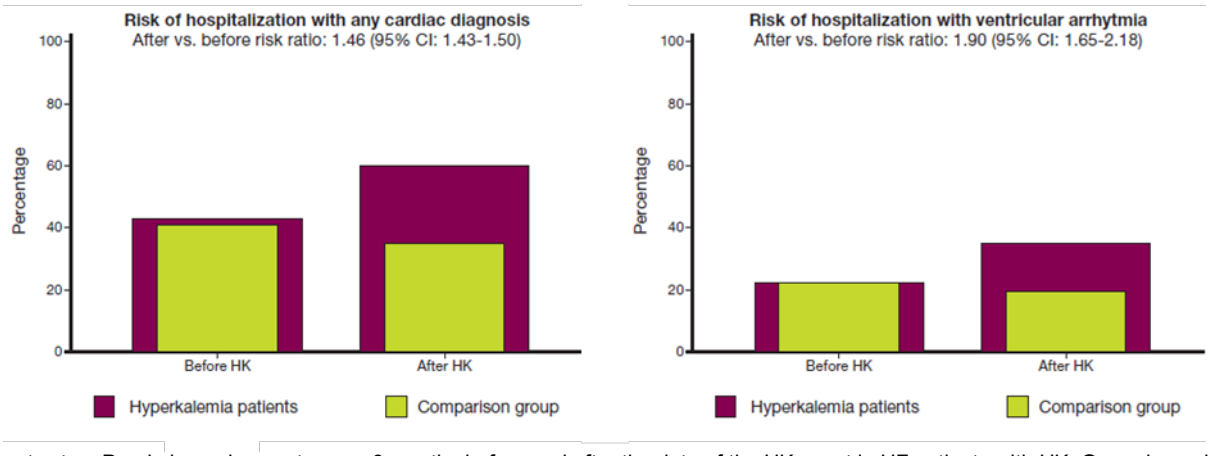
MACE and mortality is 1.17 and 1.29 for patients with an S–K level of ≥5.5–<6.0 mmol/L, respectively.[31] Thomsen *et al.* (LABKA), found that CKD patients with an S–K of ≥5.5–<6.0 mmol/L had a relative risk (RR) of 1.80 (95% CI: 1.76–1.83) for all-cause hospitalisations in the six months post-HK event compared to the 6 months prior.[54] Kovesdy *et al.* analysed 1,217,986 patients in the CKD Prognosis Consortium (CKD-PC); a global collaboration, incorporating cohorts with at least 1,000 participants, and including patients from the UK. It was found that compared with a reference S–K of 4.2 mmol/L, the adjusted HR for all-cause mortality was 1.22 (95% CI: 1.15–1.29) at an S–K of >5.5 mmol/L. Risks were similar when stratified by eGFR, albuminuria, RAASi use and across all cohorts.[32]

In a recently conducted observational study of CPRD conducted by AstraZeneca, SPARK (see Section B.2.3.1), it was found that CKD patients with an S–K level of ≥5.5–<6.0 mmol/L are at an increased risk of long-term adverse clinical outcomes such as MACE, hospitalisations, and all-cause mortality when compared with the reference normokalaemia population.[29] As described above, SPARK considered RAASi usage and adjusted for unmeasured confounders, to address concerns raised regarding the evidence presented in TA599.

B.1.3.4.2 Hyperkalaemia in heart failure

Several studies have shown a significant association between HK and risk of morbidity and mortality in patients with HF.[33, 86, 90-93] In the LABKA study analysing Danish HF patients with HK, defined as an S–K of >5.0 mmol/L (n=12,340), it was found that the risk of hospitalisation due to ventricular arrhythmia (RR: 1.90; 95% CI: 1.65–2.18) or any cardiac hospital diagnosis (RR: 1.46; 95% CI: 1.43–1.50), and mortality (HR: 3.16; 95% CI: 2.99–3.35) increased in the six months after the defining HK event compared to the prior six months (Figure 2).[33] In another prospective study analysing Spanish HF patients discharged from an acute heart failure admission (n=2,164), Nunez *et al.* found an association between elevated S–K levels and mortality.[92] In this sample, it was found that dynamic changes in S–K were independently associated with substantial differences in mortality risk, whereas S–K normalisation was independently associated with lower mortality risk (p=0.001).[92]

Figure 2: LABKA study: Risk of hospitalisation due to ventricular arrhythmia or any cardiac diagnosis



Footnotes: Purple bars show outcomes 6 months before and after the date of the HK event in HF patients with HK. Green bars show outcomes in matched HF patients without HK. Corresponding after vs before risk ratios are estimated, adjusted for competing risk of death after HK.
Abbreviations: CI: confidence interval; HK: hyperkalaemia.
Source: Adapted from Thomsen *et al.* 2017 [33]

An SLR presented in TA599 found that an increased S–K level above 5.5 mmol/L is also associated with increased hospitalisations and mortality in HF patients compared with those with

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normokalaemia (S–K level of 4.5–5.0 mmol/L). The mean HR was 2.94 (95% CI: 2.76–3.13) for all-cause mortality when compared to patients with normokalaemia.[30] The CPRD risk equation study on the CV outcomes of HK patients with HF further support these findings.[33, 34] In the CPRD risk equation study, the analysis of clinical outcomes among HF patients (n=23,541) found that the risk of mortality increased with S–K,[31, 34, 82] and in patients with an S–K of ≥5.5–6.0 mmol/L, the adjusted IRR and mortality was 1.55 (95% CI: 1.38–1.75).[34]

In a recently observational study of CPRD conducted by AstraZeneca, SPARK, (see Section B.2.3.1), it was found that HF patients with an S–K level of ≥5.5–<6.0 mmol/L are at an increased risk of long-term adverse clinical outcomes such as MACE, hospitalisations, and all-cause mortality when compared with the reference normokalaemia population.[29] As described above, SPARK considered RAASi usage and adjusted for unmeasured confounders, to address concerns raised regarding the evidence presented in TA599.

B.1.3.4.3 Summary of morbidity and mortality burden

As highlighted by the evidence presented in Section B.1.3.4, HK is associated with an increased burden to patients, carers and society. [30-33, 78, 81, 84, 86, 90-93] An S–K level of ≥5.5–<6.0 mmol/L is associated with statistically significant increases in adverse clinical outcomes such as hospitalisation, MACE, and mortality in both CKD and HF patient populations.[29, 34, 81] Elevated S–K levels are also associated with an increased risk of RAASi down-titration and discontinuation,[30, 38] which is also associated with an increased risk of hospitalisations, cardiorenal adverse events (AEs), and mortality.[94]

B.1.3.5 *Quality of life*

The QoL of patients may be affected directly by the symptoms of persistent HK which include diarrhoea, nausea and vomiting, difficulty breathing, abdominal pains, muscle pain, weakness and paralysis, and adverse clinical outcomes such as MACE events, hospitalisation or premature mortality. However, many patients may have non-specific symptoms or be asymptomatic with regards to their persistent HK and are primarily impacted from being unable to optimise or maintain their RAASi therapy which negatively impacts their underlying condition. Nevertheless, there are limited QoL data on the direct impact of HK as there are no disease-specific QoL instruments. Studies have demonstrated the association between HK and QoL using data from the Adelphi Real World CKD Disease Specific Programme (DSP).[18-19] Global analysis demonstrated that patients with CKD (non-dialysis) and HK had significantly lower QoL scores compared with their normokalaemic counterparts in three of the five domains of the Kidney Disease Quality of Life Instrument (KDQOL): burden of disease (54.9 vs 60.8; p=0.011), physical health (39.1 vs 41.6; p=0.001) and effects of kidney disease (69.6 vs 76.1; p<0.001) (Figure 3).[18] Analysis of patients in the US also showed a significant reduction in the mental health domain (44.8 vs 48.9; p=0.018).[95]

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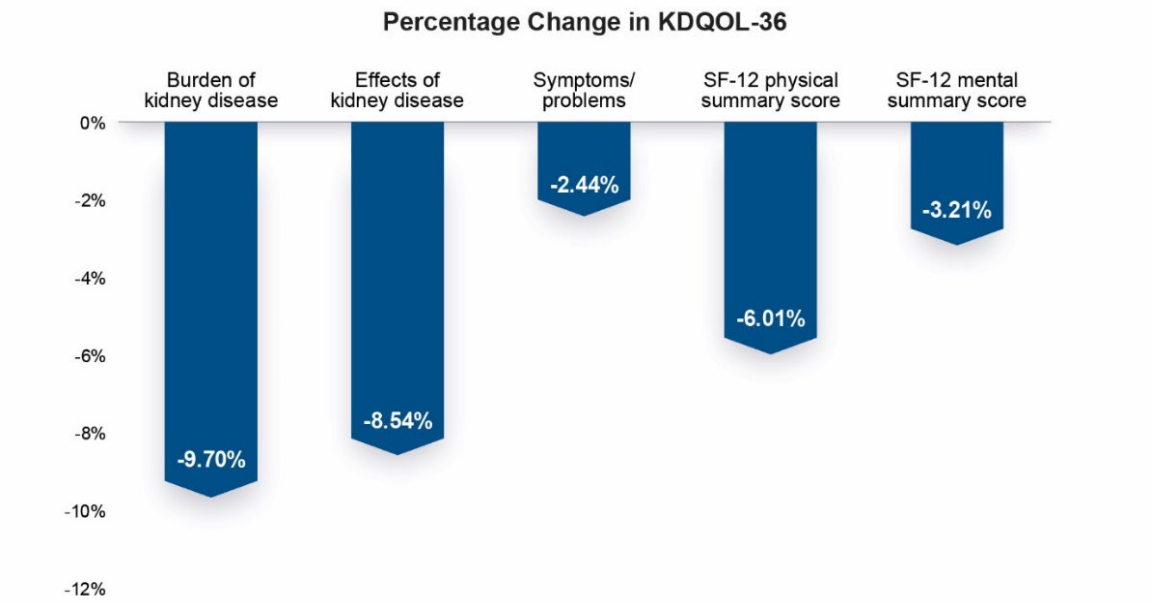
Figure 3: Percentage change in KDQOL-36 scores between non-dialysis dependent CKD patients with HK vs non-dialysis CKD patients without HK



Abbreviations: KDQOL-36: Kidney Disease Quality of Life Instrument-36; SF-12: 12-item short form survey.
Source: Grandy *et al.* 2018 [18]

Current treatment options for the management of persistent HK at a serum level of ≥5.5–<6.0 mmol/L remain limited, with the mainstay option being down-titration/discontinuation of RAASi therapy. Historically, a low K^+ diet has also been used where there can be a focus on restriction of fruits and vegetables due to concerns of high K^+ and phosphate levels.[12, 96] However, dietary restrictions that are routinely used as part of clinical practice have been shown in qualitative analyses to impact on the QoL of patients and their carers, and are not supported by rigorous RCTs to be efficacious in the management of HK.[20] Despite recommendations of a low K^+ diet to manage HK in local and international guidelines,[12, 96] this approach is increasingly seen by clinicians as being ineffective at managing HK, as found in recent consensus studies.[97, 98] In a 2022 Delphi consensus study of 520 clinicians from Europe and North America (268 cardiologists and 252 nephrologists), 80% agreed that low K^+ diets are ineffective at managing S–K levels and are counter to a healthy diet, such as the well-recognised Dietary Approaches to Stop Hypertension (DASH), with 91% agreeing that in patients whom dietary restrictions may not be appropriate, the use of K^+ binders may enable a balanced diet.[97]

Therefore, given this ineffectiveness, clinicians are increasingly unlikely to recommend a low K^+ diet (particularly with the advent of K^+ binders) and this should not be considered relevant to the decision problem being addressed in this submission.

As the only current treatment option for patients with HK an S–K ≥5.5–<6.0 mmol/L, the need for discontinuation/down-titration of RAASi therapy due to HK creates an additional burden on QoL by complicating and compromising the management of patients' underlying cardiorenal conditions, such as CKD and HF.[43, 99-101] RAASi therapy has been demonstrated to actively slow eGFR decline to ESRD stages that require dialysis,[94] a therapy well-known to negatively impact patient, family members, and carer QoL[102]

B.1.3.6 *Economic burden*

In addition to the substantial impact of persistent HK on mortality and morbidity, there is also a significant economic burden associated with persistent HK in terms of increased healthcare

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utilisation (from increased number of inpatient and outpatient visits, hospitalisations, and extended hospital length of stay [LoS]), and the costs associated with this resource use.[39, 103-106]

Total healthcare costs are considerably higher in patients with persistent HK (S–K of ≥5.0 mmol/L) compared with those without.[39, 103-106] This difference has been observed across subgroups with different comorbidities, where healthcare costs were higher among patients with CKD, HF and/or diabetes and in those with more recurrent HK events,[39, 103-105, 107, 108] including in an SLR of patients with CKD.[109]

Increased LoS can also be attributed to a reduction in RAASi dosage after an HK event. An analysis of patients with CKD and/or HF who experienced an HK event (S–K of ≥5.0 mmol/L) in Sweden (n=20,824) and Japan (n=7,789) reported that the number of all-cause hospitalised days per patient-year had increased by 8.8 and 9.4 days in Sweden and Japan, respectively, in the six-months post-HK event in patients that reduced RAASi treatment compared to those that maintained RAASi treatment.[40]

Hyperkalaemia in CKD patients and healthcare resource utilisation

The HCRU evidence presented in this submission is aligned to the evidence presented within TA599, which the EAG deemed appropriate.

In the UK, HCRU associated with CKD patients in the year after a first event of HK (S–K ≥5.5 mmol/L) were analysed using CPRD.[110] The proportion of patients using healthcare resources, such as outpatient visits, hospitalisations and laboratory tests, increased by >70% between days 3 and 7 and continued to rise over time (see Figure 4), and compared to the overall population, the mean number of HCRU was greater for patients with CKD with an incident event of HK.[110] In a large observational study analysing medical records across the UK, US, and Japan among patients with CKD stage 3–5 (DISCOVER CKD), it was found that in the CPRD population (n=24,365 matched pairs), patients with HK (S–K of ≥5.5 mmol/L) had higher all-cause hospitalisation rates per 100 person years of 71.0 (95% CI: 69.8–72.3) as compared with the propensity score (PS) matched normokalaemia controls (53.6; 95% CI: 52.7–54.5) estimated during the study period (2008–2015).[111]

Internationally, similar findings were reported. in an observational study of 157,766 patients from the Danish National Patient Registry (DNPR), CKD patients with a first event of HK (S–K of ≥5.0 mmol/L) in Northern Denmark were found to have a substantial increase in hospitalisations in the six months after the occurrence of HK compared to the six months before the event was reported, with a reported HR ratio of 1.72 (95% CI: 1.69–1.74).[107] In an analysis published in 2019 of 17,747 CKD patients from the same database, the overall mean HCRU costs in CKD patients with a first event of HK (S–K of ≥5.0 mmol/L) was €5,518 higher in the six months after the occurrence of the first HK event compared to the six months prior.[70, 107]

In the US, the DISCOVER CKD study found that among patients with CKD stage 3–5 (n=46,420), patients with HK (S–K of ≥5.0 mmol/L) had higher all-cause hospitalisation rates of 101.4 (95% CI: 100.8–102.1) per 100 person years and hospital LoS of 10 (95% CI: 4.0–27) days, compared with hospitalisation rates of 46.8 (95% CI: 46.4–47.3) per 100 person years and all-cause hospitalisation rates of 7.0 (95% CI: 3–15.0) days in the PS matched normokalaemia controls.[111] In an another study of US claims data, among 39,626 PS matched pairs, HK patients (S–K of ≥5.0 mmol/L) were found to have a higher total healthcare cost of $15,606 (95% CI: $14,648–$16,576) in the year after diagnosis, compared with normokalaemia controls. This figure rises to $25,156 (95% CI: $23,529–$26,757) among the matched pairs with comorbid CKD and/or HF.[112] This was further supported by

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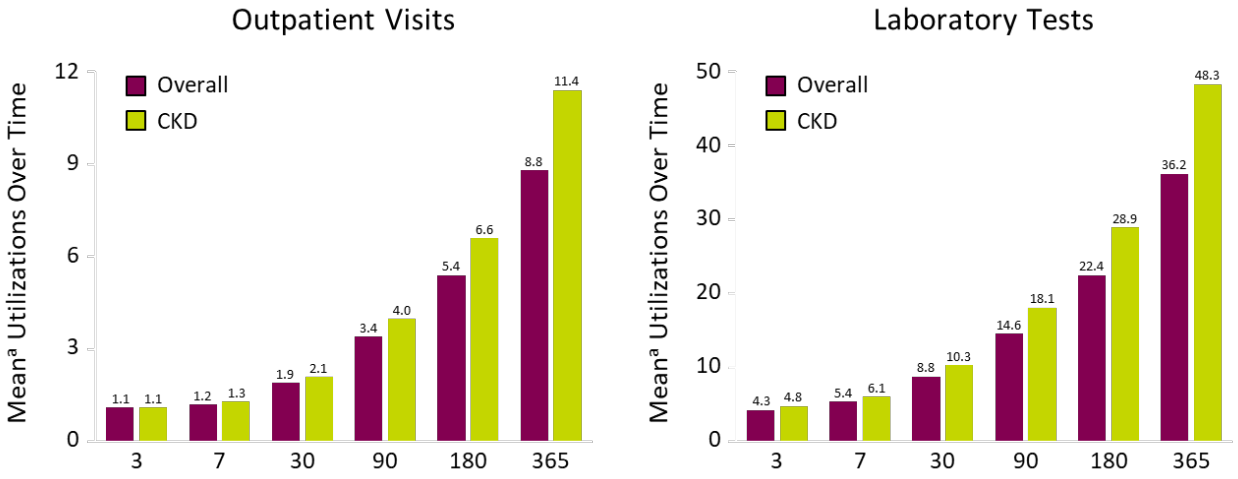
the REVOLUTIONIZE III study, a retrospective cohort study of US Optum claims and electronic health record data evaluating medical costs in adults with stage 3 or 4 CKD. In 4,549 matched pairs, patients with recurrent HK (S–K of ≥5.0 mmol/L) had significantly higher all-cause medical costs over 12 months than the matched normokalaemia cohort ($34,163 vs $15,175).[113]

Figure 4: UK CPRD analysis: mean number of healthcare resource utilisations over time in the overall population and CKD subgroup (n=34,912)



Footnotes: Mean calculated among patients who had experienced ≥1 healthcare resource utilisation.
Abbreviations: CKD: chronic kidney disease; CPRD: Clinical Practice Research Datalink.
Source: Adapted from Qin *et al.* (2017) *(Poster)*[114]

B.1.3.6.1 Hyperkalaemia in HF and healthcare resource utilisation

The HCRU evidence presented in this submission is aligned to the evidence presented within TA599, which the EAG deemed appropriate.

Resource use associated with HF patients with a first event of HK was reported as part of the LABKA study analysing the medical records of patients in northern and central Denmark.[33] Of the 12,340 incident HF patients with HK (S–K of ≥5.0 mmol/L) in this study, the proportion of patients with any acute hospitalisation increased in the 6-month period after the first HK event (73.7%), when compared with the 6-month period before the first HK event (53.3%) (RR: 1.41; 95% CI: 1.38–1.44), as did the proportion of patients admitted to intensive care (increased from 3.3% to 14.9%; RR: 5.29; 95% CI: 4.77–5.86).[33, 115] When compared with matched CKD patients without HK, the HRs for acute hospitalisations (HR: 2.57; 95% CI: 2.48–2.66) and ICU admission (HR: 4.92; 95% CI: 4.44–5.45) 6 months after the HK event were higher for those patients with HK.[115] Increased hospitalisation rates and HCRU have been observed in additional studies in patients with HK (any threshold) and HF/ CKD.[81, 116, 117]

Retrospective analyses comparing 30-day and 1-year resource utilisation and costs in the US between patients with HK (S–K of ≥5.0 mmol/L) and matched patients without HK found that the patients with HK (n=39,626 with 1:1 matched controls) incurred a higher total healthcare cost compared to controls ($4,128; p<0.01) within the first 30 days and one-year ($15,983; p<0.01) of the study period.[118] This figure rises to a higher cost difference of ($8,327; p<0.01) within the first 30 days and across 1 year ($29,574; p<0.01) in HF patients (n=3,789 matched pairs) compared with patients without HF.[118]

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Summary

Due to the increased use of healthcare resources and LoS, HK and the associated reduction in RAASi dosage is linked with considerable direct medical costs via the development of complications, such as cardiorenal outcomes, MACE events, additional disease management and premature mortality. It should be noted that given that the NICE recommended treatment for patients with HK and an S–K ≥5.5–<6.0 has not changed, there is no change to the evidence presented compared with TA599.

B.1.3.7 *Clinical pathway of care*

Patients with HK can be managed via two discrete treatment pathways depending on their S–K levels and where they present to hospital. In general, patients may present with HK in the emergency setting or with persistent HK typically presenting in the chronic setting as part of the patient's ongoing care for CKD or HF. In the chronic setting, HK may be identified in primary care by the GP or may be incidentally diagnosed as part of routine-follow up as part of the management of underlying cardiorenal comorbidities. The use of SZC for the normalisation of S–K in the emergency setting has been previously addressed in TA599.[3]

The care of HK patients comorbid with CKD and/or HF is primarily the responsibility of nephrologists, cardiologists and HF nurses who routinely manage patients with CKD and/or HF (in addition to other comorbidities) as an outpatient. In this setting, the majority of patients (approx. 80%) will be on cardiorenal protective medicines, such as RAASi therapies, and therefore patients' S–K levels will be regularly monitored.[119] UK clinical expert input from three cardiologists and two nephrologists indicated that patients' S–K would be routinely monitored if they are receiving RAASi drugs, and they would want to proactively start treatment of HK at a threshold of ≥5.5 mmol/L to enable RAASi optimisation.[119]

Currently, local guidelines such as the NICE,[4] UKKA,[12] BSH guidelines[47] recommend the down-titration of RAASi and low K^+ diet for patients with persistent HK and with an S–K level of <6.0 mmol/L (patients that are currently not recommended for treatment with SZC under the NICE TA599 guidance).[3] These local guidelines are no longer aligned with updated international guidelines, which have updated the standard care for this population since the introduction of the K^+ binders such as SZC. These updated guidelines include the KDIGO 2024 guidance,[13] which recommends initiating K^+ binders at an S–K level of ≥5.5 mmol/L. Additionally, ESC guidance,[23] the Italian Society of Nephrology guidance,[120] as well as various expert consensus reports that recommend the use of SZC in patients with a confirmed S–K of >5.0 mmol/L to enable patients to benefit from maintaining current doses of RAASi or up-titrating to an optimised RAASi dosage once normokalaemia is achieved.[46, 97, 98, 121]

A summary of the current recommendations from UK clinical experts and the anticipated positioning of SZC is presented below and is summarised in Figure 5.[119]

B.1.3.7.1 HK management in the chronic setting

There are limited treatment pathways for the management of patients with persistent HK in the chronic setting with an S–K of ≥5.5–<6.0 mmol/L. The NICE guidelines for 'Chronic Kidney Disease in Adults: Assessment and Management (NG203)' recommend the following:[4]

- Do not routinely offer a RAASi to people with CKD if their pre-treatment S–K concentration in greater than 5.0 mmol/L, and

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- Stop RAASi if the S–K increases to 6.0 mmol/L or more and other drugs known to promote HK have been discontinued.

The cut-off S–K levels routinely used in clinical practice in England to initiate HK treatment are most relevant to this submission. The diagnosis and treatment initiation threshold of HK is an S–K level of ≥5.5 mmol/L in the chronic setting based on based on UK expert opinion and local clinical guidelines, such as the UK Kidney Associations Clinical Practice Guidelines and the British Society of Heart Failure position statement for HK.[12, 24]

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

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

Furthermore, clinical experts indicated that HK is a significant challenge in clinical practice, and that initiating/optimising RAASi therapy is typically limited by the increased risk of HK; particularly those patients with HF and more advanced stages of CKD. In addition, UK clinical practice now lags behind international standards in the prescription of pharmacological interventions to remove excess K^+.[122] In a recently conducted multinational longitudinal study, TRACK, analysing the initial management decisions of HK patients (n=1,330) in the UK, Spain, Italy, Germany, Italy, and the US, it was found that in the UK clinical setting, HK patients were less likely to be recommended to start/ increase or maintain K^+ binder therapy as compared with Italy, Spain, US, and the overall cohort across all countries, and were more likely to discontinue/down-titrate ACEi/ARB/ARNi treatment compared with Italy, Spain and the US, despite having a higher percentage of patients with an of S–K ≥5.5–<6.0 mmol/L (36%) compared with the overall cohort (27%). Instead, the mainstay treatment option is down-titration/discontinuation of RAASi therapy.[122]

According to interviews conducted with UK clinical experts for the management of CKD to support the partial reappraisal of TA599, in the absence of K^+ binders clinicians would begin down-titrating RAASi for patients with S–K ≥5.5–<6.0 mmol/L.[4] However, even in the absence of formal NICE guidance within this population, clinical experts report treating these patients with K^+ binders, because HF and CKD clinicians recognise the value of optimising and maximising RAASi treatment, more so today than in 2019, and therefore actively look to treat patients in alignment with ESC guidelines.[23] Furthermore, in patients with S–K ≥5.5–<6.0 mmol/L clinicians report proactive use of K^+ binders to facilitate the up-titration/optimisation of RAASi treatment.[23]

In line with updated international guidelines and UK clinical expert opinion, SZC is anticipated to be used as an alternative treatment option to down-titration and discontinuation of RAASi therapy at potassium thresholds of ≥5.5–<6.0 mmol/L in the chronic setting.

B.1.3.7.2 Clinical pathway of care and anticipated positioning of SZC in UK clinical practice

The current pathway of care and anticipated positioning of SZC in the UK for patients with persistent HK with S–K ≥5.5–<6.0 mmol/L is summarised in Figure 5 below.

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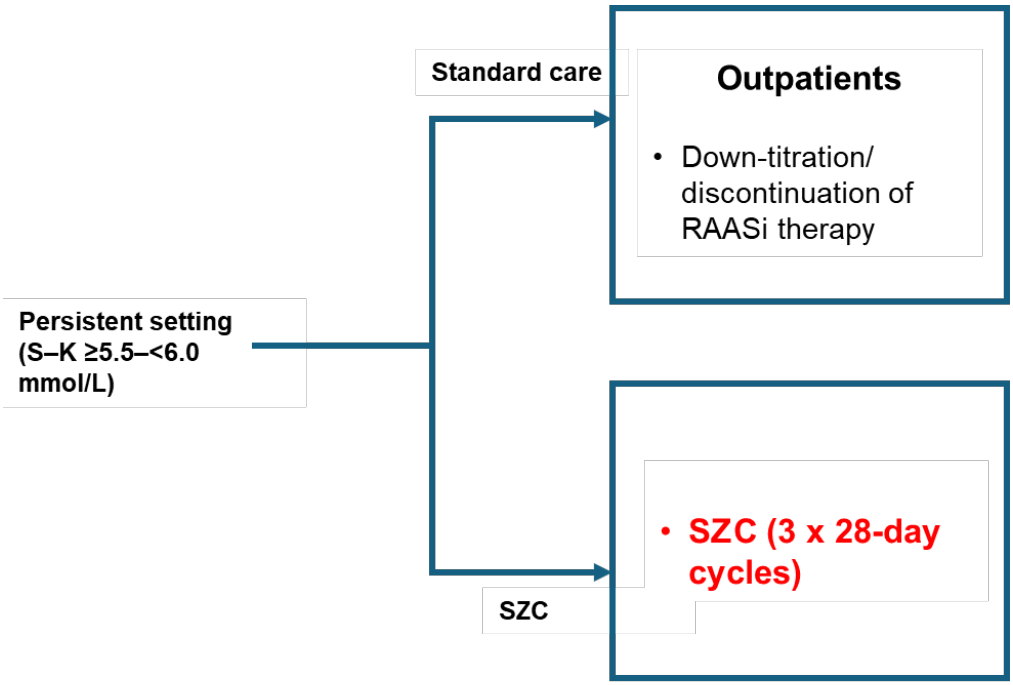
Figure 5: Clinical pathway of care and anticipated positioning of SZC in UK clinical practice



Management of RAASi therapies in the persistent setting (S–K of ≥5.5–<6.0 mmol/L for standard care:

- Initiation of RAASi not recommended if S–K ≥5.0 mmol/L
- Down-titration/ discontinuation of RAASi if S–K ≥5.5–<6.0 mmol/L
- Discontinuation of RAASi if S–K ≥6.0 mmol/L

Footnotes: *As per UK clinical guidelines[4, 47-49]
Abbreviations: K^+: potassium cation; RAASi: renin-angiotensin-aldosterone system inhibitor; SZC: sodium zirconium cyclosilicate.

B.1.3.8 *Equality considerations*

SZC is now licenced in patients who are receiving chronic haemodialysis.[5] This population was not considered in TA599 as SZC did not have a license for this population and these patients were not included in the ZS clinical trial programme. This is a population of high unmet need with evidence that approximately two-thirds of patients undergoing haemodialysis experience an episode of HK with S–K ≥5.5 mmol/L each month after the long interdialytic interval.[123, 124] Compared to those at earlier CKD stages, those undergoing haemodialysis have additional management options to manage S–K, as dialysis can rapidly reduce S–K, primarily depending on dialysate K+ concentration. Therefore, current management of hyperkalaemia can also include management of S–K through changing the dialysis prescription.

Evidence for the safety and efficacy of SZC as a treatment for pre-dialysis HK comes from the DIALIZE study, which was a double-blind, placebo-controlled, phase 3b multicentre study evaluating the use of SZC 5 g once daily on non-dialysis days (titrated towards maintaining normokalaemia over 4 weeks).[6] Of 97 patients receiving SZC, 41.2% met the primary end point of maintaining a pre-dialysis S–K of 4.0–5.0 mmol/L during at least three of four haemodialysis treatments over a 4-week stable-dose evaluation period (without rescue therapy), and were as such deemed treatment responders; compared with 1.0% of 99 patients receiving placebo (P<0.001).[6] As such this study concludes that SZC is an effective and well-tolerated treatment for pre-dialysis HK in patients with end-stage renal disease undergoing adequate haemodialysis. However, patients in DIALIZE were followed for a total of 10 weeks, and as such this study is not suitable for assessing the cost-

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effectiveness of treatment with SZC in patents receiving chronic haemodialysis.[6] Additionally ADAPT, was a prospective, randomised, open-label, 2-by-2 crossover study which investigated the use of SZC alongside a dialysate solution with a higher concentration of K^+ in patients receiving chronic haemodialysis as an alternative to use of dialysate solutions with a lower concentration of K^+. It was found that patients receiving SZC had significantly reduced incidence of recorded atrial fibrillation, of other arrhythmias, and of hypokalaemia after haemodialysis.[125]

SZC has been previously incorporated into the emergency COVID-19 guidelines for the management of dialysis patients in the NICE guidelines (NG160) as an important measure to allow a delay in dialysis until COVID-19 test results are known.[126] The guidelines also recommended the prescription of K^+ binders to allow the frequency of dialysis to be reduced, and reduce the risk of transferring patients undergoing dialysis to a hospital without dialysis facilities.[126] Therefore, SZC has already demonstrated value within the NHS in the dialysis population. Furthermore, recent international clinician consensus-based recommendations have highlighted specific potassium binders should play a role in the management of hyperkalaemia in ESKD.[98]

Those undergoing haemodialysis are overall a high-risk and complex patient group, with a high amount of unmet patient need and health inequality. For this reason, haemodialysis is often highly individualized for each patient, including the need to manage S–K levels between and during dialysis treatments. Whilst for many patients it may be possible to manage S–K levels though modification of dialysate K^+ concentration there will some on haemodialysis where this may not be clinically appropriate , such as those known to be at high risk of hypokalaemia after dialysis. Conversely, whilst dialysis can be effective in managing hyperkalaemia temporarily some patients will remain at risk of persistent HK during the long interdialytic window.

There are a paucity of data for SZC reporting on longer term outcomes suitable for economic modelling, and as such, dialysis patients are not included in the decision problem assessed in this submission. However, restricting access to SZC in this population after previously allowing access in NG160 on the basis of insufficient data to demonstrate cost-effectiveness would preclude the small number of patients from having the option of a safe and effective treatment if it is clinically appropriate for them to have it and would result in inequitable access across the full group of people for which SZC has marketing authorisation. Therefore, AstraZeneca consider it would be reasonable to include this small subset of the total population in any wider positive NICE recommendation to allow individual clinicians to decide on the clinical need of SZC treatment in addition to management of S–K levels as part of haemodialysis treatment.

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B.2. Clinical effectiveness

Summary of clinical evidence previously evaluated by NICE

SZC has previously been evaluated in TA599, and was recommended for use by NICE in patients with life-threatening emergency HK and persistent HK if patients have comorbid CKD (stage 3b–5) or HF with an S–K of ≥6.0 mmol/L.[3]

The clinical effectiveness of SZC was established in TA599 on the basis of the ZS trials. SZC has been demonstrated to be highly effective in reducing S–K levels over the first 48 hours as an acute treatment. Furthermore, sustained benefits with SZC have been demonstrated through a maintenance phase up to 12 months. Within ZS-004, a multicentre, multi-phase, multi-dose, prospective, randomised, double-blind, placebo-controlled maintenance Phase 3 study, the mean S–K value between maintenance phase study days 8–29 was significantly smaller for all of the SZC treatment groups vs the placebo group ($p<0.001$), demonstrating sustained reductions during days 8–29 in the active SZC treatment arms.[7, 127-130] Furthermore, in ZS-005, an open-label extension Phase 3 study for study ZS-004, normokalaemia was maintained over 12 months (extended dosing phase), with 88.4% (95% CI: 85.7–90.8) and 98.8% (95% CI: 97.6–99.5) of patients reporting a mean S–K value ≤5.1 mmol/L and ≤5.5 mmol/L respectively from month 3 to month 12.[7, 131] Additional supportive studies (ZS-002 and ZS-003) further support the effectiveness of SZC in achieving S–K normalisation.[7, 132-134]

In the original appraisal of SZC, uncertainties were raised by NICE and the EAG which meant that the cost-effectiveness of SZC in the treatment of patients with persistent HK and an S–K of ≥5.5–<6.0 mmol/L could not be established.[3] The main uncertainties raised were that:[3]

- There was a paucity of clinical data linking S–K levels and long-term clinical outcomes (mortality, hospitalisations, MACE).
- Clinical evidence did not adequately demonstrate that SZC usage allows reinitiation, up-titration or maintenance of optimum RAASi dosage.
- Clinical evidence did not adequately demonstrate the relationship between RAASi dosage and long-term clinical outcomes.

Changes since the 2019 TA599 NICE evaluation

The association between elevated S–K and/or RAASi down-titration and adverse clinical outcomes, as well as the capacity of K^+ binder therapy to normalise S–K levels and enable optimised use of RAASi, is well accepted in clinical guidelines.[13, 21, 22] Following the regulatory approval and reimbursement of SZC for the treatment of HK in the UK and internationally, it has been possible to collect real-world data on SZC usage to further investigate these uncertainties. To this end, two real-world evidence (RWE) studies were conducted by AstraZeneca to specifically address the uncertainties raised in TA599: SPARK[29] and a re-analysis of the ZORA study.[135, 136] This is aligned with NICE's RWE framework which outlines the importance of using real-world data to resolve gaps in knowledge and drive forward access to innovations for patients.[137]

SPARK

The SPARK study was initiated specifically to address the concerns raised by NICE in TA599 and is a UK-specific, retrospective, observational, longitudinal study conducted using secondary data extracted from the CPRD and linked datasets.[29] This study adds to those conducted previously

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which have found a relationship between increased S–K levels and the incidence of long-term clinical outcomes by adjusting for multiple additional confounders, including RAASi usage which was raised as a key concern during decision-making in TA599, and exploring the potential impact of any remaining unknown confounders.[3] The incidence rate ratios (IRRs) obtained from the SPARK study demonstrate that in patients with HF or CKD treated with either SZC or standard care there is a clear 'U-shaped' relationship between S–K and hospitalisation, MACE, and mortality, as stratified by S–K levels and eGFR, and adjusted by comorbidities and co-medications, including RAASi usage.[29] These results are consistent with those presented previously,[30, 31, 34, 81, 82, 86]and are compelling evidence that this association is not due to any unidentified confounder. However in addition, e-values were calculated to quantify the strength of the unmeasured confounder needed to reverse the observed relationships.[29]

ZORA

The ZORA study is used to address the concerns raised by NICE in TA599 that SZC had not adequately demonstrated that SZC usage allows reinitiation, up-titration or maintenance of optimum RAASi dosage, irrespective of S–K levels.[3] The study was an observational, cohort study programme performed using secondary data extracted from health registers and hospital medical records from the US, Japan, and Spain, where SZC is available for those with persistent HK and S–K ≥5.5–<6.0 mmol/L.[39, 135] The study investigated real-world usage of RAASi medication in patients with CKD and/or HF who are experiencing HK.[135] An additional subgroup analysis provides the proportions of persistent HK patients that down-titrate or discontinue RAASi dosage after 180 days since the incident HK event at each S–K level after receiving SZC treatment or standard care.[136] The proportion of patients who remained on any RAASi therapy (stabilised or up-titrated) at 180 days were consistently higher in the SZC cohorts than in the no K^+ binder cohorts across all countries. This result was consistent across S–K categories.[135]

RAASi Systematic Literature Review (SLR)

An additional SLR update was conducted to identify RCT evidence on RAASi treatment in CKD and HF to address the RAASi treatment-related uncertainties raised in TA599.[3] The 2024 update identified 100 publications published since 2019 reporting on clinical studies that met the inclusion criteria. Of these, 69 were SLRs (62 were full publications, 7 were conference abstracts), the remaining 31 included studies were RCTs (27 full publications, 4 conference abstracts).[138] Of the 31 included RCT publications, 15 were primary publications, with a further 16 secondary reports identified. Of the 15 RCTs identified, 8 were in HF and 7 in CKD. Further, 4 of the 15 RCTs were RAASi down-titration/discontinuation studies (2 in CKD and 2 in HF); the remaining 11 focused on long-term outcomes with RAASi versus placebo, with 5 in CKD and 6 in HF. Of the 69 SLRs identified, 38 were in HF and 31 in CKD. Of the 69 SLRs, 7 covered RAASi down-titration/discontinuation, with 5 in HF and 2 in CKD. The remaining 62 SLRs focused on long-term outcomes with RAASi versus placebo, with 33 in HF and 29 in CKD.

This SLR update provides a comprehensive overview of the latest research relevant to the use of RAASi in patients with CKD or HF in terms of long-term effects on CV events, mortality, and hospitalisation and also markers of disease progression (e.g. LVEF, NYHA functional status for HF and change in eGFR and progression to ESRD for CKD). Evidence on the impact of RAASi discontinuation or down-titration was also sought. Aligned with the findings of the previous SLR, the identified evidence suggests that RAASi is an effective treatment for patients with HF and CKD with findings consistently showing benefits across assessed outcomes. The need to manage HK which may develop in patients treated with RAASi may involve down-titration or

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discontinuation. There is less SLR and RCT evidence for the effect that down-titration or discontinuation may have on HF or CKD patients, particularly regarding effects on S–K.

B.2.1 *Identification and selection of relevant studies*

An SLR was conducted in April 2018, and subsequently updated in June 2024, to identify all relevant clinical evidence for the efficacy and safety of SZC for patients with persistent HK.

The original SLR (up to 2018) identified 73 relevant publications across 13 RCTs, whilst the 2024 update identified 38 publications relating to 22 RCTs. Of these, only citations identified relating to three RCTs (ZS-002, ZS-003, ZS-004) were considered relevant to the decision problem of the current submission. Publications relating to two further RCTs (ZS-004E, ZS-005), which are AstraZeneca studies of SZC, were also identified in searches but were excluded in the initial SLR. Three abstracts relating to ZS-005 were excluded on the basis of being congress proceedings over three years old,[139-141] and a publication by Roger *et al.* (2019) was excluded as it reported on the open-label extension of the HARMONIZE study and therefore did not meet the RCT inclusion criterion.[142]

Full details of the SLR methodology used to identify and select the clinical evidence relevant to the technology being appraised is presented in Appendix D.

SZC is currently recommended for use by NICE in patients with life-threatening emergency HK and persistent HK if patients have comorbid CKD (stage 3b–5) or HF with an S–K of ≥6.0 mmol/L.

As the clinical efficacy of SZC in normalising S–K has already been established in the original appraisal and no new RCTs for SZC investigating clinical efficacy have been conducted, no new clinical evidence is presented for the efficacy of SZC.[3] The focus of this reappraisal is to present evidence addressing the uncertainty previously identified in TA599[3] to demonstrate the benefit of expanding reimbursement of SZC to persistent HK patients with an S–K of ≥5.5–<6.0 mmol/L. Clinical evidence for the efficacy of SZC from RCTs previously presented in TA599 is presented in Appendix O.

The uncertainties raised by NICE and the EAG were primarily related to a lack of long-term data for SZC, due to SZC's recent introduction to the market. However, as SZC has now been used in clinical practice since 2019, a considerable amount of real-world data now exists. Therefore, to address the uncertainties raised in TA599, two real-world evidence (RWE) studies were conducted by AstraZeneca: SPARK and a re-analysis of the ZORA study. The approach of utilising RWE to resolve gaps in knowledge and drive forward access to innovations for patients is consistent with NICE's transformation plan.[143]

The SPARK study analysed the relationship between increased S–K levels and the incidence of long-term clinical outcomes in patients with HF or CKD treated with either SZC or standard care.[29] The inclusion of the SPARK study in this submission aims to address the uncertainty that literature sources citing observational studies used to provide the relationship between elevated S–K and long-term outcomes did not adjust for RAASi usage and did not have a method to adjust for unknown confounders.[3] The IRRs obtained from the SPARK study demonstrate the relationship between S–K and hospitalisation, MACE, and mortality, as stratified by S–K levels and eGFR, and adjusted by co-medications, comorbidities and RAASi usage.[29] In addition, e-values were calculated to quantify the strength of the unmeasured confounder needed to reverse the observed relationships.[29]

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The ZORA study investigated real-world usage of RAASi medication in patients with CKD and/or HF who are experiencing HK.[135] Inclusion of the ZORA re-analysis in this submission aims to address the uncertainty around the lack of evidence demonstrating that SZC allows a greater proportion of patients to receive guideline dosages of RAASi drugs compared with those not treated with SZC, irrespective of S–K levels.[3] The additional subgroup analysis of the multi-national observational ZORA study addresses this evidence gap by providing the proportions of persistent HK patients that down-titrate or discontinue RAASi dosage after 180 days since the incident HK event at each S–K level, after receiving SZC treatment or standard care.[136] Further details on the SPARK and ZORA studies are provided in Sections B.2.3.1 and B.2.3.2, respectively. A summary of the uncertainties addressed in the current appraisal is provided in Table 4.

Furthermore, an additional SLR was conducted to identify RCT and SLR evidence on RAASi treatment in CKD and HF to address the RAASi treatment-related uncertainties raised in TA599. The 2024 update identified 100 publications published since 2019 reporting on clinical studies that met the inclusion criteria. Of these, 69 were SLRs (62 were full publications, 7 were conference abstracts), the remaining 31 included studies were RCTs (27 full publications, 4 conference abstracts). Of the 114 publications identified for inclusion, 46 reported on RCTs and 68 were SLRs.[138] Of the 31 included RCT publications, 15 were primary publications, with a further 16 secondary reports identified. Of the 15 RCTs identified, 8 were in HF and 7 in CKD. Further, 4 of the 15 RCTs were RAASi down-titration/discontinuation studies (2 in CKD and 2 in HF); the remaining 11 focused on long-term outcomes with RAASi versus placebo, with 5 in CKD and 6 in HF. Of the 69 SLRs identified, 38 were in HF and 31 in CKD. Of the 69 SLRs, 7 covered RAASi down-titration/discontinuation, with 5 in HF and 2 in CKD. The remaining 62 SLRs focused on long-term outcomes with RAASi versus placebo, with 33 in HF and 29 in CKD.

This SLR update provides a comprehensive overview of the latest research relevant to the use of RAASi in patients with CKD or HF in terms of long-term effects on CV events, mortality, and hospitalisation and also markers of disease progression (e.g. LVEF, NYHA functional status for HF and change in eGFR and progression to ESRD for CKD). Aligned with the findings of the previous SLR, the identified evidence suggests that RAASi is an effective treatment for patients with HF and CKD, with findings consistently showing benefits across assessed outcomes. Patients treated with RAASi may develop HK, leading to the need for RAASi down-titration or discontinuation; evidence on the impact of RAASi discontinuation or down-titration was also sought in the SLR. Less SLR and RCT evidence was identified for the effect that RAASi down-titration or discontinuation may have on HF and CKD patients than the effectiveness of RAASi treatment, particularly regarding effects on S–K.

Table 4: List of uncertainties in TA599 and approach taken in the current appraisal

Uncertainty	TA599	Current appraisal	Rationale for approach
Association between S–K and long-term outcomes (MACE, hospitalisation, and mortality)	Evidence was obtained from a literature search (Luo *et al.*[81] and Desai *et al.*[108] for the CKD and HF populations, respectively). No direct evidence was generated by AstraZeneca	SPARK,[29] an observational study using data from CPRD has been conducted by AstraZeneca to provide high-quality evidence of the association between S–K and long-term outcomes	The observational studies presented in TA599 (Luo *et al.*[81] and Desai *et al.*[108]) did not adjust for RAASi usage or adjust for unmeasured confounders, and thus the independence of the relationship between S–K and long-term outcomes could not be reliably established. SPARK provides IRRs which demonstrate the relationship between S–K and

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Uncertainty	TA599	Current appraisal	Rationale for approach
			hospitalisation, MACE, and mortality, as stratified by S–K levels and eGFR, and adjusted by co-medications, comorbidities and RAASi usage.[29] In addition, e-values were calculated to quantify the strength of the unmeasured confounder needed to reverse the observed relationships[29]
Effectiveness of SZC treatment in maintaining RAASi therapy in HK patients	No evidence was presented by AstraZeneca as this was not measured as part of the clinical trial programme	A post-hoc analysis of the multi-national observational study ZORA has been conducted by AstraZeneca to provide high-quality evidence for the effectiveness of SZC in facilitating patients to maintain RAASi treatment.[135, 136]	The evidence package in TA599 did not present any evidence to adequately demonstrate that SZC usage modified RAASi treatment patterns independent of S–K levels, as such the relationship was assumed to not exist.[3] To provide evidence that treatment with SZC enables a greater proportion of patients to receive guideline dosages of RAASi treatment compared with untreated patients, irrespective of S–K levels, a subgroup analysis of the multinational observational study ZORA was conducted. ZORA provides evidence for the proportion of persistent HK patients that down-titrate or discontinue RAASi treatment in the 180 days following incident HK event based on whether the patient received SZC or not. These results have been stratified by S–K level[136]
The relationship between RAASi treatment dosages and long-term treatment outcomes	Evidence was obtained from a literature search (Xie *et al.*[94] for mortality and CV event risk in the CKD population and Flather *et al.*[144] for hospitalisation risk in the HF population). No direct evidence was generated by AstraZeneca	An SLR was conducted to investigate long-term outcomes in patients discontinuing/ down-titrating RAASi therapy (see Appendix K)	An SLR was conducted to identify published literature reporting on these outcomes of interest (see Appendix K). Meta-analyses identified by the SLR reported outcomes for patients with CKD. RAASi discontinuation was associated with significantly increased risks of CV events, all-cause mortality (including in patients discontinuing due to HK) and MACE.[67, 68] A meta-analysis (Siddiqi 2022) reporting outcomes for patients with HF reported that, compared with patients that continued their therapy following an HK event, treatment discontinuation was associated with a statistically significant increase in all-cause

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Uncertainty	TA599	Current appraisal	Rationale for approach
			mortality.[145] Among HF patients receiving lower doses of RAASi therapy (akin to a down-titration), two publications reported statistically significant increases in all cause mortality.[64, 65] One of these studies, Chen *et al.* (2023) reported significantly lower odds of all-cause mortality with high-dose (mean daily dose ≥200 mg) versus low-dose (mean daily dose <200 mg) sacubritril/valsartan for patients with left ventricular ejection fraction (LVEF) <40% (OR: 0.23; 95% CI: 0.11–0.47)[65]

Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure; HK: hyperkalaemia; IRR: incidence rate ratio; MACE: major adverse cardiovascular events; LVEF: left ventricular ejection fraction; OR: odds ratio; S-K: serum potassium; SLR: systematic literature review; SZC: sodium zirconium cyclosilicate.

B.2.2 *List of relevant clinical effectiveness evidence*

As previously noted, the clinical effectiveness of SZC was established in TA599 on the basis of the ZS trials and therefore no new clinical evidence is presented for the efficacy of SZC.[3] A summary of clinical evidence for SZC from clinical trials presented in TA599 is provided below and full details are provided in Appendix O. However, the submission focuses on the presentation of real-world clinical evidence to address key uncertainties from TA599,[3] as detailed in Sections B.2.3.1 and B.2.3.2.

B.2.2.1 *Summary of clinical evidence from clinical trials*

Table 5. Clinical effectiveness evidence for study ZS-002

Study	**ZS-002, NCT01493024, Ash *et al.*, 2015 [9]**				
Study design	Multicentre, prospective, randomised, double-blind, placebo- controlled, Phase 2 study with three dose cohorts				
Population	Patients aged >18 years with stable Stage 3 CKD, an estimated glomerular filtration rate of 30–60 ml/min per 1.73 m^2 estimated by CKD Epidemiology Collaboration (CKD-EPI) equation, serum potassium levels between 5.0 and 6.0 mEq/L and with the ability to have repeated blood draws or effective venous catheterisation				
Intervention(s)	Sodium zirconium cyclosilicate				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes	X	**Indicate if trial used in the economic model**	Yes	
	No			No	X
Rationale if trial not used in model	Dose-escalating study with only 24 patients receiving a licensed dose of SZC (10 g)				

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Reported outcomes specified in the decision problem	• S–K levels • Time to normalisation • AE of treatment
All other reported outcomes	• Changes from baseline for sodium, magnesium, calcium, bicarbonate and blood urea nitrogen • Serum calcium, magnesium, sodium, blood urea nitrogen, creatinine, bicarbonate • Urinary sodium, potassium, creatinine excretion, • Urinary sediment and urea nitrogen excretion

Abbreviations: AE: adverse event; CKD: chronic kidney disease; HK: hyperkalaemia; S–K: serum potassium; SZC: sodium zirconium cyclosilicate.

Table 6: Clinical effectiveness evidence for Study ZS-003

Study	**ZS-003, NCT01737697, Packham *et al.*, 2015 (ZS-003) [7, 132-134]**				
Study design	Multicentre, two-stage, double-blind, placebo-controlled, Phase 3 study				
Population	Patients aged >18 years of age with an i-STAT potassium value between 5.0 and 6.5 mmol/L at screening and the ability to have repeated blood draws or effective venous catheterisation				
Intervention(s)	Sodium zirconium cyclosilicate				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	**Yes**	X	**Indicate if trial used in the economic model**	**Yes**	X
	No			**No**	
Rationale if trial not used in model	N/A				
Reported outcomes specified in the decision problem	• S–K levels • Time to normalisation • AE of treatment				
All other reported outcomes	• Changes from baseline for sodium, magnesium, calcium, bicarbonate and blood urea nitrogen • The proportion of patients receiving RAASi is reported within the patient baseline characteristics				

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

Table 7: Clinical effectiveness evidence for Study ZS-004

Study	**ZS-004, NCT02088073, Kosiborod *et al.*, 2014 (004) [7, 127-130]**				
Study design	Multicentre, multi-phase, multi-dose, prospective, randomised, double-blind, placebo-controlled maintenance Phase 3 study				
Population	Adult patients aged >18 years of age with an i-STAT potassium value ≥5.1 mmol/L				
Intervention(s)	Sodium zirconium cyclosilicate				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	**Yes**	X	**Indicate if trial used in the economic model**	**Yes**	X
	No			**No**	

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Study	ZS-004, NCT02088073, Kosiborod *et al.*, 2014 (004) [7, 127-130]
Rationale if trial not used in model	N/A
Reported outcomes specified in the decision problem	• S–K levels • Use of RAASi therapy • Time to normalisation • AE of treatment
All other reported outcomes	• Changes from baseline for sodium, magnesium, calcium, bicarbonate and blood urea nitrogen

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

Table 8: Clinical effectiveness evidence for Study ZS-004E

Study	ZS-004E [7, 131]				
Study design	An open-label extension Phase 3 study on HARMONIZE, study ZS-004				
Population	All patients who completed Study ZS-004 and had an i-STAT potassium value between 3.5 and 6.2 mmol/L, inclusive, or who prematurely discontinued the Extended Dosing Phase of Study ZS-004 due to hypokalaemia or HK and had a mean i-STAT potassium value between 3.5 and 6.2 mmol/L were eligible to participate in Study ZS-004E				
Intervention(s)	Sodium zirconium cyclosilicate. No mandated dietary restrictions or changes in RAASi therapy were required				
Comparator(s)	None				
Indicate if trial supports application for marketing authorisation	**Yes**	X	**Indicate if trial used in the economic model**	**Yes**	
	No			**No**	X
Rationale if trial not used in model	The ZS-005 study provides more robust long-term data due to the limitations in the study design of this extension study. As explained in the original submission TA599,[3] a meta-analysis is not feasible.				
Reported outcomes specified in the decision problem	• S–K levels • Time to normalisation • AE of treatment				
All other reported outcomes	• Changes from baseline for sodium, magnesium, calcium, bicarbonate, blood urea nitrogen, creatinine, phosphorus, and serum aldosterone				

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

Table 9: Clinical effectiveness evidence for Study ZS-005

Study	ZS-005 [139-141]
Study design	Prospective, international, open-label, single-arm Phase 3 study
Population	Adult outpatients (aged ≥18 years) with HK (defined as an S–K ≥5.1 mmol/L)
Intervention(s)	Sodium zirconium cyclosilicate. No mandated dietary restrictions or changes in RAASi therapy were required

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Study	ZS-005 [139-141]				
Comparator(s)	None				
Indicate if trial supports application for marketing authorisation	**Yes**	X	**Indicate if trial used in the economic model**	**Yes**	X
	No			**No**	
Rationale if trial not used in model	N/A				
Reported outcomes specified in the decision problem	• S–K levels • Use of RAASi therapy • Time to normalisation • AE of treatment				
All other reported outcomes	• Changes from baseline for sodium, magnesium, calcium, bicarbonate and blood urea nitrogen				

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

B.2.2.2 *Summary of clinical evidence from observational studies*

As noted above and agreed with NICE, the focus of this submission is in presenting additional evidence to address the specific uncertainties raised in the TA599.[3] Clinical evidence from two observational studies is presented, SPARK and a re-analysis of the ZORA study.[29, 135] Key details for the studies are presented below.

Table 10: Clinical effectiveness evidence for SPARK

Study	SPARK [29]				
Study design	UK-specific retrospective, observational, longitudinal study using secondary data extracted from Clinical Practice Research Datalink (CPRD) linked datasets (CPRD Aurum, CPRD GOLD, Hospital Episode Statistics (HES) APC, and Office for National Statistics [ONS]). Data were collected for patients diagnosed between 1st January 2016–1st January 2019.				
Population	Patients aged ≥18 years in the UK with a recorded S–K measurement, a diagnosis of HK, or a prescription of K^+ binder in their medical records from primary or secondary care. For the analysis of clinical characteristics and treatment patterns for CKD and/or HF patients with S–K ≥5.0 mmol/L (objective 3; Table 12), propensity score matching or weighting were applied to balance cohorts on baseline characteristics, including covariates on the outcomes investigating the effects of K^+ binder treatment on RAASi therapy modification.				
Intervention(s)	No intervention				
Comparator(s)	None				
Indicate if trial supports application for marketing authorisation	Yes		**Indicate if trial used in the economic model**	Yes	X
	No	X		No	

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Rationale if trial not used in model	NA
Reported outcomes specified in the decision problem	• Use of RAASi therapy • Hospitalisations • Major adverse cardiac events (MACE) • Mortality • Kidney function decline
All other reported outcomes	N/A

Abbreviations: AE: adverse event; CPRD: Clinical Practice Research Datalink; HES: Hospital Episode Statistics; HK: hyperkalaemia; MACE: major adverse cardiac events; ONS: Office for National Statistics; RAASi: renin-angiotensin-aldosterone system inhibitors; S–K: serum potassium.

Table 11: Clinical effectiveness evidence for ZORA

Study	**ZORA** [135]				
Study design	Observational, longitudinal cohort study conducted using secondary data extracted from health registers and medical claims data in the US (Optum's Clinfomatics Data Mart), Japan (Medical Data Vision [MDV]), and Spain (BIG-PAC). Data were collected between July 2019–December 2022 for the US, May 2020–December 2022 for Japan, and June 2021–December 2022 for Spain. Patients were identified as one of two cohorts: SZC receivers and no K^+ binder. Both cohorts were followed for 180 days after the index HK event for outcomes assessment. An additional subgroup analysis was conducted to stratify study outcomes by S–K levels (≥5.0–<5.5 mmol/L, ≥5.5–<6.0 mmol/L, and ≥6.0 mmol/L) to obtain data for the ≥5.5–<6.0 mmol/L subgroup using data from the US and Japan. This analysis used data collected from July 2019–March 2024 for the US and May 2020–April 2024 for Japan to increase the sample size in the K^+ strata and ensure that the most contemporary data available at the time of analysis were captured.				
Population	In both patient cohorts, patients aged ≥18 years with a diagnosis of CKD and/or HF, and an outpatient prescription for RAASi medication within six months prior to indexing were eligible for inclusion. Patients receiving haemodialysis at baseline were excluded. For the SZC cohort, patients were required to have at least 120 days of continuous SZC treatment. Patients in both cohorts were required to have at least 180 days of available follow-up data to allow for outcome assessment. Propensity score matching was applied to balance the baseline characteristics and covariates between the cohorts.				
Intervention(s)	Sodium zirconium cyclosilicate				
Comparator(s)	No prescribed K^+ binder medication (controls)				
Indicate if trial supports application for marketing authorisation	Yes		**Indicate if trial used in the economic model**	Yes	X
	No	X		No	
Rationale if trial not used in model	The primary reported outcomes of the study published by Rastogi *et al*.[135] are not used to inform the economic model. The Rastogi study analysed the likelihood of maintaining RAASi therapy following an HK				

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Study	ZORA [135]
	event in those treated with SZC or no K^+ binder, however this analysis did not stratify by S–K levels, and most of the patient population had missing data on laboratory S–K values.[135] As such, an ad-hoc re-analysis of the ZORA study was conducted to provide evidence on the decision problem population, by stratifying patient populations based S–K values, using more current datasets from the US and Japan, to provide a more complete recording of S–K levels.[136]
Reported outcomes specified in the decision problem	• Discontinued RAASi • Down-titrated RAASi • Stabilised RAASi • Up-titrated RAASi These outcomes were aggregated into: • Maintained RAASi • Reduced RAASi
All other reported outcomes	N/A

Abbreviations: CKD: chronic kidney disease; HF: heart failure; HK: hyperkalaemia; K^+: potassium cation; MACE: major adverse cardiac events; MDV: Medical Data Vision; ONS: Office for National Statistics; RAASi: renin-angiotensin-aldosterone system inhibitors; SZC: sodium zirconium cyclosilicate.

B.2.3 *Clinical evidence from observational studies*

B.2.3.1 *SPARK*

In the assessment of TA599, NICE raised concerns relating to the evidence presented to demonstrate the association between persistent HK and adverse clinical outcomes, as the studies presented did not adjust for RAASi usage or adjust for unmeasured confounders, and thus the independence of the relationship between S–K and long-term outcomes could not be reliably established. To address these concerns, AstraZeneca have conducted the SPARK study. SPARK investigates the relationship between S–K and hospitalisation, MACE, and mortality, stratified by S–K levels and eGFR. In line with the NICE RWE framework and to address the concerns raised by NICE in TA599, the SPARK study took steps to minimise the risk of bias, and adjusted by an additional 30+ confounders than the studies used to inform TA599, including co-medications, comorbidities and RAASi usage.[29] In addition, to explore the likely effect of any residual confounding, e-values were calculated to quantify the strength of the unmeasured confounder needed to reverse the observed relationships.[29] More broadly, the SPARK study used data from CPRD and as such the study can be considered to have used high-quality, granular data from a population that is representative of the general UK population.[146]

B.2.3.1.1 Study design

SPARK was a UK-specific, retrospective, observational, longitudinal study conducted using secondary data extracted from the CPRD and linked datasets.[29] This study included data from patients aged ≥18 years in the UK with a recorded S–K measurement, a diagnosis of HK, or a prescription for a K^+ binder in their medical records from primary or secondary care between 1st January 2016 and 1st January 2019.[29] An overview of the study design is provided in Figure 6. Patients were followed until exit from the database (loss to follow-up), death, or end of database

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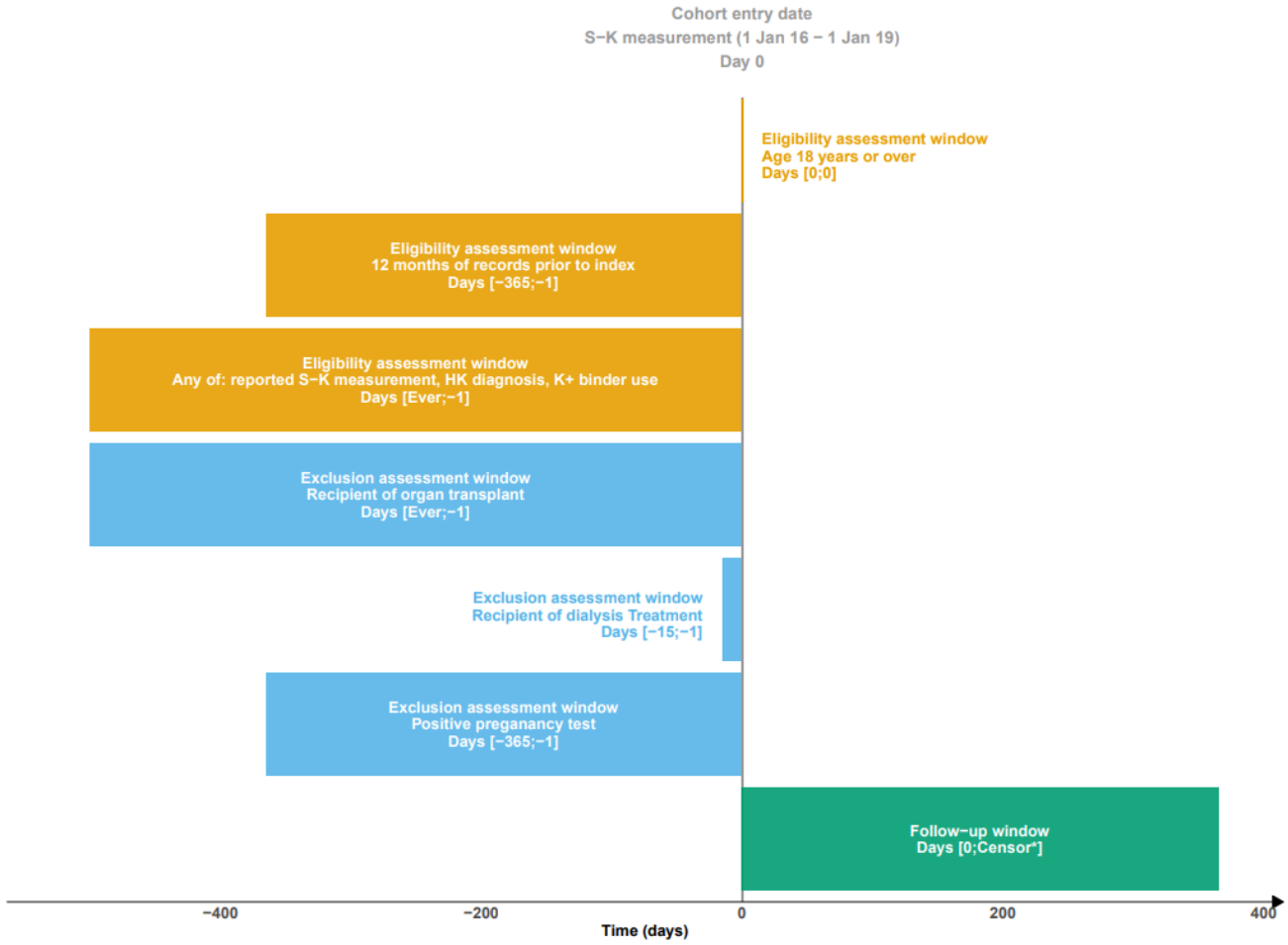
period (last data collection date).[29] Baseline data applied a lookback period of 12 months and laboratory data from the date nearest to index date during the lookback period was utilised.[29]

Figure 6: Schematic of the SPARK study design



Footnotes: *Earliest of: end of continuous enrolment, last date of available data or date of death (where data on death are available).

B.2.3.1.2 Data source

CPRD contains primary care records (primary care consultations, prescriptions issued by GPs plus in-hospital high-cost drugs, laboratory tests ordered in primary care) for 60 million patients, of which 18 million are currently registered active patients and is considered to be broadly representative of the general UK population in terms of age, sex, and ethnicity.[146, 147] Data from CPRD datasets (Aurum and GOLD) were linked to the Office for National Statistics (ONS) death registration database, and the Hospital Episodes Statistics (HES) database, which contains information on all admissions, inpatient stays, outpatient appointments, and emergency episodes recorded within NHS hospitals in England.[29] Eligible patients and corresponding patient characteristics were identified using Systematised Medical Nomenclature for Medicine–Clinical Terminology (SNOMED-CT), read codes, and International Classification of Diseases (ICD)-10/ICD-9 codes.[29] A summary of patient attrition is presented in Section B.2.3.1.4.

B.2.3.1.3 Study objectives and outcomes measures

The SPARK study had three primary objectives: to describe patient characteristics and treatment patterns of adults with an S–K value and/or an HK diagnosis, to investigate the association between

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S–K levels and clinical outcomes for these patients, and to demonstrate the ability to maintain optimal RAASi dose by S–K level through the use of SZC.[29] Further details on the SPARK study objectives are provided in Table 12.[29]

Table 12: SPARK study objectives and outcomes

Objectives	Study Population	Outcomes
Objective 1: To describe patient characteristics and treatment patterns stratified by demography, S–K levels, and comorbidities at baseline	Adults with an S–K value and/or HK diagnosis	• Distribution of disease occurrence and characteristics of patients • Treatment patterns with number and type of RAASi medication
Objective 2: To describe the association between S–K levels and clinical outcomes (MACE, all-cause death, all-cause hospital admissions, eGFR decline)	Adults with an S–K value and/or HK diagnosis	Outcome described among all incident CKD and HF patients: • Kidney function decline • MACE (CV deaths, myocardial infraction, stroke) • Mortality (all-cause, or CV, HF or CKD related) • Hospitalisations • Primary care and outpatients appointments
Objective 3: To demonstrate the ability to maintain optimal RAASi dose by S–K level through the use of SZC (i.e. quantify and compare SZC users and non-users who discontinue, down-titrate, and/or return to optimal RAASi dose, and time to return to optimal dose)	Adults with S–K ≥5.0 mmol/L and comorbid CKD and/or HF before their qualifying HK event (index date), who were on RAASi treatment within specified time window	• Patterns of RAASi usage (discontinuation, down-titration, and return to maximum dose after discontinuation) in the SZC and standard care cohorts

Abbreviations: CKD: chronic kidney disease; CV: cardiovascular; eGFR: estimated glomerular filtration rate; GDMT: guideline-directed medical therapy; HF: heart failure; MACE: major adverse cardiovascular events; RAASi: renin-angiotensin-aldosterone system inhibitors; S–K: serum potassium.

B.2.3.1.4 Patient eligibility

Eligibility criteria for the SPARK study are presented in Table 13.[29]

Table 13: Overview of inclusion and exclusion criteria for the SPARK study

Inclusion criteria	Exclusion criteria

For all objectives:
• Patients aged ≥18 years old at index date
• At least 12 months of records before index date
  ○ For primary objective 3, at least 90 days of follow-up post-index
For primary objectives 1 and 2:
• Records of any of the following before 1st January 2019:
  ○ A reported S–K measurement
  ○ HK, including either a diagnosis of HK (SNOMED-CT, read code, ICD-10 E87.5) in any position recorded in inpatient hospital setting (including emergency department)
  ○ K^+ binder use
• An S–K measurement between 1st January 2016–1st January 2019
For primary objective 3:
	• Patients currently treated with dialysis (14 days prior to index date)
	• Organ transplant (prior ever)
	• Pregnancy in the 12 months prior to index date

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Inclusion criteria	Exclusion criteria

• Either of the following between 1st January 2004–31st December 2023:
  ○ HK, including either a diagnosis of HK (SNOMED-CT, read, ICD-10 E87.5) in any position recorded in inpatient hospital setting (including emergency department)
  ○ K^+ binder use
• A reported S–K measurement of ≥5.0 mmol/L nearest to HK diagnosis or K^+ binder initiation
• A prior diagnosis of CKD and/or HF
• On RAASi treatment within 120 days prior to index date and up to 180 days after index date	

Abbreviations: CKD: chronic kidney disease; HF: heart failure; hHF: heart failure hospitalisation; HK: hyperkalaemia; ICD: International Classification of Diseases; K^+: potassium cation; RAASi: renin-angiotensin-aldosterone system inhibitors; S–K: serum potassium; SNOMED-CT: Systematized Nomenclature of Medicine - Clinical Terms.

The index date definitions used in the SPARK study varied depending on the objective under investigation. The index date was defined as:[29]

- The date of the latest S–K measurement in the specified period (1st January 2016–1st January 2019) for primary objectives 1 and 2
- The date of the closest S–K measurement before an HK diagnosis or the first prescription for a K^+ binder for primary objective 3

Figure 7 presents a summary of the patient attrition for the SPARK study.

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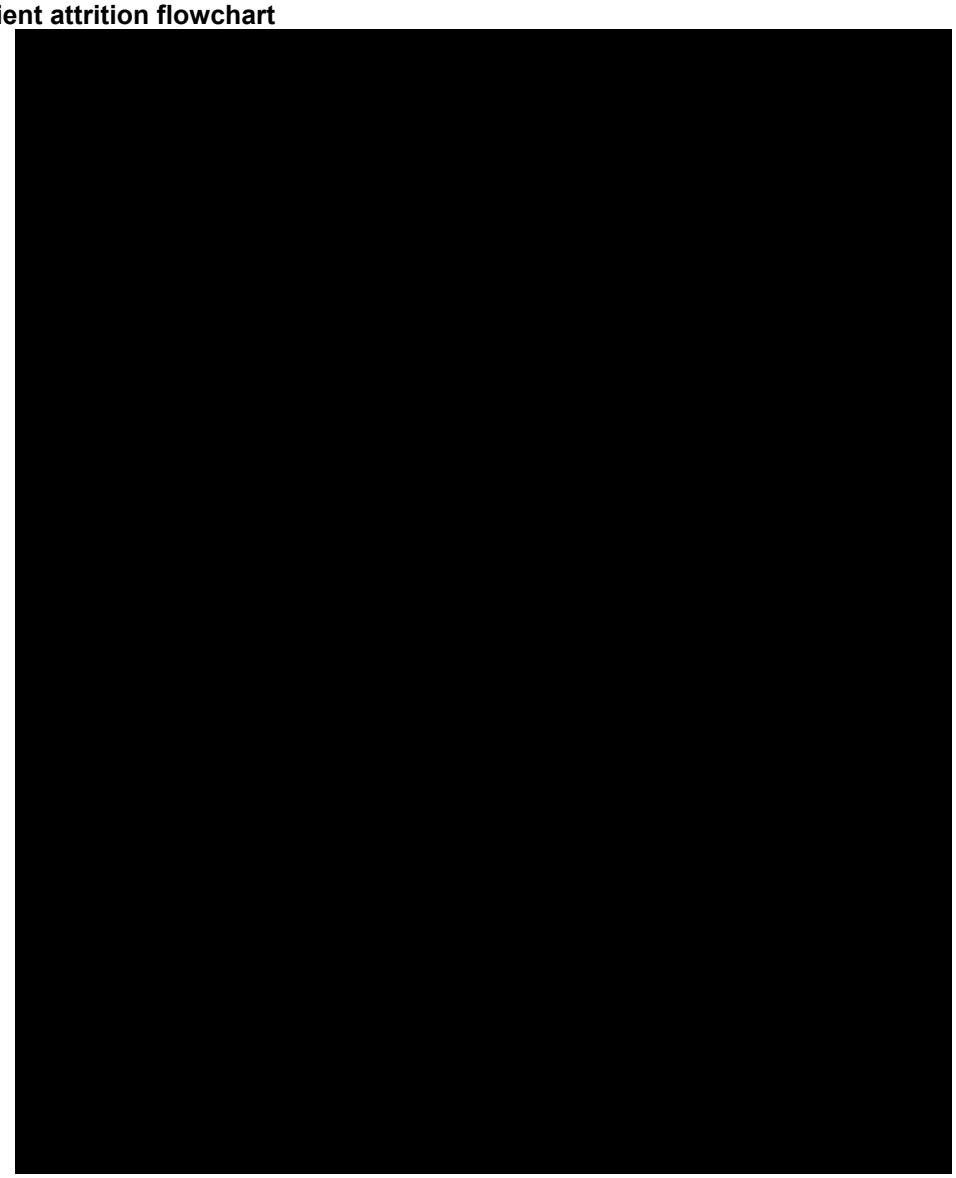
Figure 7: Patient attrition flowchart



Abbreviations: CPRD: Clinical Practice Research Datalink; HES: Hospital Episode Statistics:

B.2.3.1.5 Statistical analysis

For each objective, descriptive analyses were performed to gain an understanding of the qualitative and quantitative nature of the data collected and the characteristics of the cohort studied.[29] Continuous variables were summarised using means with standard deviations (SDs), medians with interquartile ranges (IQRs), and minimum and maximum values.[29] The number and percentages of patients were used to summarise categorical variables, including a separate category for patients with missing data at baseline.[29] Missing data were quantified for all study variables, but no attempts were made to impute them.[29]

Summary statistics were used to describe treatment patterns and drug utilisation.[29] Multivariable regression models were performed to evaluate the association between S–K level and clinical outcomes, stratified by variables of interest to account for confounding variables.[29] A generalised estimating equations (GEE) model was used to estimate adjusted IRRs by incorporating a working correlation structure to account for within-cluster or repeated-measures dependencies. The model adjusts for all specified covariates simultaneously, including patient demographics, clinical histories,

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comorbidities, clinical measurements, and concomitant medications, providing marginal interpretations of the IRRs that reflect the average effect of each predictor across the population while accounting for the influence of other variables in the model. The full list of adjusted covariates can be found in Appendix M.3 and Appendix M.4 for the CKD and HF patient groups, respectively.

For objective 3, to address known confounders, cases and controls were PS-matched from relevant, captured data points, in addition to analysing the cohorts overall.[29] Cox proportional hazards models were used to calculate hazard ratios between groups, adjusting for all relevant covariates.[29] The full list of adjusted baseline characteristics can be found in Appendix M.2.

A summary of the analyses conducted and sub-group stratification is presented in Table 14.[29]

Table 14: Summary of statistical analyses conducted

Objectives	Summary of statistical analyses	Stratification
Objective 1: To describe patient characteristics, clinical characteristics and treatment patterns	Patient characteristics and clinical details (including medications) on the index date were summarised. The closest laboratory value to the index date (in the year before or on the index date) was used for laboratory values. For comorbidities, all available medical history data was summarised for any time prior to the index date.	Baseline characteristics were summarised for the base cohort according to inclusion/exclusion criteria, as well as stratified into subgroups by the following variables: • S–K levels • HK diagnosis post-index, if yes • Presence of CKD/HF as comorbidities • KDIGO eGFR groups • Prior RAASi use (within 90 days before index), if yes
Objective 2: To describe the association between S–K levels and clinical outcomes	Outcomes were described for all incident CKD patients and HF patients. This includes kidney function decline, MACE, hospitalisation and death. Hospitalisations related to events of interest (all-cause, CKD, HF) within 1 year on/after the index were summarized. Event rates are estimated per 100 PY. The rates for first events and recurrent non-fatal events are separately summarized. Hospitalizations beyond 1 year of the index were explored and summarised where data availability allowed. Death (all-cause or cardiovascular, HF or CKD related) were summarised where data availability allowed. Event rates were estimated per 100 PY Generalised estimating equations (GEE) are used to model the association between S–K and major outcomes including all-cause death, MACE and all-cause hospitalisation. An IRR was calculated as well as an e-value to address residual confounding. Analysis will be repeated in each eGFR category, and in each KDIGO eGFR category.	Outcomes were stratified by the following variables: • S–K levels • HK diagnosis post-index, if yes • Presence of CKD/HF as comorbidities • eGFR stages • KDIGO eGFR groups

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Objectives	Summary of statistical analyses	Stratification

Objective 3:
To describe clinical characteristics and treatment patterns for CKD and/or HF patients with S–K of 5.0 mmol/L or above)
	RAASi treatment patterns within 120 days prior to index date and up to 180 days after index were assessed and compared between the subgroups descriptively for:
	• Patients on max RAASi prior to index that
	  ○ Discontinue
	  ○ Discontinue and later return to max dose (and average weeks taken)
	  ○ Down-titrate
	  ○ Down-titrate and later return to max dose (and average weeks taken)
	• Patients on sub-max RAASi prior to index that discontinue
	Analyses were performed using Kaplan-Meier method for proportion and cumulative proportion of outcome events. Cox proportional hazards regression were used to estimate hazard ratio.
		Subgroups of interest include:
		• Potassium binder use
		  ○ On any potassium binder
		  ○ On SZC treatment
		  ○ Not on any potassium binder
		• S–K level
		  ○ ≥5.0–<5.5 mmol/L
		  ○ ≥5.5–<6.0 mmol/L
		  ○ ≥6.0 mmol/L
		• SGLT2i use (yes/no)

Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; GEE: generalised estimating equations; GP: general practitioner; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; hHF: heart failure hospitalisation; HK: hyperkalaemia; IRR: incidence rate ratio; KDIGO: Kidney Disease Improving Global Outcomes; MACE: major adverse cardiac events; PY: person years; RAASi: renin-angiotensin-aldosterone system inhibitors; SGLT2i: sodium/glucose cotransporter 2 inhibitor; S–K: serum potassium; SZC: sodium zirconium cyclosilicate.

B.2.3.1.6 Patient characteristics

The first primary objective of the SPARK study was to describe treatment patterns stratified by demography, S–K levels and comorbidities at baseline. Overall, a total of [redacted] UK patients met the inclusion criteria and were included in the base cohort.[29] At baseline, the mean age was [redacted] years, [redacted] patients [redacted] were female, and [redacted] were current smokers.[29] In the base cohort, [redacted] had been diagnosed with an HK event, [redacted] and [redacted] patients were comorbid with CKD and HF, respectively, and [redacted] had received RAASi treatment by baseline.[29] A total of [redacted] patients had been diagnosed with both CKD and HF.[29] The baseline median S–K concentrations among the CKD and HF cohorts were [redacted] mmol/L and [redacted] mmol/L, respectively, compared with [redacted] mmol/L in the base cohort.[29] Within the base cohort, [redacted] patients were identified as having a serum potassium of ≥5.5–<6.0 mmol/L at baseline.[29] An overview of key patient characteristics and clinical histories is provided in Table 15; full details are provided in Appendix M.1.

For objective 3, patients on K^+ binder and those not on K^+ binder were propensity score matched on baseline characteristics and analyses performed on both the overall and matched cohorts Appendix M.2.[29]

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Table 15: Baseline patient characteristics and clinical histories of UK patients, stratified by serum potassium category and comorbid HF or CKD at baseline

Characteristics	Base Cohort	S–K ≥5.5 to <6.0	S–K ≥5.5	HK	CKD	HF	CKD and HF	Prior RAASi	CKD 3 or above
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient demographics, n (%)									
Age (Years), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Current smoker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical measurements at baseline, mean (SD)									
BMI (kg/m²)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SBP (mmHg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DBP (mmHg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S–K (mmol/L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR (mL/min/1.73 m²)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical history at baseline, n (%)									
HK	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IHD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Congestive HF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CAD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment history at baseline, n (%)									
Any RAASi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
β-Blocker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Characteristics	Base Cohort	S–K ≥5.5 to <6.0	S–K ≥5.5	HK	CKD	HF	CKD and HF	Prior RAASi	CKD 3 or above
Thiazide diuretic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loop diuretic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calcium channel blockers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NSAIDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bendroflumethiazide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Indapamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hydrochlorothiazide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chlorthalidone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bronchodilators	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: eGFR reported is calculated using the eGFR CKD-EPI method.
Abbreviations: BMI: body mass index; CAD: coronary artery disease; CKD: chronic kidney disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HF: heart failure; HK: hyperkalaemia; IHD: ischaemic heart disease; NSAID: nonsteroidal anti-inflammatory drug; PS: propensity score; RAASi: renin-angiotensin-aldosterone system inhibitors; SBP: systolic blood pressure; S–K: serum potassium; SD: standard deviation.

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B.2.3.1.7 Study results

Association between S–K levels and clinical outcomes

The SPARK study collected data on a range of outcomes. The evidence from the SPARK study presented in this section focuses on the outcomes of interest from the final NICE scope: MACE, hospitalisations and mortality. Within both the CKD (no HF) and HF (no CKD) populations, adjusted IRRs for MACE, all-cause mortality and hospitalisations were found to exhibit U-shaped association patterns with S–K (Figure 8 and Figure 10, respectively).[29]

Generalised estimating equations (GEE) models were used to analyse the association between S–K and major clinical outcomes, with IRRs as the outputs.[29] Amongst patients with CKD (no HF), an S–K level of ≥5.5–<6.0 mmol/L was associated with [redacted] incidence rates of MACE, mortality, and hospitalisations than an S–K level of ≥4.5–<5.0 mmol/L, with IRRs [redacted] and [redacted] respectively (Figure 8).[29] Despite the addition of multiple additional confounders these results and 'U-shaped' association between S–K levels and adverse clinical outcomes for CKD or HF patients are consistent with results reported previously,[30, 31, 34, 81, 82, 86] which should provide reassurance that this association is not due to any unidentified confounder.

To further qualify the sensitivity of these IRR values to residual confounding, the strength of associations of a hypothetical unmeasured confounder with clinical outcome and S–K level that would be required to nullify or reverse the observed beneficial effect of normokalaemia was computed using e-values.[29] Results demonstrated that an unmeasured confounder would need to be simultaneously highly correlated with the clinical outcome and imbalanced between S–K groups to reverse or nullify these findings.[29] For MACE, mortality, and hospitalisations, the CI e-values corresponding to the IRR reported above were [redacted], [redacted] and [redacted], respectively.[29] Taking MACE as an example, this CI e-value means that the confounder-MACE and confounder-S–K correlations would need to be simultaneously at least [redacted] on the RR scale to move the 95% CI to include 1.00 and render results statistically non-significant.[29] For comparison, in the same population, the covariate with the largest IRR for MACE, mortality and hospitalisations respectively are [redacted], [redacted], and [redacted].[29] Therefore, it is highly unlikely for any remaining unknown confounder to nullify the relationship. A full list of risk factors and their respective IRR is included in Appendix M.3 and M.4 for CKD and HF patients, respectively.

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Figure 8: Adjusted IRRs for MACE, death, and hospitalisations in CKD patients

Footnotes: IRRs are adjusted using the S–K level of ≥4.5-<5.0 as a reference.
Abbreviations: CKD: chronic kidney disease; IRR: incident rate ratio; MACE: major adverse cardiac event.

The relationship between hospitalisations and S–K levels for patients with CKD persisted across different levels of renal function. The IRR for hospitalisation remained [redacted] at the 95% confidence level for patients with an S–K of ≥5.5–<6.0 mmol/L relative to the reference S–K level of ≥4.5–<5.0 mmol/L (Figure 9 and Table 16), indicating that the [redacted] in hospitalisations [redacted] of renal function.[29]

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Figure 9: Adjusted IRRs for hospitalisations as a function of S–K and eGFR in UK CKD patients

Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; IRR: incident rate ratio; S–K: serum potassium.

Table 16: Adjusted IRRs and associated CIs for hospitalisations as a function of S–K and eGFR in UK CKD patients

Variable	Adjusted IRR by S–K level (mmol/L) (95% CI)						
	S–K <3.5	S–K ≥3.5 to <4.0	S–K ≥4.0 to <4.5	S–K ≥4.5 to <5.0	S–K ≥5.0 to <5.5	S–K ≥5.5 to <6.0	S–K ≥6.0
eGFR <30 (mL/min/ 1.73 m^2)							
eGFR 30–40 (mL/min/ 1.73 m^2)							
eGFR 40–50 (mL/min/ 1.73 m^2)							
eGFR 50–60 (mL/min/							

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Variable	Adjusted IRR by S–K level (mmol/L) (95% CI)						
	S–K <3.5	S–K ≥3.5 to <4.0	S–K ≥4.0 to <4.5	S–K ≥4.5 to <5.0	S–K ≥5.0 to <5.5	S–K ≥5.5 to <6.0	S–K ≥6.0
1.73 m^2)							
eGFR ≥60 (mL/min/ 1.73 m^2)	[redacted]						
All eGFR	[redacted]						

Footnotes: Values are represented by IRR (95% CI interval).
Abbreviations: CI: confidence interval; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; IRR: incident rate ratio; S–K: serum potassium.

Additionally, the strength of associations of a hypothetical unmeasured confounder with hospitalisations and S–K level that would be required to nullify or reverse the observed beneficial effect of normokalaemia stratified by eGFR was computed using e-values.[29] For S–K ≥5.5–<6.0 mmol/L, the CI e-values corresponding to the IRRs ranged from [redacted] for eGFR <30–≥60 mL/min/1.73 m^2 (Table 17).[29]

Table 17: e-values and CI e-values associated with the IRRs for hospitalisations as a function of S–K and eGFR in UK CKD patients

Variable	e-value by S–K level (mmol/L) (CI e-value)						
	<3.5	≥3.5 to <4.0	≥4.0 to <4.5	≥4.5 to <5.0	≥5.0 to <5.5	≥5.5 to <6.0	≥6.0
eGFR <30 (mL/min/ 1.73 m^2)	[redacted]						
eGFR 30–40 (mL/min/ 1.73 m^2)	[redacted]						
eGFR 40–50 (mL/min/ 1.73 m^2)	[redacted]						
eGFR 50–60 (mL/min/ 1.73 m^2)	[redacted]						
eGFR ≥60 (mL/min/ 1.73 m^2)	[redacted]						

Abbreviations: CI: confidence interval; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; IRR: incident rate ratio; S–K: serum potassium.

Among patients with HF (no CKD), an S–K level of ≥5.5–<6.0 mmol/L was associated with [redacted] incidence rates of mortality and hospitalisations at the 95% confidence level compared with an S–K level of ≥4.5–<5.0 mmol/L, with adjusted IRRs of [redacted], and [redacted], respectively (Figure 10).[29] The adjusted IRR for MACE was [redacted] for patients with an S–K level of ≥5.5–<6.0 mmol/L compared with an S–K level of ≥4.5–<5.0 mmol/L [redacted].[29]

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To qualify the sensitivity of these IRR values to residual confounding, the strength of associations of a hypothetical unmeasured confounder with clinical outcome and S–K level that would be required to nullify or reverse the observed beneficial effect of normokalaemia was computed using e-values.[29] Results demonstrated that an unmeasured confounder would need to be simultaneously highly correlated with the clinical outcome and imbalanced between S–K groups to reverse or nullify these findings.[29] For mortality and hospitalisations, the CI e-values corresponding to the IRR reported above were [redacted] and [redacted], respectively.[29]

Figure 10: Adjusted IRRs for MACE, death, and hospitalisations in HF patients

Footnotes: IRRs are adjusted using the S–K level of ≥4.5-<5.0 as a reference.
Abbreviations: HF: heart failure; IRR: incident rate ratio; MACE: major adverse cardiac event.

Similar to patients with CKD, the relationship between hospitalisation and S–K levels for patients with HF persisted across different levels of renal function. The IRR for hospitalisation for patients with an S–K level of ≥5.5–<6.0 mmol/L remained [redacted] at the 95% confidence level relative to the reference S–K level of ≥4.5–<5.0 mmol/L (Figure 11 and Table 18), indicating that the [redacted] in hospitalisations was [redacted] of renal function.[29] In only the subgroup of patients with an eGFR of 40–50 mL/min/1.73 m^2 was the relationship between [redacted] S–K and hospitalisation [redacted], representing an outlier.[29] For comparison, the IRR across all eGFRs was [redacted] between an S–K level of ≥5.5–<6.0 mmol/L and the an S–K level of ≥4.5–<5.0.[29]

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Figure 11: Adjusted IRRs for hospitalisations as a function of S–K and eGFR in UK HF patients

Abbreviations: eGFR: estimated glomerular filtration rate; HF: heart failure; IRR: incident rate ratio; S–K: serum potassium.

Table 18: Adjusted IRRs and associated CIs for hospitalisations as a function of S–K and eGFR in HF patients

Variable	S–K <3.5	S–K ≥3.5 to < 4.0	S–K ≥4.0 to < 4.5	S–K ≥4.5 to 5.0	S–K ≥5.0 to < 5.5	S–K ≥5.5 to < 6.0	S–K ≥6.0
eGFR <30 (mL/min/ 1.73 m^2)							
eGFR 30–40 (mL/min/ 1.73 m^2)							
eGFR 40–50 (mL/min/ 1.73 m^2)							
eGFR 50–60 (mL/min/ 1.73 m^2)							
eGFR ≥60 (mL/min/							

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Variable	S–K <3.5	S–K ≥3.5 to < 4.0	S–K ≥4.0 to < 4.5	S–K ≥4.5 to 5.0	S–K ≥5.0 to < 5.5	S–K ≥5.5 to < 6.0	S–K ≥6.0
1.73 m^2)							
All eGFR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: Values are represented by IRR (95% CI).
Abbreviations: CI: confidence interval; eGFR: estimated glomerular filtration rate; HF: heart failure; IRR: incident rate ratio; S–K: serum potassium.

Additionally, the strength of associations of a hypothetical unmeasured confounder with hospitalisations and S–K level that would be required to nullify or reverse the observed beneficial effect of normokalaemia stratified by eGFR was computed using e-values.[29] For S–K ≥5.5–<6.0 mmol/L, the CI e-values corresponding to the IRRs ranged from [redacted] for eGFR <30–≥60 mL/min/1.73 m^2 (Table 19).[29]

Table 19: e-values and CI e-values associated with the IRRs for hospitalisations as a function of S–K and eGFR in UK HF patients

Variable	e-value by S–K level (CI e-value)						
	S–K <3.5	S–K ≥3.5 to <4.0	S–K ≥4.0 to <4.5	S–K ≥4.5 to <5.0	S–K ≥5.0 to <5.5	S–K ≥5.5 to <6.0	S–K ≥6.0
eGFR <30 (mL/min/ 1.73 m^2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR 30–40 (mL/min/ 1.73 m^2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR 40–50 (mL/min/ 1.73 m^2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR 50–60 (mL/min/ 1.73 m^2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR ≥60 (mL/min/ 1.73 m^2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; eGFR: estimated glomerular filtration rate; HF: heart failure; IRR: incident rate ratio; S–K: serum potassium.

Although outcome data from the population comorbid with CKD and HF are not available, [redacted] of patients with either CKD or HF were found to be comorbid with both diseases ([redacted]), representing a substantial proportion of patients. Patients simultaneously experiencing both CKD and HF are expected to be at a greater risk of HK events compared to the populations experiencing one of these conditions in isolation, which are presented in this submission. This represents an uncaptured benefit to a population beyond that addressed in the decision problem.

Maintenance of Optimal RAASi dose

Whilst the SPARK study conducted an analysis of CPRD data to assess the ability of SZC to enable patients with CKD or HF to maintain optimal RAASi dosage (i.e. quantify and

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compare SZC users and non-users who discontinue, down-titrate, and/or return to optimal RAASi dose), these data were ultimately deemed insufficient to conduct a meaningful analysis.[29] Following the application of the study inclusion criteria, the sample size of SZC users in the UK was too small to yield robust results, particularly when assessing subgroups based on S–K measurements: [redacted] on SZC had a RAASi prescription, of which only [redacted] had optimised RAASi and S–K ≥5.5–<6.0 mmol/L.[29] This is not unexpected because, in UK clinical guidelines, SZC is not recommended for patients with an S–K of <6.0 mmol/L for the treatment of persistent HK,[3] and few patients are prescribed SZC outside of the guideline recommendation. Furthermore, given the lack of licenced SGLT-2 inhibitors for patients with CKD or HF during the data collection period, there were very few SGLT-2 inhibitor users in the sample and therefore the subgroup of interest of SGLT-2 inhibitor users was not measured.[29] Given the limitations associated with these UK data, the RWE study ZORA, which analyses medical records for patients from the US (n=582), Japan (n=888), and Spain (n=104) where treatment guidelines have a lower threshold for using SZC to treat persistent HK,[13] was used to provide evidence of increased odds of RAASi maintenance with SZC usage for the decision problem population (see Section B.2.3.2).

Summary

SPARK was conducted by AstraZeneca to address the concerns raised by NICE relating to the CPRD evidence presented in TA599 to demonstrate the association between persistent HK and adverse clinical outcomes. Previous studies did not adjust for RAASi usage or for unmeasured confounders, and thus the independence of the relationship between S–K and long-term outcomes could not be reliably established. SPARK addresses these concerns by investigating the relationship between S–K and hospitalisation, MACE, and mortality, stratified by S–K levels and eGFR. In line with the NICE RWE framework, the SPARK study also took steps to minimise the risk of bias, and adjusted by an additional 30+ confounders than the studies used to inform TA599, including co-medications, comorbidities and RAASi usage.[29] In addition, e-values were employed to quantify the strength of the unmeasured confounder needed to reverse the observed relationships, and demonstrated that it is unlikely for any remaining unknown confounder to nullify the observed relationships between S–K and MACE, mortality and hospitalisation.[29]

Results from the SPARK study demonstrate that patients with CKD or HF with S–K levels ≥5.5–<6.0 mmol/L have a statistically significant higher incidence rate of mortality and hospitalisations compared with patients with an S–K level of ≥4.5–<5.0 mmol/L. Furthermore, CKD patients with S–K levels ≥5.5–<6.0 mmol/L also have a statistically significantly higher incidence rate of MACE compared to those with S–K levels ≥4.5–<5.0 mmol/L.[29] This relationship between hospitalisations and S–K levels persisted across different levels of renal function for both patients with CKD and those with HF.[29] Overall, these results demonstrate that patients with CKD or HF with S–K levels ≥5.5–<6.0 mmol/L are at an increased risk of adverse clinical outcomes compared with patients with S–K levels ≥4.5–<5.0 mmol/L.[29]

Due to UK clinical guidance, few patients with an S–K <6.0 mmol/L have received SZC for the treatment of persistent HK. As a result, the analysis conducted in SPARK to assess the ability of SZC to enable patients with CKD or HF to maintain optimal RAASi dosage was not possible as data were ultimately deemed insufficient to conduct a meaningful analysis. In the

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absence of suitable UK data (due to the restrictions placed on the use of SZC in these patients), data from other geographies has been utilised to explore this relationship for the purposes of cost effectiveness analyses (see Section B.2.3.2).

B.2.3.1.8 Quality assessment

A completed NICE dataSAT is included in Appendix M.5.

The SPARK used one of the largest longitudinal data sources in the UK and the methods and definitions used align with UK clinical practices and relevant previous observational studies.[29] Nevertheless, data may be limited by the accuracy of diagnoses coding and data on prescriptions issued from the hospital setting were not directly captured.[29]

B.2.3.2 *ZORA*

ZORA was an observational, cohort study programme performed using secondary data extracted from health registers and hospital medical records from the US, Japan, and Spain.[39, 135] The analysis published by Rastogi *et al.* (2024) analysed data from patients aged ≥18 years with an index HK event, comorbid with CKD and/or HF receiving RAASi therapy.[135] Patients were grouped into two cohorts: those receiving SZC, and those not receiving any prescribed K^+ binders.[135] The index date was defined as the initiation of SZC therapy for the SZC cohort, and the discharge date of an inpatient episode or date of outpatient care visit with a recorded HK diagnosis for the no K^+ binder cohort.[135] Patients were followed until 180 days after the index event.[135] PS matching (up to 1:4 SZC: no K^+ binder) was applied to balance the SZC cohort to the no K^+ binder cohort on baseline demographics (age, sex) and other covariates such as comorbidities, comedications, and HK severity.[135] The complete list of adjusted covariates is available in Appendix N.1. Logistic regression analysis was performed to compare the odds of maintained RAASi therapy at six months in the SZC compared with the no K^+ binder cohorts.[135]

A subgroup analysis of patients stratified by S–K level was conducted in an ad-hoc re-analysis of ZORA.[136] For this additional analysis, only data from the US and Japan were included due to lack of approval to use the BIG-PAC dataset for this analysis. PS matching using the same methodology was reapplied to each stratified S–K level to balance the SZC cohort to the no K^+ binder cohort. The complete list of adjusted covariates is available in Appendix N.3. This additional analysis was used to inform the economic model.

B.2.3.2.1 Data source

Health claims and hospital medical records identified in Optum's Clinfomatics Data Mart database from the US, the Medical Data Vision (MDV) database from Japan, and the BIG-PAC database from Spain.[135] The Optum Clinformatics Data Mart is a de-identified administrative health database which contains claims data from individuals with commercial health insurance and Medicare Advantage plans.[148] The database provides comprehensive details on enrolment information, diagnoses, and procedures documented in both inpatient and outpatient care settings, along with information on prescription medications and some coverage of laboratory results.[148] The MDV database captures healthcare data such as information on diagnoses, procedures and prescriptions recorded in inpatient and outpatient care settings for approximately 38 million patients from hospitals across Japan, as well as laboratory test results from a subset of hospitals.[149] The BIG-PAC administrative database

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includes anonymised electronic medical records data from primary and secondary care within the Spanish national health system across seven regions, collecting data from approximately 2 million patients.[150]

The study period considered in the analysis by Rastogi *et al.* (2024) varied by data source: the collection period began when SZC became available in each respective country and ended at the last date of available data from each data source.[135] This corresponded to July 2019–December 2022 for the US, May 2020–December 2022 for Japan, and June 2021–December 2022 for Spain.[135] In the re-analysis of ZORA stratifying patients by S–K levels, data from the US and Japan are used, with the study period being July 2019–March 2024 for the US and May 2020–April 2024 for Japan.[136]

B.2.3.2.2 Patient eligibility

An overview of the inclusion and exclusion criteria used in the ZORA study analysis conducted by Rastogi *et al.* (2024) and the ad-hoc re-analysis stratifying patients by S–K levels is provided in Table 20.

Table 20: Inclusion and exclusion criteria used in Rastogi *et al.* (2024)[135] and the S–K subgroup analysis

Inclusion criteria	Exclusion criteria
• Age at least 18 years old at index • Diagnosis of CKD and/or HF • Outpatient prescription for at least one type of RAASi medication within 120 days prior to the index date • At least 12 months of medical records before the index date • At least 180 days of available follow-up data post index date • For the SZC cohort, a prescription of SZC and ≥120 days of continuous SZC treatment, with a gap in supply of no longer than 7 days • For the no K^+ binder cohort, an index event of inpatient or outpatient diagnosis of HK (defined as >5.0 mmol/L)	• Patients treated with haemodialysis 12 months prior to the index date • Prescription for any K^+ binder in the 180 days of follow-up for patients in the no K^+ binder cohort

Abbreviations: CKD: chronic kidney disease; HF: heart failure; HK: hyperkalaemia; K^+: potassium cation; RAASi: renin-angiotensin-aldosterone system inhibitors; SZC: sodium zirconium cyclosilicate.

All potential index dates for each patient were screened for eligibility.[135] In cases where a patient had multiple eligible index dates for the same cohort at different time points, the index date for inclusion in that cohort was selected at random.[135] If a patient had eligible index dates for both cohorts at different time points, the patient was included in both cohorts at the corresponding index date.[135]

B.2.3.2.3 Patient characteristics

Propensity score matching was conducted in Rastogi *et al.* (2024) and the subgroup reanalysis based on stratified groups in order to achieve balance (<0.2 standardised mean difference [SMD]) between the SZC cohort and the no K^+ binder cohort with respect to potential confounders. The list of 33 matching variables was identified a-priori through subject matter knowledge.

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For the Rastogi *et al.* (2024) analysis, prior to PS matching, 582 patients from the US met the study eligibility criteria for the SZC cohort, 888 from Japan and 104 from Spain.[135] The majority of patients in the US and Spanish SZC cohorts did not have a preceding HK diagnosis recorded within the 30 days prior to index (58.8% and 51.0%, respectively).[135] Across both geographies, the characteristics of patients with and without a recorded preceding HK diagnosis were considered to be sufficiently similar to be combined into a common SZC cohort.[135] Nearly all patients (97.9%) in the Japanese cohort of SZC-treated patients had a documented preceding HK diagnosis and all were included irrespective of documentation of an HK diagnosis.[135] Regarding the no K^+ binder cohorts, 102,537, 22,771 and 2,274 patients from the US, Japan, and Spain, respectively, met the study eligibility criteria prior to PS matching.[135]

After PS matching, the SZC cohorts consisted of 565, 776 and 56 patients from the US, Japan and Spain, respectively, were included in the SZC cohorts, and 2,068, 2,629 and 203 patients, respectively, were included in the no K^+ binder cohorts.[135]

In the ZORA re-analysis stratifying by the S–K subgroup of interest to this appraisal, the SZC and control (no K^+ binder) cohorts were stratified by HK severity. Table 21 and Table 22 present an overview of the PS-matched baseline patient demographics stratified by S–K subgroups for the SZC treated and no K^+ binder treated cohort in Japan and the US, respectively, from the ZORA re-analysis of subgroups stratified by S–K. The PS distributions before matching and the SMD before and after matching are provided in Appendix N.3. After PS matching, the SZC cohorts consisted of [redacted] and [redacted] patients from Japan and the US, respectively, in the subgroup with S–K of ≥5.5–<6.0 mmol/L. In the no K^+ binder cohort, [redacted] and [redacted] patients were included from the Japan and US, respectively.[135]

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Table 21: Patient characteristics of the propensity score-matched SZC and no-K^+ binder cohorts stratified by S–K level at baseline (Japan population)

	SZC				No K^+ binder			
Covariates	**S–K ≥5.0–<5.5**	**S–K ≥5.5–<6.0**	**S–K ≥6.0**	**Any S–K**	**S–K ≥5.0–<5.5**	**S–K ≥5.5–<6.0**	**S–K ≥6.0**	**Any S–K**
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex (female), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CKD, n (%)[a]								
CKD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Concomitant conditions, n (%)								
Heart failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical measurement at baseline[a]								
eGFR test, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR categories, n (%)								
eGFR <15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR 15–29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR 30–44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR 45–59	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR 60–89	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eGFR >90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Max S–K value, mean (SD)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RAASi usage at baseline, n (%)[c]								
ACEi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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	SZC				No K^+ binder			
MRA	[redacted]							

Footnotes: [a]Measured 12-months prior to the index date excluding index. [b]Measured 14-days prior to the index date including index. [c]Measured 1230-days prior to the index date excluding index.
Abbreviations: ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNi: angiotensin receptor-neprilysin inhibitor; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; K^+: potassium cation; MRA: mineralocorticoid receptor antagonist; RAASi: renin-angiotensin-aldosterone system inhibitor; S–K: serum potassium; SD: standard deviation; SZC: sodium zirconium cyclosilicate.

Table 22: Patient characteristics of the propensity score-matched SZC and no-binder cohorts stratified by S–K level at baseline (US population)

	SZC				No K^+ binder			
Covariates	**S–K ≥5.0–<5.5**	**S–K ≥5.5–<6.0**	**S–K ≥6.0**	**Any S–K**	**S–K ≥5.0–<5.5**	**S–K ≥5.5–<6.0**	**S–K ≥6.0**	**Any S–K**
N	[redacted]							
Age, years, mean (SD)								
Sex (female), n (%)								
CKD, n (%)[a]								
CKD								
Stage 3								
Stage 4								
Stage 5								
Concomitant conditions, n (%)								
Heart failure								
Diabetes								
Clinical measurement at baseline[a]								
eGFR test, N (%)								
eGFR, mean (SD)								
eGFR categories, n (%)								
eGFR <15								
eGFR 15–29								
eGFR 30–44								
eGFR 45–59								
eGFR 60–89								
eGFR >90								

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	SZC				No K^+ binder			
Max S–K value, mean (SD)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RAASi usage at baseline, n (%)[c]								
ACEi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARNi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MRA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a]Measured 12-months prior to the index date excluding index. [b]Measured 14-days prior to the index date including index. [c]Measured 1230-days prior to the index date excluding index.
Abbreviations: ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNi: angiotensin receptor-neprilysin inhibitor; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; K^+: potassium cation; MRA: mineralocorticoid receptor antagonist; RAASi: renin-angiotensin-aldosterone system inhibitor; S–K: serum potassium; SD: standard deviation; SZC: sodium zirconium cyclosilicate.

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B.2.3.2.4 Study objectives and outcomes measures

The primary outcome of the ZORA analysis conducted by Rastogi *et al.* (2024) was the proportion of patients who maintained RAASi therapy at 180 days post-index.[135] The objective of the additional subgroup analysis of ZORA was to determine the proportions of patients discontinuing or down-titrating RAASi therapy stratified by recorded S–K levels (≥5.0–<5.5 mmol/L, ≥5.5–<6.0 mmol/L, and ≥6.0 mmol/L).[136]

The definition of maintained vs reduced RAASi therapy was based on which RAASi classes were used (ACEi, ARB, ARNi and MRA) and the doses for which the patients had prescriptions before the index date (using a 120-day look-back period) vs at 180 days post-index (also using a 120-day look-back period).[135] Patients with maintained RAASi therapy were defined as those with post-index prescriptions for at least the same number of RAASi classes as pre-index.[135] Consequently, this category included stabilised RAASi usage (use of the same number of RAASi classes and doses) and up-titrated RAASi usage (use of additional RAASi classes and/or higher doses).[135] Reduced RAASi therapy was defined as RAASi therapy that was discontinued (no filled prescription for any RAASi class) or down-titrated (use of fewer RAASi classes or when the dose of at least one pre-index RAASi class was reduced by ≥25% post-index).[135]

B.2.3.2.5 Statistical analysis

The study outcomes were analysed in the PS-matched cohorts.[135] In the Rastogi *et al.* analysis of ZORA, all covariates assessed in the US and Japanese cohorts had an absolute SMD of <10% after matching, while some covariates remained unbalanced in the Spanish cohorts.[135] Subgroup analyses were performed for patients with CKD, HF, CKD and HF, and diabetes.[135] For each of the subgroup analyses, PS matching was performed using the cases and controls in the corresponding subgroup.[135] The PS distributions before and after matching are provided in Appendix N.1.[135]

In the ad-hoc re-analysis of ZORA analysing the decision problem population in this appraisal, the SZC and control (no K^+ binder) cohorts were stratified by HK severity (defined by the maximum S–K level recorded in the two weeks prior to the index date) among those with available data on S–K. After stratification, the sample size in each stratum was small (<100). Logistic regression was used to predict the PS;[151, 152] when too many variables or variable categories (i.e. degrees of freedom) are included, the PS will be more extreme.[151, 153] Principles of modelling were used to reduce the degrees of freedom, including removal of variables with very small numbers of cases or controls for one level (often resulting in high collinearity) and selection of variable form where information was represented in multiple ways.[154-156] Furthermore, variables which were already well balanced (<0.1 SMD) were removed from the matching model in order to improve prediction based on the remaining variables.[152] This last step was performed iteratively to ensure balance was maintained. Balance for all variables in the final cohorts was reported graphically, noting variables which could not achieve balance.

In both sets of analyses, proportions of patients in the SZC and no K^+ binder cohorts who up-titrated, stabilised, down-titrated or discontinued RAASi therapy at 180 days post-index vs pre-index were calculated, alongside p values for differences between groups calculated from chi-squared (χ^2) tests.[135] A cross-country meta-analysis was conducted using a random effects model on logit transformed proportions.[135]

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In the Rastogi *et al.* analysis of ZORA, logistic regression analysis was performed to compare the odds of maintained RAASi therapy in the SZC vs no K^+ binder cohorts.[135] Covariates that were not sufficiently balanced between the cohorts after PS-matching (SMD >10%) were considered for inclusion in the multivariable model, while ensuring that there was a minimum of ten outcome events per covariate.[135] A cross-country meta-analysis of the ORs and associated 95% CIs was performed using a random effects model.[135]

B.2.3.2.6 Study results

Evidence from the ZORA study is presented to address uncertainties surrounding the link between SZC usage and discontinuation, up-titration or maintenance of optimum RAASi dosage. Two analyses were conducted for the ZORA dataset: the ZORA analysis conducted by Rastogi *et al.*[135] which includes the primary analysis and subgroup analysis stratifying by comorbidities, and the unpublished ad-hoc ZORA re-analysis, which contains an additional subgroup analyses stratifying by S–K level.[136] The ad-hoc re-analysis of ZORA was used to inform the economic model in the current appraisal, as this analysis directly informs the RAASi treatment patterns at each S–K level (see Section B.3.3.1 for more details).[136]

In the ZORA analysis conducted by Rastogi *et al.*, the proportion of patients using each RAASi class decreased in both cohorts from pre-index to 180 days post-index, although reductions were numerically larger in the no K^+ binder cohort.[135] The proportions who remained on any RAASi therapy (stabilised or up-titrated) at 180 days were consistently higher in the SZC cohorts than in the no K^+ binder cohorts across all countries (US: 80.2% vs 64.8%, p<0.0001; Japan: 90.7% vs 64.8%, p<0.0001; Spain: 82.1% vs 64.0%, p=0.0102).[135] When meta-analysed across countries, this result remained consistent, with over double the odds of RAASi maintenance (OR: 2.56; 95% CI: 1.92–3.41; p<0.0001; I^2 = 68.8%) in the SZC cohort compared with the no K^+ binder cohort.[135] These results observed were consistent across all three countries investigated.[135] Full results of the primary analysis presented by Rastogi *et al.* can be found in Appendix N.2.

Subgroup analyses

In the ZORA analysis conducted by Rastogi *et al.* stratifying by comorbidity and the additional subgroup analysis stratified by S–K, subgroup analyses were performed for the US and Japanese cohorts for patients with CKD, HF, and CKD and HF.[135] Subgroup analyses were not conducted for the Spanish cohorts due to the limited sample size and the lack of prior approval for this analysis.[135] An overview of the baseline patient demographics and characteristics of the subgroups is provided in Appendix N.3.[135]

In the ZORA analysis conducted by Rastogi *et al.,* the results of the subgroup analyses were consistent with the primary analysis both across patient subgroups and across countries.[135] In patients with CKD, the proportion of patients who remained on any RAASi therapy (down-titrated, stabilised, and up-titrated) at 180 days was consistently higher in the SZC cohorts than in the no K^+ binder cohorts (US: 80.6% vs 65.8%, p<0.0001; Japan: 88.6% vs 59.8%, p<0.0001). Similar results were observed in the HF subgroup (US: 78.8% vs 65.7%; p=0.0008; Japan: 90.4% vs 66.7%; p<0.0001).[135] Full results of the subgroup analysis presented by Rastogi *et al.* can be found in Appendix N.2.

In the ad-hoc re-analysis of ZORA, subgroup analysis was performed for the US and Japanese cohorts, where patients were stratified by S–K levels (≥5.0–<5.5 mmol/L, ≥5.5–

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<6.0 mmol/L, and ≥6.0 mmol/L).[136] An overview of the PS matched baseline patient characteristics of the subgroups is provided in Table 21 and Table 22 for the Japan and US cohort, respectively, and the pre-matched baseline characteristics are presented in Appendix N.2. The proportion of patients that discontinued, down-titrated, stabilised, or up-titrated their RAASi therapy in the SZC cohort vs the no K^+ binder cohort stratified by S–K level in the US and Japan and meta-analysed across countries are shown in Table 23 and Table 24, respectively.

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Table 23: Proportions of patients who discontinued, down titrated, stabilised and up-titrated their RAASi therapy by country, stratified by S–K levels

	US			Japan		
Subgroup	**SZC**	**No K^+ binder**	**p value**	**SZC**	**No K^+ binder**	**p value**
≥5.0–<5.5 mmol/L, proportion (95% CI)	[redacted]	[redacted]		[redacted]	[redacted]	
Discontinued	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Down-titrated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stabilised	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Up-titrated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥5.5–<6.0 mmol/L, proportion (95% CI)	[redacted]	[redacted]		[redacted]	[redacted]	
Discontinued	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Down-titrated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stabilised	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Up-titrated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥6.0 mmol/L, proportion (95% CI)	[redacted]	[redacted]		[redacted]	[redacted]	
Discontinued	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Down-titrated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stabilised	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Up-titrated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any S–K, proportion (95% CI)	[redacted]	[redacted]		[redacted]	[redacted]	
Discontinued	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Down-titrated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stabilised	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Up-titrated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: p values for differences between the SZC cohort vs the no K^+ binder cohort in the proportions of patients who discontinued, down-titrated, stabilised and up-titrated their RAASi therapy at 180 days post-index vs pre-index were calculated using the $\chi 2$ test. P values were not estimated where the event count is less than 5 individuals.
Abbreviations: CI: confidence interval; K^+: potassium cation; NE: not estimable; S–K: serum potassium; SZC: sodium zirconium cyclosilicate.

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The results of the ad-hoc ZORA re-analysis of subgroups stratified by S–K levels were consistent with the primary analysis and consistently [redacted] for the proportion of patients who discontinued, down-titrated, stabilised, or up-titrated their RAASi therapy. These results remain robust across US and Japan data (Table 23), and meta-analysed across countries (Table 24). In the US and Japan populations, the proportions of patients with an S–K of ≥5.5–6.0 mmol/L that discontinued RAASi was [redacted] in the SZC cohort compared with [redacted] in the no K^+ binder cohort, respectively, with both results reaching statistical significance(p <0.0001). Patients receiving SZC in the ≥5.5–<6.0 mmol/L population also had higher proportions of RAASi stabilisation in the US and Japan populations, with [redacted] stabilising their RAASi in the SZC cohort compared with [redacted] in the no K^+ binder cohort, respectively. In both countries, the difference was [redacted] and [redacted], for the US and Japan populations respectively. In the same subgroup of the Japan population (but not the US population), the proportion of patients in the SZC cohort ([redacted]) that up-titrated their RAASi dosage was [redacted] higher compared with the no K^+ binder cohort ([redacted]). These results demonstrate that SZC therapy is effective in enabling patients to maintain pre-HK RAASi treatment, which is considered a key treatment aim amongst clinicians seeking to protect CKD and/or HF patients against cardiorenal adverse outcomes.

When meta-analysed across countries, the results are consistent with that observed in individual countries, with [redacted] patients discontinuing RAASi and stabilising their RAASi dosage respectively compared with [redacted] in the no K^+ binder cohort for the subgroup with S–K of ≥5.5–<6.0 mmol/L.

Due to low sample sizes for the analysis in the S–K of ≥5.5–<6.0 mmol/L subgroup, except for [redacted] differences in proportion were [redacted] at the p<0.05 level. Nevertheless, SZC treatment was associated with lower proportions of RAASi discontinuation in the decision problem population.

Table 24: Proportions of patients who discontinued, down titrated, stabilised and up-titrated their RAASi therapy meta-analysed across countries, stratified by S–K levels

Subgroup	SZC	No K^+ binder	Odds ratio	p value
≥5.0–<5.5 mmol/L– proportion (95% CI)	[redacted]	[redacted]		
Discontinued	[redacted]	[redacted]	[redacted]	[redacted]
Down-titrated	[redacted]	[redacted]	[redacted]	[redacted]
Stabilised	[redacted]	[redacted]	[redacted]	[redacted]
Up-titrated	[redacted]	[redacted]	[redacted]	[redacted]
≥5.5–<6.0 mmol/L– proportion (95% CI)	[redacted]	[redacted]		
Discontinued	[redacted]	[redacted]	[redacted]	[redacted]
Down-titrated	[redacted]	[redacted]	[redacted]	[redacted]
Stabilised	[redacted]	[redacted]	[redacted]	[redacted]
Up-titrated	[redacted]	[redacted]	[redacted]	[redacted]

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≥6.0 mmol/L–proportion (95% CI)	[redacted]	[redacted]		
Discontinued	[redacted]	[redacted]	[redacted]	[redacted]
Down-titrated	[redacted]	[redacted]	[redacted]	[redacted]
Stabilised	[redacted]	[redacted]	[redacted]	[redacted]
Up-titrated	[redacted]	[redacted]	[redacted]	[redacted]
Any S–K–proportion (95% CI)	[redacted]	[redacted]		
Discontinued	[redacted]	[redacted]	[redacted]	[redacted]
Down-titrated	[redacted]	[redacted]	[redacted]	[redacted]
Stabilised	[redacted]	[redacted]	[redacted]	[redacted]
Up-titrated	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: The proportions were meta-analysed across countries using a random effects model on logit transformed proportions.
Abbreviations: CI: confidence interval; K^+: potassium cation; S–K: serum potassium; SZC: sodium zirconium cyclosilicate.

Summary

The ZORA analysis conducted by Rastogi *et al.* (2024) demonstrated that treatment with SZC is associated with over double the odds of maintaining (stabilised or up-titrated) RAASi therapy following an HK event compared with no K^+ binder treatment (meta-analysed across all countries at six months: OR: 2.56; 95% CI 1.92–3.41; p<0.0001; I^2 = 68.8%).[135] These results observed were consistent across all three countries investigated.[135] Results of subgroup analyses of patients with CKD, HF, and CKD and HF were consistent with the primary analysis, supporting international guidelines for patients with CKD and HF which recommend novel K^+ binder treatment to maintain RAASi therapy after an HK event.[13, 135]

In the re-analysis of ZORA, results of the additional subgroup analysis of patients stratified by S–K values were [redacted] with the primary analysis, [redacted] of SZC in the proportions receiving guideline directed RAASi therapy. In the US and Japan populations, the proportion of patients that discontinued RAASi therapy was [redacted] among patients treated with SZC compared to no K^+ binder, with [redacted] and [redacted] in the SZC cohort discontinuing RAASi compared with [redacted] and [redacted] in the no K^+ binder cohort, respectively in the subgroup with an S–K of ≥5.5–<6.0 mmol/L. In the same populations, [redacted] in the US and [redacted] in Japan stabilised their RAASi dosage in the SZC cohort compared with [redacted] and [redacted] in the no K^+ binder cohort, respectively. In the same subgroup of the Japan population, a [redacted] proportion of patients in the SZC cohort ([redacted]) compared with the no K^+ binder cohort ([redacted]) up-titrated their RAASi dosage, indicating that SZC therapy can allow patients to maintain pre-HK RAASi as well as preventing RAASi down-titration and discontinuation. When meta-analysed across countries, the results are consistent with that observed in individual countries, with [redacted] and [redacted] patients discontinuing RAASi and stabilising their RAASi dosage respectively compared with [redacted] in the no K+ binder cohort for the subgroup with S–K of ≥5.5–<6.0 mmol/L. Although [redacted] is lacking due to small sample sizes, the results demonstrate a unidirectional trend towards greater RAASi usage in those using SZC therapy in the subgroup with S–K level of ≥5.5–<6.0 mmol/L.

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In summary, the results from the ZORA analysis by Rastogi *et al.* and the re-analysis of ZORA demonstrate that SZC treatment helps facilitate the maintenance and guideline-concordant RAASi therapy after an HK event in the decision problem population.[135] According to interviews conducted with UK clinical experts for the management of CKD to support the partial reappraisal of TA599, experts were all in agreement that whilst these data are not specific to the UK, results are generalisable to the UK population and the results reflect their clinical experience. Furthermore, all clinical experts stated that with K^+ binders, patients would be more likely to maintain RAASi dosage during an HK event if patients received a K^+ binder.[23]

B.2.3.2.7 Quality assessment

A completed NICE dataSAT is included in Appendix N.6.

The ZORA analysis conducted by Rastogi *et al.* (2024) included a large number of patients from three different countries, including a geographically diverse population of patients.[135] Importantly, despite baseline differences between populations and data sources, the study found that there was consistent and statistically significantly greater odds of maintaining RAASi therapy with SZC versus no K^+ binder treatment across the three countries, demonstrating the robustness and generalizability of these findings.[135] Nevertheless, since all patients were required to have at least 180 days of follow-up this study may be associated with immortal time bias, however this affected the SZC and no K^+ binder cohorts equally.[135] Finally, despite propensity score matching being used to balance the two cohorts at index, there is a risk of residual confounding due to unmeasured confounders.

B.2.4 *Interpretation of clinical effectiveness evidence*

HK, while often asymptomatic, can lead to fatal cardiac arrhythmias such as asystole or ventricular fibrillation. HK is common in patients with CKD and a GFR <60 mL/min/m^2 and in those with HF and diabetes mellitus. RAASi therapies are foundational therapies for treating CKD and heart failure HF, significantly reducing morbidity and mortality. The use of RAASi therapy is pivotal to all national and international guidelines for the management of HF and/or CKD and represent gold-standard guideline directed medical treatment for these conditions.[4, 13, 21, 26, 46-49] However, their use is often limited due to HK leading to reduced doses or discontinuation. Despite the vital cardiorenal protective effects provided by RAASi therapies, these medicines increase S–K levels by reducing renal excretion of K^+ which can lead to HK. In the absence of effective well-tolerated K^+ binders, clinicians are often faced with the need to down-titrate or discontinue these cardiorenal protective medicines. Data demonstrate that patients on sub-optimal doses of these RAASi medications have increased morbidity and mortality. Therefore, there is a distinct need to introduce an effective, well-tolerated, and easy to administer medication to allow patients to continue taking RAASi therapy, whilst effectively controlling potassium levels and reducing the risk of CV events and death. This is aligned with the clinician goal of achieving guideline directed medical therapy for patients with CKD and/or HF.

Aside from the down-titration or discontinuation of life-saving RAASi therapy, the only treatment option currently available to patients with S–K is strict adherence to a low K^+ diet, which in practice is poorly adhered to and adversely impacts patient QoL.

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SZC is a K^+ binder which differs in mode of action to other K^+ binders such as calcium resonium and patiromer. It is highly selective for potassium and begins exchanging Na^+ and H^+ ions in the stomach and small intestine, which explains its rapid onset of action. It also does not cause other electrolyte imbalances, such as hypomagnesaemia, as other K^+ binders have been shown to cause.[157, 158]

SZC is currently recommended for use by NICE in patients with life threatening emergency HK and persistent HK if patients have comorbid CKD (stage 3b–5) or HF with an S–K of ≥6.0 mmol/L as appraised in the original submission TA599.[3] In the original appraisal of SZC, it was accepted that the clinical evidence package sufficiently demonstrates that SZC normalises S–K.[3]

The main uncertainties raised in TA599[3] are addressed through the observational evidence presented as outlined in Table 25.

Table 25: Summary of updates to uncertainties raised in TA599

Uncertainty	Limitations of TA599	Current appraisal
Association between S–K and long-term outcomes (MACE, hospitalisation, and mortality)	Evidence was obtained from a literature search (Luo *et al.*[81] and Desai *et al.*[108] for the CKD and HF populations, respectively). No direct evidence was generated by AstraZeneca. The observational studies presented in TA599 (Luo *et al.*[81] and Desai *et al.*[108]) did not adjust for RAASi usage or adjust for unmeasured confounders, and thus the independence of the relationship between S–K and long-term outcomes could not be reliably established. As such, the committee preferred to remove the relationship between S–K and long-term outcomes from the cost effectiveness analysis used for decision making.	SPARK was conducted by AstraZeneca to address the concerns raised by the committee relating to the evidence presented in TA599 to demonstrate the association between persistent HK and adverse clinical outcomes. Previous studies did not adjust for RAASi usage or for unmeasured confounders, and thus the independence of the relationship between S–K and long-term outcomes could not be reliably established. SPARK addresses these concerns by investigating the relationship between S–K and hospitalisation, MACE, and mortality, stratified by S–K levels and eGFR, in line with the NICE RWE framework. SPARK provides IRRs which clearly demonstrate the relationship between S–K and hospitalisation, MACE, and mortality, as stratified by S–K levels and eGFR.[67] Importantly, the SPARK study also took steps to minimise the risk of bias, and adjusted by an additional 30+ confounders than the studies used to inform TA599, including co-medications, comorbidities and RAASi usage.[67] In addition e-values were employed to quantify the strength of the unmeasured confounder needed to reverse the observed relationships, and demonstrated that it is unlikely for any remaining unknown confounder to nullify the observed relationships between S–K and MACE, mortality and hospitalisation.[67]
Effectiveness of SZC treatment in maintaining RAASi therapy in HK patients	No evidence was presented by AstraZeneca as the effectiveness of SZC in maintaining RAASi therapy was not measured as part of the clinical trial programme. As such, this relationship was assumed to not exist.	Since the original appraisal (TA599), K^+ binders are now in use in many geographies, in accordance with international guidelines and as such data are now available to explored this relationship. ZORA, analysed data from patients with an HK event comorbid with CKD and/or HF and receiving RAASi therapy.[135] Results of this analysis by Rastogi *et al.* (2024) demonstrated that treatment with SZC was

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Uncertainty	Limitations of TA599	Current appraisal
		associated with over double the odds of maintaining (stabilised or up-titrated) RAASi therapy following an HK event compared with no K^+ binder treatment.[135] Furthermore, the study found that RAASi discontinuation was less frequent with SZC treatment than for patients with no K^+ binder treatment, with over twice as many patients discontinuing RAASi therapy in the no K^+ binder cohort vs the SZC cohort.[135] Results of subgroup analyses of patients with CKD, HF, and CKD and HF were consistent with the primary analysis. In the re-analysis of ZORA, analysing subgroups stratified by S–K levels (≥5.0–<5.5 mmol/L, ≥5.5–<6.0 mmol/L, and ≥6.0 mmol/L), the results were consistent with the primary analysis by Rastogi *et al.* [redacted] of SZC in the proportions receiving guideline RAASi therapy. In a meta-analysis of the ≥5.5–<6.0 mmol/L subgroup across the US and Japan, SZC was associated with a [redacted] proportion of patients that discontinued RAASi therapy and a [redacted] proportion that stabilised RAASi dosage compared with those not receiving a K^+ binder.[136] In the Japan population, SZC usage was associated with a [redacted] proportion of patients that up-titrated their RAASi therapy compared with those not receiving a K^+ binder.[136] These results are supported by the recently published REALIZE-K prospective, double-blind, randomised withdrawal trial.[159] This study investigated the optimisation of spironolactone (an MRA) in patients with heart failure and reduced ejection fraction (HFrEF) and HK (n=203). During open-label run-in, participants underwent spironolactone titration (target: 50 mg/daily); those diagnosed with HK initiated SZC. Participants achieving normokalemia (S–K 3.5–5.0 mEq/L) on SZC and spironolactone ≥25 mg/daily were randomised to continued SZC or placebo for six months. The primary endpoint was the proportion of participants achieving normokalaemia whilst maintaining ≥25 mg/daily of spironolactone. The results of the REALIZE-K study demonstrated that patients were more likely to continue receiving spironolactone ≥25 mg/daily (81% vs 50%; OR: 4.33 [95% CI: 2.50–7.52]; p<0.001) in the six months after the randomisation period for participants randomised to receive on-going SZC as compared with the placebo group which discontinued in the randomisation period.[159] However, this study investigated a subset of the population relevant to the NICE

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Uncertainty	Limitations of TA599	Current appraisal
		decision problem and [redacted] had an S–K level of ≥5.5–<6.0 mmol/L and were receiving a SZC dose licensed in the UK. In summary, the results of the ZORA study demonstrate that SZC helps patients maintain and potentially return to guideline directed RAASi therapy after an HK event.[135]
The relationship between RAASi treatment dosages and long-term treatment outcomes	Evidence was obtained from a literature search (Xie *et al.*[94] and for mortality and CV event risk in the CKD population and Flather *et al.*[144] for hospitalisation risk in the HF population). No direct evidence was generated by AstraZeneca	As discussed in Section B.2.1, an SLR was conducted to investigate the use of RAASi in patients with HK. The use of RAASi therapy is pivotal to all national and international guidelines for the management of HF and/or CKD and represent gold-standard guideline directed medical treatment for these conditions. However, their use is often limited due to HK leading to reduced doses or discontinuation This SLR investigated long-term outcomes in patients discontinuing/down-titrating RAASi medications.[138] ***Chronic Kidney Disease*** For patients with CKD, RAASi discontinuation was associated with statistically significantly increased risks of CV events, all-cause mortality (including in patients discontinuing due to HK) and MACE. A meta-analysis conducted by Tang *et al*. found that discontinuation of RAASi was shown to statistically significantly increase the risk of CV events (HR: 1.25 [95% CI: 1.17–1.32]) and mortality (HR: 1.42 [95% CI: 1.23–1.62]). In patients who discontinue RAASi specifically due to HK, there was also a statistically significant increased risk of mortality (HR: 1.48 [95% CI: 1.29–1.70]).[67] Similarly, a meta-analysis conducted by Nakayama *et al*. found that discontinuation of RAASi was shown to statistically significantly increase the risk of mortality (HR: 1.41 [95% CI: 1.23–1.63]) and MACE (HR: 1.20 [95% CI: 1.15–1.25]).[68] The SLR did not identify any evidence of increased risk arising from RAASi dose modifications or for hospitalisation following RAASi discontinuation. ***Heart Failure*** For patients with HF, a meta-analysis reported on the risk of all-cause mortality in HF patients discontinuing RAASi therapy (specifically MRA). This study reported that compared with patients that continued their therapy following an HK event, treatment discontinuation was associated with a statistically significant increase in all-cause mortality (an increase of 31%).[145] Furthermore, an RCT (HF-ACTION) reported that among 1,999 ambulatory patients

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Uncertainty	Limitations of TA599	Current appraisal
		with chronic HFrEF, discontinuation of RAASi treatment resulted in a statistically significant increase in all-cause mortality (HR: 1.86 [95% CI: 1.28–2.68]). This study also demonstrated that patients discontinuing RAASi were at a numerically increased risk of CV mortality or HF hospitalisation, although after adjusting for baseline characteristics this result was not statistically significant.[66] Among HF patients receiving lower doses of RAASi therapy (akin to a down-titration), two publications reported statistically significant increases in all cause mortality. A meta-analysis conducted by Sun *et al*. evaluated target RAASi (specifically ACEi/ARBs) dose (defined as 50–99% of guideline-recommended dose) versus sub-target RAASi doses in elderly patients (>60 years) with HFrEF and reported statistically significantly lower rates of all-cause mortality among patients receiving the target RAASi dose (HR: 0.92 [95% CI: 0.87–0.98]).[64] A further meta-analysis reported statistically significantly lower odds of all-cause mortality with high-dose (mean daily dose ≥200 mg) versus low-dose (mean daily dose <200 mg) sacubritril/valsartan for patients with LVEF <40% (OR: 0.23 [95% CI: 0.11–0.47]).[65] There was considerable heterogeneity in the results reported for the effect of RAASi dose modifications on hospitalisation outcomes.[138]

Abbreviations: ACEi: angiotensin-converting-enzyme inhibitor; ARB: angiotensin II receptor blocker; CKD: chronic kidney disease; CI: confidence interval; CV: cardiovascular; eGFR: estimated glomerular filtration rate; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; HR: hazard ratio; IRR: incidence rate ratio; MACE: major adverse cardiac event; OR: odds ratio; RAASi: renin-angiotensin-aldosterone system inhibitor; S–K: serum potassium; SZC: sodium zirconium cyclosilicate.

B.2.5 *Strengths and limitations of the clinical evidence base for the technology*

The key strengths and limitations are summarised below.

Strengths

The SPARK study used one of the largest longitudinal data sources in the UK and included [redacted] UK patients in the base cohort.[29] Furthermore, the methods and definitions used were based on clinical and methodological expertise, aligning with UK clinical practices and relevant previous observational studies.[29] As such, the patient population included in the study is reflective of the patient population observed in UK clinical practice. Results from the SPARK study demonstrated that patients with CKD or HF with S–K levels ≥5.5–<6.0 mmol/L have [redacted] incidence rates of mortality and hospitalisations than patients with an S–K level of ≥4.5–<5.0 mmol/L, and CKD patients with S–K levels ≥5.5–<6.0 mmol/L have a [redacted] incidence rate of MACE than those with S–K levels ≥4.5–<5.0 mmol/L.[29] Further analysis showed that an unmeasured confounder would need to be simultaneously highly correlated with the clinical outcome and imbalanced between S–K groups to reverse or nullify these findings.[29]

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The ZORA analysis conducted by Rastogi *et al.* included a large number of patients from three different countries,[135] and demonstrated that treatment with SZC is associated with statistically significantly greater odds of maintaining RAASi therapy with SZC versus no K^+ binder treatment across the three countries [135] To avoid potential confounding, a large number of covariates such as concomitant medication and comorbidities were PS-matched, to enhance the robustness of study findings.

In the ad-hoc re-analysis of ZORA, patients were stratified by S–K level to demonstrate specific treatment effectiveness in the decision problem population. A logistic regression was also used to predict PS-scores. Although the sample size at each S–K level was small after stratification (<100), variables included in the PS-matching was selected using principles of modelling, to remove the categories with very small number of cases that can lead to skewed scores. In another method to improve robustness, variables which were already well-balanced (<0.1 SMD) were removed from the matching model to improve the accuracy of prediction in the remaining variables.

While the ZORA study is not UK-specific, clinical expert opinion considers the study findings to be generalisable to the UK population.[23]

Limitations

The observational data used in the studies were not originally collected for research purposes and therefore the accuracy of diagnoses coding may be limited.[29, 135] Additionally, due to the non-randomised design of the studies, there was a risk of residual confounding.[29, 135] However, to explore the likely effect of any residual confounding, e-values were calculated to quantify the strength of the unmeasured confounder needed to reverse the observed relationships.[67] An analysis of these e-values demonstrated that it is unlikely for any remaining unknown confounder to nullify the observed relationships between S–K and MACE, mortality and hospitalisation.

Whilst SPARK stratified patients by S–K levels and eGFR, this was not considered for NYHA and LVEF as these variables are poorly coded within the CPRD data. However, this is not expected to impact overall results given the SPARK study used data from CPRD and as such can be considered to have used high-quality, granular data from a population that is representative of the general UK population.

Due to UK clinical guidance, few patients with an S–K <6.0 mmol/L have received SZC for the treatment of persistent HK. As a result, the analysis conducted in SPARK to assess the ability of SZC to enable patients with CKD or HF to maintain optimal RAASi dosage was not possible as data were ultimately deemed insufficient to conduct a meaningful analysis. In the absence of suitable UK data (due to the restrictions placed on the use of SZC in these patients), data from other geographies has been utilised to explore this relationship.

In the ZORA study, all patients were required to have at least 180 days of follow-up after the index date resulting in immortal time bias.[135] However, this affected the SZC and no K^+ binder cohorts equally.[135] The SZC cohort in the ZORA study was also required to have at least 120 days of continuous SZC treatment to capture patients with longer-term SZC treatment.[135] This means that findings may have limited generalisability for patients with shorter SZC use durations.[135] In the ad-hoc re-analysis of ZORA stratifying patient cohorts by S–K levels, due to low sample sizes, there was a low statistical power to differentiate

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differences in RAASi therapy changes, with only differences in [redacted]. [136] This finding is however consistent with the expectation for how patients would be managed in the UK based on expert clinical feedback.

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B.3. Cost-effectiveness

Summary of economic evidence previously evaluated by NICE

The model used in this submission is largely aligned with that used in TA599, incorporating the NICE committee and EAG's preferences, where applicable.[3] All inputs used and approaches taken in the model for the current appraisal, aside from those detailed below, are aligned with those previously deemed appropriate in TA599.

Changes since the 2019 TA599 NICE evaluation

The key development in the treatment landscape for HK since the 2019 TA599 evaluation has been the introduction of K^+ binders (SZC and patiromer). Following the regulatory approval and reimbursement of SZC for the treatment of HK in the UK and internationally, it has been possible to collect real-world data on SZC usage to inform inputs that were previously informed by literature studies.

In TA599, the relationship between S–K and long-term outcomes was informed by literature that did not adjust for RAASi usage and did not have a method to assess the impact of any residual confounders.[3] The observational SPARK study, included as part of the clinical evidence in the current appraisal, includes additional adjustment for additional covariates and an estimation of the effect size of unmeasured confounders needed to nullify the measured outcomes.[29] As such, data from the SPARK study were used to inform the relationship between S–K and long-term outcomes in preference of the literature previously used to inform TA599.[3]

At the time of TA599 there was no evidence to adequately demonstrate SZC would lead to beneficial RAASi modification independent of S–K levels. The subgroup analysis of the observational ZORA study was used to inform this relationship in the current submission as the study includes additional cohort-level outcomes of the effect of SZC on RAASi treatment patterns stratified by S–K level and covariate.[136]

The model submitted for TA599 originally used a treatment duration of 52 weeks in the chronic setting and a lifetime duration in the revised base case. However, this was originally based on clinical assumptions prior to the introduction of SZC and more recent Market Research reports a median duration of treatment of patients with HK of [redacted] days between October 2022 and December 2022 and [redacted] days between July 2023 and August 2023.[160] Furthermore, clinical expert opinion confirmed a 12 week treatment duration in the chronic setting to be more aligned with clinical practice and therefore a 12 week duration is used in the base case.[23]

To ensure relevance to the current decision problem population all costs have been inflated to the current cost year and clinical trial evidence is sourced specifically from those with S–K of ≥5.5–<6.0 mmol/L, aligned to the approach taken during TA599.

Incremental cost-effectiveness analysis results

The cost-effectiveness results demonstrate SZC is a cost-effective treatment option for those with persistent HK and S–K of ≥5.5–<6.0 mmol/L across both the CKD & HF population. These results are consistent across a range of sensitivity and scenario

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analyse, with SZC maintaining cost-effectiveness in all PSA simulations below the WTP threshold of £20,000.

These results are likely to be conservative as several additional benefits are not included in the QALY calculation including enabling the use of SGLT-2 inhibitors, modelling those comorbid with CKD or HF, demonstrating that patients on SZC have increased likelihood of RAASi up-titration, and applying costs and disutility of low K^+ diet.

B.3.1 *Published cost-effectiveness studies*

An SLR update was conducted on the 18th June 2024 to identify existing cost-effectiveness studies conducted in the management of HK in adults. This SLR was conducted as an update of a previous SLR (conducted 27th April 2018) to support the original appraisal for SZC in HK (TA599).[3] The purpose of this original SLR and the subsequent update was to identify economic evaluations, health-state utility values (HSUVs), and cost/resource use studies conducted in HK.

In line with guidance from the Centre for Reviews and Dissemination (CRD), the population, interventions, comparators, outcomes and study type (PICOS) principle was used to define the following review questions:[161]

- What cost-effectiveness analyses have been conducted in the treatment of HK?
- What studies have been conducted which provide utilities and disutilities of patients with HK?
- What are the costs and resource use associated with the management of HK?

For this economic SLR, a single search strategy was used to identify cost-effectiveness, HRQoL (Section B.3.4), and cost and resource use studies (Section B.3.5). A full write up of the methods used to identify all relevant studies, and a description and quality assessment of the cost-effectiveness studies identified are provided in Appendix G.

A total of 35 cost-effectiveness studies were identified. The NICE STA user guide recommends that an overview of each cost-effectiveness study is required only if it is relevant to decision-making in England.[162] Therefore, extraction was performed for cost-effectiveness studies conducted from a UK or Irish perspective (n=8) and a detailed summary is provided in Table 26. A tabulated summary of the 27 excluded cost-effectiveness studies from countries outside of the UK/Ireland is presented in Appendix G. Quality assessment of these studies can also be found in Appendix G.

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Table 26. Summary list of published UK cost-effectiveness studies (1/3)

Study	TA599[3]	SMC2288[163]	TA623[15]
Year	2019	2020	2020
Country	England & Wales	Scotland	England & Wales
Intervention, Comparator	SZC, standard care	SZC, standard care	Patiromer, RAASi discontinuation (no patiromer/ standard care)
Summary of model	Based on a **patient-level, fixed-time increment stochastic simulation model** previously published (Bakhai et al 2018): Objective was to quantify the potential health and economic value associated with sustained potassium management and optimal RAASi therapy in heart failure patients. • Patients with HF • Lifetime horizon (length NR) • 4-week cycle length • 3.5% discount • Health states include NYHA Stage I, II, III, IV, and HF mortality (death), as well as CKD health states • Stage 3a, 3b, 4, 5) and CKD mortality (death), with CKD 5 patients leaving the model due to treatment change. • Events are also included in the model (HK event, arrhythmia, CV event, MACE, hospitalisation, RAASi change, TRAE) and all-cause mortality • UK healthcare payer perspective • Deterministic sensitivity analyses were conducted • Cost and utility value inputs were derived from published literature	**Patient-level, fixed-time increment, stochastic simulation:** • Patients with HK with CKD Stage 3b–5 and/or HF • Lifetime horizon (80 years) • Cycle length NR • Health states: HF NYHA Stages I to IV, CKD Stages 3b–5, RAASi changes, treatment-related adverse events, treatment initiation/discontinuation, HK events, cardiovascular events, hospitalisation, mortality, RRT • Under the PAS, a discount is offered on the list price of the medicine (rate NR) • Scottish NHS perspective • Sensitivity analysis NR Utility values were sourced from published literature	Objective was to evaluate the impact of patiromer on time to HK and RAASi discontinuation rather than progression of CKD **Markov model:** • CKD Stage 3–4 with mild HK and on RAASi • Health states: CKD, ESRD (CKD progression), death, and CV health states • Lifetime horizon (35 years) • Cycle length of 1 month • Discount rate 3.5% • Perspective of the NHS and PSS in England and Wales • Probabilistic sensitivity analysis was performed

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Study	TA599[3]	SMC2288[163]	TA623[15]
Patient population (average age in years)	Patients with NYHA heart failure (aged 64.1 years)	Patients with HK (defined as an S–K of ≥6.0 mmol/L) with CKD Stage 3b–5 and/or HF (age NR)	CKD stage 3–4 with HK and on RAASi (age 65 years)
QALYs / LYs (intervention, comparator)	**Base case** • CKD – incremental QALYs: 0.708 • HF – incremental QALYs: 0.818	**Discounted results – lifetime horizon** • Patiromer–spironolactone–ACEI: 2.79 QALYs, 5.29 LYs • ACEI-only: 2.60 QALYs, 4.62 LYs	**Discounted PAS results** • Incremental QALYs: 0.10 • Incremental LYG: 0.11
Costs (currency) (intervention, comparator)	GBP (year NR) **Total costs** • NR (CiC)	GBP (year NR) **Total cost, HF outpatient** • SZC: £26,439 • Standard care: £20,978 • Incremental: £5,461 **Total cost, CKD outpatient** • SZC: £45,646 • Standard care: £41,543 • Incremental: £4,103	GBP (year NR) **Total costs** • NR (CiC)
ICER (per QALY gained)	**ICER – Outpatient setting** Original company submission base case: CKD patients • SZC: £26,111/QALY HF patients • SZC: £12,928/QALY Revised base case CKD patients • SZC: £11,644/QALY HF patients • SZC: £18,158/QALY **ICER – emergency setting** Original company submission base case:	**ICER for PAS (base case at list price)** • HF outpatient: £7,005/QALY • CKD outpatient: £9,438/QALY	**ICER for the PAS price results** • Patiromer vs no patiromer: Dominant (−£14,651/QALY)

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Study	TA599[3]	SMC2288[163]	TA623[15]
	CKD patients • SZC: dominates HF patients • SZC: £4,924/QALY Revised base case: CKD patients • SZC: dominates HF patients • SZC: dominates		

Abbreviations: ACEi: angiotensin-converting enzyme inhibitor; CiC: commercial-in-confidence; CKD: chronic kidney disease; CV: cardiovascular; HF: heart failure; HK: hyperkalaemia; ICER: incremental cost-effectiveness ratio; LY: life year; LYG: life years gained; MACE: major adverse cardiovascular events; NHS: National Health Service; NR: not reported; NYHA: New York Heart Association; PAS: patient access scheme; PSS: personal social services; QALY: quality-adjusted life year; RAASi: renin-angiotensin-aldosterone system inhibitor; RRT: renal replacement therapy; S–K: serum potassium; SZC: sodium zirconium cyclosilicate; TRAE: treatment-related adverse event.

Table 27: Summary list of published UK cost-effectiveness studies (2/3)

Study	Bakhai [164]	Ward[165]	Ward[166]
Year	2018	2023	2022b
Country	UK	UK	UK
Intervention, Comparator	Optimal S–K management and ongoing RAASi therapy (treatment arm), patients who discontinued RAASi treatment to avoid HK	Patiromer, standard care	Patiromer, standard care
Summary of model	This study developed a model to quantify the potential health and economic value associated with sustained potassium management and optimal RAASi therapy in heart failure patients A simulation model was designed to characterise the progression of heart failure across NYHA functional classifications, and predict long-term health and economic outcomes according to S–K levels and/or RAASi use	The objective was to evaluate the cost effectiveness of patiromer in the UK healthcare setting, and to evaluate the relationship between HK incidence and optimal RAASi management, and lifetime economic outcomes HK events were stratified by severity in the model (5–5.5 mmol/L, 5.5–6 mmol/L, >6 mmol/L) **Markov model**	The objective was to evaluate the cost effectiveness of patiromer compared with the Standard care for the treatment of HK in patients with CKD with and without HF **Markov model** • Health states for patients with CKD: CKD Stages 3–5, Dialysis, transplant • Health states for patients with HF: NYHA Stage I–IV • Patients were modelled from CKD Stage 3 and CKD Stage 4 through ESRD and RRT, with or without HF

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Study	Bakhai [164]	Ward[165]	Ward[166]
	Patient-level simulation model • Fixed-time increment stochastic simulation to model the natural history of heart failure progression over a lifetime horizon. • Disease progression was modelled according to transitions between NYHA functional classifications (I–IV) (health states), using monthly probabilities sourced from Yao et al (2007). As well as health states NYHA I–IV and Death. • Events were also included for emergency HK, arrhythmia, hospitalisation, change in RAASi use • No relationships were modelled between HF progression and either RAASi use or S–K levels, since no suitable data were identified • Simulated patients progressed through the model until death from disease-specific or general causes	• Constructed to simulate a cohort of HK patient with CKD with or without HF • Health states for patients with CKD: CKD Stages 3–5, Dialysis, transplant • Health states for patients with HF: NYHA Stage I–IV Monthly cycle length • Lifetime horizon (length NR) • Monthly cycle length • UK healthcare payer's perspective • Discount rate of 3.5% • Probabilistic and deterministic sensitivity analysis were undertaken • Cost and utility inputs taken from NHS reports and from literature	• Horizon NR • Cycle length NR • NHS perspective • Discount rate of 3.5% • Probabilistic and one-way sensitivity analyses were conducted • Costs and utility values inputs sourced from NHS resources and published literature
Patient population (average age in years)	Patients with HF and normokalaemia aimed at preventing HK (73 years at baseline)	Patients with HK with advanced CKD with and without HF (Mean: 65.30 years old, SE: 0.89)	Patients with HK and CKD, with and without HF (age NR)
QALYs, LYs (intervention, comparator)	**Undiscounted results** Total QALYs • Treatment arm: 4.53 • Control arm: 3.79 • Incremental: 0.74 LYs • Treatment arm: 8.31 • Control arm: 6.93 • Incremental: 1.38	**Discounted results – lifetime horizon** Patiromer: • 6.356 QALYs • 8.935 LYs Standard care: • 6.156 QALYs • 8.670 LYs **Undiscounted results** Patiromer:	**Discounted results** Patiromer: • 5.19 QALYs • 6.94 LYs Standard care: • 5.13 QALYs • 6.88 LYs

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Study	Bakhai [164]	Ward[165]	Ward[166]
	Discounted results Total QALYs • • Treatment arm: 3.72 • Control arm: 3.19 • Incremental: 0.53 LYs • Treatment arm: 6.79 • Control arm: 5.81 • Incremental: 0.99	• 8.176 QALYs • 11.685 LYs Standard care: • 7.904 QALYs • 11.321 LYs	
Costs (currency) (intervention, comparator)	GBP (2014–15) **Undiscounted costs** • Treatment arm: £7,016 • Control arm: £6,977 • Incremental: £38 **Discounted costs:** • Treatment arm: £5,734 • Control arm: £5,843 • Incremental: −£110	GBP (2019–2020) **Total discounted costs** • Patiromer: 116,675 • Standard care: 113,701 **Total undiscounted costs** • Patiromer: 168,834 • Standard care: 164,306	GBP (2019–2020) **Incremental discounted cost** • Patiromer vs standard care: £970.60 per patient
ICER (per QALY gained)	**Net monetary benefit (NMB)** **Undiscounted results** • NMB at £20,000 WTP threshold: £14,753 • NMB at £30,000 WTP threshold: £22,149 **Discounted results** • NMB at £20,000 WTP threshold: £10,679 • NMB at £30,000 WTP threshold: £15,964	**ICER** **Discounted:** Patiromer vs standard care: • £14,816/QALY **Undiscounted:** Patiromer vs standard care: • £16,672/QALY	**ICER** Patiromer vs standard care: • £16,667/QALY

Abbreviations: CKD: chronic kidney disease; HF: heart failure; HK: hyperkalaemia; LYs: life years; NHS: National Health Service; NMB: net monetary benefit; NR: not reported; NYHA: New York Heart Association; QALYs: quality-adjusted life years; RAASi: renin-angiotensin-aldosterone system inhibitor; SE: standard error; S–K: serum potassium; WTP: willingness to pay.

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Table 28: Summary list of published UK cost-effectiveness studies (3/3)

Study	Ward[167]	Ward[165]
Year	2022a	2022c
Country	Ireland	Ireland
Intervention, Comparator	Patiromer, standard care	Patiromer, standard care
Summary of model	To evaluate the cost-effectiveness of patiromer compared with standard care for the treatment of HK in patients with CKD with and without HF from the perspective of the healthcare payers in Ireland **Markov model** • Patients with HK and CKD with and without HF • Health states: CKD Stage 3, 5 or 5, dialysis, transplant, NYHA Stage I, II, III, or IV • Lifetime horizon (years NR) • Cycle length NR • Discount rate 4% • Payer perspective in Ireland • Cost inputs sourced from Healthcare Pricing Office ABF 2020 Admitted Patient Price List, NICE Clinical guidelines for CKD and from published literature • Probabilistic and one-way sensitivity analyses were conducted	To develop a *de novo* disease progression and cost-effectiveness model to evaluate the clinical and economic outcomes associated with the use of patiromer for the treatment of HK in patients with CKD with and without HF **Markov model** • Patients with HK and CKD with and without HF • Health states: CKD Stage 3, 5 or 5, dialysis, transplant, NYHA Stage I, II, III, or IV • Discount rate of 4% • Lifetime horizon (years NR) • Monthly cycle length • Payer perspective in Ireland • Cost inputs source NR • Probabilistic sensitivity analysis was conducted
Patient population (average age in years)	Patients with HK and CKD, with and without HF (age NR)	Patients with HK and CKD, with and without HF (age NR)
QALYs, LYs (intervention, comparator)	**Discounted results** Patiromer: • 5.07 QALYs • 6.78 Lys Standard care: • 5.02 QALYs	**Total QALYs** **Discounted results** Patiromer: • 6.148 QALYs • 8.622 LYs Standard care:

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Study	Ward[167]	Ward[165]
	• 6.72 LYs	• 5.955 QALYs • 8.368 LYs Incremental: • 0.194 QALYs • 0.254 LYs **Undiscounted results** Patiromer: • 8.141 QALYs • 11.628 LYs Standard care: • 7.870 QALYs • 11.264 LYs Incremental: • 0.271 QALYs • 0.364 LYs
Costs (currency) (intervention, comparator)	Euro 2019–2020 **Total costs:** • NR	Euro 2019–2020 Per patient cost, patiromer vs SoC, **Discounted total costs:** • Total costs: €183,014 vs €178,035 • HK: €1250 vs €1476 • CKD: €30,488 vs €29,487 • RRT: €101,136 vs €99,927 • MACE: €7871 vs €7926 • Hospitalisation: €36,646 vs €35,758 • RAASi drug use: €331 vs €284 • RAASi titration: €2891 vs €3177 **Undiscounted total costs:** • €281,807 vs €273,959

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ICER (per QALY gained)	**ICER** • Discounted: €1,734/QALY	**ICER** • Discounted: €25,719/QALY • Undiscounted: €28,920/QALY

Abbreviations: CKD: chronic kidney disease; HF: heart failure; HK: hyperkalaemia; ICER: incremental cost-effectiveness ratio; LY: life year; MACE: major adverse cardiovascular events; NR: not reported; NYHA: New York Heart Association; QALY: quality-adjusted life year; RAASi: renin-angiotensin-aldosterone system inhibitor; RRT: renal replacement therapy; S–K: serum potassium.

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B.3.2 *Economic analysis*

Of the eight UK or Irish cost-effectiveness analyses identified, three were HTA documents of which two assessed SZC versus standard care (NICE TA599,[3] SMC2288)[163] and one assessed patiromer versus standard care (NICE TA623),[15] all aimed at treating HK in adults. Four of the eight UK/Irish cost-effectiveness analyses identified consisted of linked publications in HK patients and CKD with or without HF in the UK (n=2) or Ireland (n=2), assessing the cost effectiveness of patiromer compared with standard care. The one remaining economic evaluation identified, relevant to the UK/Ireland, assessed the cost effectiveness of optimal S–K management and ongoing RAASi therapy (treatment arm) compared with patients discontinuing RAASi therapy (control arm) in patients with HF and normokalaemia, aimed at preventing HK.[164]

In total, five of the eight analyses identified used a Markov model, including the four linked publications and one model submitted for NICE appraisal (NICE TA623),[15] whilst the remaining three records used a patient simulation model (PLS) consisting of disease health states and specified events. Where reported, all models adopted a lifetime horizon and monthly or four-week cycle length. In the PLS models, the progression of CKD was modelled through CKD stages, via continuous eGFR decline until the incidence of ESRD, while the progression of HF was modelled according to transitions between New York Heart Association (NYHA) classes I–IV. In these appraisals, patients with HK entered the PLS at baseline. And each individual patient has a simulated time-dependent trajectory of S–K that was linked to cardiovascular events, hospitalisation and mortality via published rates.

Based on the precedence set by these studies, the PLS model previously assessed and considered suitable for decision-making by NICE in TA599 was considered the most appropriate model structure for this partial update.[3] The PLS model captures the transience and complexity of HK management in patients with CKD or HF, while enabling the modification of RAASi therapies including down-titration or discontinuation. The presented PLS model in the current submission is an updated version of that previously appraised in TA599, with the model structure updated to align with the outcome of resulting discussion in TA599 and to the decision problem population of interest for this partial update.[3] In addition, input sources were updated with RWE studies commissioned specifically to address concerns raised by NICE in TA599 and with relevant clinical and economic evidence that accurately reflect current clinical practice in the NHS captured in the SLRs.

A comparison between the final appraisal determination (FAD) model from TA599 and the economic model used in the current appraisal is provided in Table 29.

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Table 29. Comparison between the FAD model from TA599 and the economic model used in the current appraisal

Model Parameter	TA599 FAD model	Current appraisal	Justification
Structure	PLS model		Considered appropriate in TA599[3]
Health States	Multiple populations are considered in the model; Final decision-making model had persistent population entering the model with S–K ≥6.0 mmol/L and the emergency population at ≥6.5 mmol/L	Only the decision problem population of patients with persistent S–K ≥5.5–<6.0 mmol/L is considered in the model	The modelled population is restricted to the decision problem population as per the NICE final scope
Population	A combined ICER of patients comorbid with CKD or HF included in the submission. Separate ICERs for the CKD and HF populations were submitted during clarification questions and used for decision-making. No ICERs presented for those comorbid with CKD and HF	Separate ICERs for the CKD and HF populations for the deterministic base case are submitted alongside the combined ICER of patients comorbid with CKD or HF in the current submission. Sensitivity analysis is presented for the combined population only	Aligned with the preference of the NICE committee in TA599[3] The exclusion of those comorbid with CKD and HF can be considered a conservative approach
Treatment Duration	• 28 days in the emergency setting • 52 weeks in the chronic setting • Lifetime in the chronic setting (revised base case)	• 12 weeks in the chronic setting	The treatment durations utilised in TA599 were underpinned by clinical assumptions alone in the absence of SZC being available in the UK. This assumption has been updated based on Market Research which reports the median duration of treatment of patients with HK was [redacted] days between October 2022 and December 2022 and [redacted] days between July 2023 and August 2023. These assumptions are also aligned with further clinical expert opinion gathered during the development of this appraisal.[23] Therefore, the treatment duration utilised in the updated model is aligned with current clinical practice.
S–K trajectories	• Trajectories for the SZC arm were derived from pooled ZS-004[127] and ZS-005[139] trial data, informed by the ≥5.5–<6.0 mmol/L S–K population • Trajectories for the standard care arm were derived from the placebo arm of ZS-003. The rate of S–K decline in the correction phase of the		Restricted to decision problem population as relevant for this current partial review of TA599. S–K trajectories are derived as per the EAG preferred method in TA599[3]

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Model Parameter	TA599 FAD model	Current appraisal	Justification
	standard care arm is conservatively assumed to carry on to a third day using linear extrapolation, and S–K remains unchanged in the maintenance phase • S–K changes of −0.115 and −0.23 mmol/L are incurred upon RAASi therapy down-titration and discontinuation, respectively		
Data sources informing relationship between S–K and long-term outcomes	• Luo *et al.* was used for the CKD population (IRR for death, MACE, hospitalisations)[81] • Desai *et al.* was used for the HF population (IRR for death, MACE, hospitalisations)[108]	• SPARK data were used for the CKD and HF populations (IRR for death, MACE, hospitalisations)[29]	The observational SPARK study is included as part of the clinical evidence in the current appraisal. (See Section B.2.3.1). SPARK was conducted by AstraZeneca to address the concerns raised by NICE relating to the CPRD evidence presented in TA599 to demonstrate the association between persistent HK and adverse clinical outcomes. Previous studies did not adjust for RAASi usage or for unmeasured confounders, and thus the independence of the relationship between S–K and long-term outcomes could not be reliably established. SPARK addresses these concerns by investigating the relationship between S–K and hospitalisation, MACE, and mortality, stratified by S–K levels and eGFR. In line with the NICE RWE framework, the SPARK study also took steps to minimise the risk of bias, and adjusted by an additional 30+ confounders than the studies used to inform TA599, including comorbidities and co-medications, including RAASi usage.[67] In addition, e-values were employed to quantify the strength of the unmeasured confounder needed to reverse the observed relationships, and demonstrated that it is unlikely for any remaining unknown confounder to nullify the observed relationships between S–K and MACE, mortality and hospitalisation.[67]
Data sources informing relationship between RAASi modification and long-term outcomes	• The proportion of patients that down-titrate and discontinue RAASi at ≥5.5 and ≥6.0 mmol/L was provided by Epstein *et al.*[16] • Assumed to be the same for both SZC and standard care	• Provided by data from the ZORA re-analysis at the S–K level and treatment level	Given that K^+ binders are not currently reimbursed within the UK for the population of relevance the decision problem, the observational study ZORA is included as part of the clinical evidence in the current appraisal (See Section B.2.3.2). The ZORA re-analysis examines medical records for patients from the US and Japan where treatment guidelines have a lower

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Model Parameter	TA599 FAD model	Current appraisal	Justification
	arms lacking evidence to the contrary		threshold for using SZC to treat persistent HK. This study includes additional arm-level outcomes for the effect of SZC on RAASi treatment patterns stratified by S–K level and covariates. UK clinical experts agreed that whilst these data are not specific to the UK, results are generalisable to the UK population and the results reflect their clinical experience.[23]
Data sources informing relationship between RAASi usage and long-term outcomes	Link between RAASi use and long-term outcomes (hospitalization, CV events and mortality): • Provided by Flather *et al.* for hospitalisations, of HF patients, sub-max RAASi dosage assumed to offer 35.9% benefit of max RAASi[144] • Provided by Xie *et al.* mortality and CV events, sub-max RAASi dosage assumed to offer 50% benefit of max RAASi[94]	Link between RAASi use and long-term outcomes (hospitalization, CV events and mortality): • Provided by Flather *et al.* for hospitalisations, of HF patients, sub-max RAASi dosage assumed to offer 35.9% benefit of max RAASi[144] • Provided by Chen *et al*. for mortality of HF patients, sub-max RAASi dosage assumed to offer 50% benefit of max RASSi[65] • Provided by Xie *et al.* mortality and CV events, sub-max RAASi dosage assumed to offer 50% benefit of max RAASi[94]	Considered appropriate as per the committee preferred base case in TA599.[3] Additional data identified for the relationship between RAASi usage and mortality in HF patients through clinical SLR
Utility values	Utility values of CKD and HF health states: • EAG preferred values derived from TA599 for CKD health states • Gohler *et al.* for HF health states[168]		Considered appropriate as per the committee preferred base case in TA599.[3] Furthermore, an additional SLR conducted in support of this partial resubmission has identified consistent results.
HCRU	HCRU costs: • All RAASi dosage alterations are performed in the outpatient setting	• CKD patient time-in state costs by stage are based on Kent *et al.*[169] • RAASi drug costs are obtained from the BNF	RAASi dosage alteration resource use is aligned to committee preferences in TA599.[3] Kent *et al.*[169] was used to inform time in state costs for CKD patients, consistent with recent appraisals in the CKD indication, such as TA775.[170] This source was considered to be appropriate by the NICE committee as

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Model Parameter	TA599 FAD model	Current appraisal	Justification
	• CKD patient time-in state costs by stage are based on NICE CG182 [51] • RAASi drug costs are obtained from the MIMs database		per the TA775 appraisal.[170] All costs have been updated to the 2023 cost year using the NHS cost Inflation Index (NHSCII) or the Personal Social Services (PSS) Pay & Prices Index.[171]

Abbreviations: BNF: British National Formulary; CKD: chronic kidney disease; EAG: external assessment group; FAD: final appraisal determination; HCRU: healthcare resource use; HF: heart failure; HK: hyperkalaemia; IRR: incidence rate ratio; MACE: major adverse cardiovascular events; MIMS: Monthly Index of Medical Specialities; NHSCII: National Health Service cost inflation index; PLS: patient level simulation; PSS: personal social services; RAASi: renin-angiotensin-aldosterone system inhibitor; S–K: serum potassium; SZC: sodium zirconium cyclosilicate.

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B.3.2.1 *Patient population*

In line with the decision problem for this partial update to the guidance for SZC in HK, the patient population included in the model comprises adults with persistent HK with an S–K of ≥5.5–<6.0 mmol/L. This is a narrower population than the licensed indication, as it does not include the emergency HK population, or the persistent HK population with an S–K of ≥6.0 mmol/L, as SZC is already recommended in these populations following the TA599 appraisal.[3]

As discussed in Section B.1.3.3, HK is usually a consequence of an underlying health condition resulting in impaired K^+ excretion. The most common of which are CKD and HF. Therefore, in line with underlying health conditions observed clinical practice and in the clinical trial programme for SZC, patients in the model have a co-diagnosis of HK and an underlying condition, including:

- CKD stage 3a–5 (CKD stage 3b–5 in the base case) (see Table 30), or
- NYHA functional class I, II, III or IV (see Table 31)

The patient population is assumed to enter the model with an S–K of [redacted] mmol/L, which is the mean S–K value of the ≥5.5–<6.0 mmol/L cohort within the pooled ZS-004 and ZS-005 trial dataset.[127, 139]

Table 30. CKD staging definitions

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

Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.
Source: Levey *et al.* 2005 [172]

Table 31. HF staging definitions

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

Abbreviations: HF: heart failure; NYHA: New York Heart Association.
Source: American Heart Association 2017[173]

B.3.2.2 *Model structure*

As discussed in Section B.1.3.3, clinical outcomes in patients with HK depend significantly on individual S–K profiles. As such, a PLS model was deemed to be an appropriate structure. The justification for the structure was considered during the evaluation of TA599 and was considered appropriate.[3]

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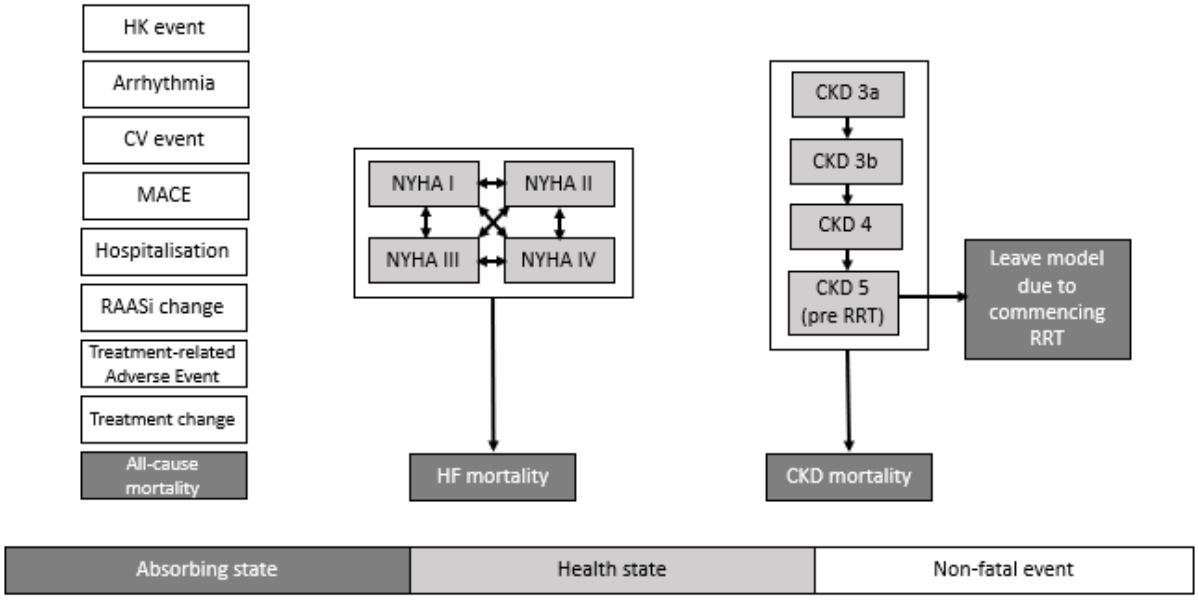
The model was designed to compare SZC against standard care in the target patient population. The model was developed as a patient-level, fixed-time increment stochastic simulation in Microsoft® Excel. The model's core calculations are undertaken within Visual Basic for Applications (VBA).

Figure 12 represents a simplified flow diagram depicting the health states and events captured by the model.

Figure 12. Flow diagram summarising the SZC model health states (shaded) and events (unshaded)



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

Cohorts of simulated patients with advanced CKD or HF enter the model at their first HK event. As can be seen, the progression of HF patients is modelled via transitions between NYHA classifications (I–IV), while the progression of CKD patients is modelled via the decline of eGFR on a continuous scale. For CKD patients, progression through CKD stages are tracked until the onset of ESRD and the initiation of RRT. The structures of the CKD and HF component of the model are based on well-documented existing models.[81,174]

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

Patients exit the model due to death or following the introduction of RRT.

Whilst the cost-effectiveness model could be adapted to model patients receiving RRT and SZC is now licenced in patients who are receiving chronic haemodialysis,[5] this population was not considered in TA599 and patients with haemodialysis were not included in the original ZS clinical trial programme. The license was subsequently revised in 2020 to extend indication for the treatment of patients receiving chronic haemodialysis via the EMA centralised procedure following further evidence from the DIALIZE and ADAPT studies.[5, 6, 125] The current clinical data on the use of SZC in dialysis patients is limited to the DIALIZE and

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ADAPT studies.[6, 125] Whilst these studies demonstrate that SZC is safe and efficacious at reducing S–K in patients receiving chronic haemodialysis, there are still a paucity of data reporting on the association between S–K and long-term health or resource use outcomes in this population, as such they were not included in the decision problem. Furthermore, appropriate cost-effectiveness modelling of SZC amongst patients in receipt of haemodialysis is complicated as RRT and transplantation are not cost-effective treatments.[175, 176] As an adaptation of the model structure would simulate patients receiving RRT as separate health states within the patient population, the inherent lack of cost-effectiveness associated with RRT and transplantation potentially negatively impacts the overall cost-effectiveness of SZC, thus obscuring the decision problem and targeted nature of this partial update, that is expanding the current positive guidance for those with persistent HK to a those with S–K ≥5.5–<6.0 mmol/L.

It should be noted that those SZC has been previously incorporated into the emergency COVID-19 guidelines for the management of dialysis patients in the NICE guidelines (NG160) as an important measure to allow a delay in dialysis until COVID-19 test results are known.[126] The guidelines also recommended the prescription of K^+ binders to allow the frequency of dialysis to be reduced, and reduce the risk of transferring patients undergoing dialysis to a hospital without dialysis facilities.[126] Therefore, SZC has already demonstrated value within the NHS in the dialysis population. Furthermore, international clinician consensus-based recommendations have highlighted specific potassium binders should play a role in the management of hyperkalaemia in ESKD.[98] Whilst a small proportion of the licensed population, AstraZeneca recognise those undergoing dialysis are a population of high unmet need and health inequality. Those with persistent HK undergoing haemodialysis and the challenges in evaluating the cost-effectiveness in this population is further discussed in section B.1.3.8.

Inputs to the model are included based on a hierarchy of evidence consistent with NICE's Reference Case. Where possible, direct trial evidence is used to inform parameters. However, the clinical trial programme for SZC, including those that subsequently recruited haemodialysis patients, does not adequately capture the relationship between S–K and the risk of long-term clinical outcomes such as mortality, MACE, and hospitalisation. The uncertainty in this relationship was raised by the committee in the original appraisal TA599,[3] as such, RWE studies have now been conducted to specifically address NICE's concerns on this relationship (see Section B.2.3).

An observational cohort study conducted using data from the UK CPRD (SPARK) investigates the relationship between S–K and hospitalisation, MACE, and mortality, stratified by S–K levels and eGFR. The SPARK study took steps to minimise the risk of bias, and adjusted by an additional 30+ confounders than the studies used to inform TA599, including co-medications, comorbidities and RAASi usage.[29] In addition, to explore the likely effect of any residual confounding, e-values were calculated to quantify the strength of the unmeasured confounder needed to reverse the observed relationships (Section B.2.3.1).[29] As such, SPARK can be considered a robust source of data for cost-effectiveness modelling. It was not feasible to use UK CPRD data to identify the relationship between SZC and RAASi usage for those with persistent HK and S–K ≥5.5–<6.0 mmol as SZC is currently not recommended for this population in England. Therefore a re-analysis of the multi-national observational study (ZORA) using data from the US and Japan was used to compare the

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likelihood of maintained RAASi therapy at six months following HK among patients treated with SZC or standard care. Specifically, this re-analysis stratified by S–K level is used to inform the proportions of patients that discontinue or down-titrate RAASi therapy at each S–K level (Section B.2.3.2). According to interviews conducted with UK clinical experts for the management of CKD to support the partial reappraisal of TA599, experts were all in agreement that whilst these data are not specific to the UK, results are generalisable to the UK population and the results reflect their clinical experience.[23]

Where inputs could not be sourced from direct clinical trial evidence, or RWE studies, validated published literature sources and national-level guidelines (such as NICE clinical guidelines) were used. Finally, if there are no other sources available, expert opinion were used to inform parameters.

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

The time horizon for the model is lifetime (80 years) or until RRT initiation to reflect all important differences in costs and outcomes between the technologies being compared. As a standard modelling assumption, no patient can survive past age 100, therefore an 80-year time horizon was selected to ensure that any adult aged >20 years initiated into the model would end as a result of transitioning into an absorbing state. The cycle length is four weeks (28 days) to reflect the design of the ZS-004 and ZS-005 trials.[127, 139] However, in order to capture more granular changes in S–K and dosing of SZC in the initial treatment phase, the first 4-week period is broken into shorter cycle lengths, described in Table 32. Due to the varying cycle lengths, no half-cycle correction was required, and as such this is not applied in the model.

Table 32. Summary of cycle lengths applied from start of simulation

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

The key features of the economic analysis with justification are presented in Table 33, which also compares the current model structure from the model structure presented in the original appraisal TA599.[3]

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B.3.2.3 *Key features of the de novo model structure*

Table 33. Features of the economic analysis

Factor	Chosen values		Justification
	TA599[3]	Current Appraisal	
Time horizon	Lifetime (80 years from first event), unless RRT is initiated in which case model ends at RRT		NICE reference case. No patient may survive after 100 years. Model terminates at RRT as: • RRT is considered an unrelated future cost • RRT obscures decision problem See Section B.3.2.2 for further information
Cycle length	28 days after the first 5 cycles (initial management has various cycle lengths)		Reflects the design of the ZS-004 and ZS-005 trials[127, 139]
Were health effects measured in QALYs; if not, what was used?	Yes		NICE reference case
Discount of 3.5% for utilities and costs	Yes		NICE reference case. The impact of alternative discount rates has been tested in sensitivity analyses
Perspective (NHS/PSS)	UK NHS PSS		NICE reference case
Treatment waning effect?	N/A		Treatment effect is based on direct data from the ZS-004 and ZS-005 trials, and treatment ceases after three cycles. An assumption is made that subsequent re-treatment (if required) would be equivalent to first-time treatment. Therefore, no extrapolation is required considering waning.
Source of utilities	No HRQoL data was collected in ZS-004[127] and ZS-005[139] trials (see Section Appendix O). Therefore, utility values were sourced from published literature		NICE reference case
Source of costs	Sources of cost data included the BNF for drug costs, published literature and national cost databases (NHS Reference Costs). Costs were inflated to the current cost year using the National Health Service Cost and Inflation Index (NHSCII) and PSS Pay and Prices index.		NICE reference case

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

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B.3.2.4 *Intervention technology and comparators*

In line with the decision problem (Section B.1.1), the model evaluates the use of SZC against standard care in the patients with persistent HK with an S–K of ≥5.5–<6.0 mmol/L. In this population, no targeted therapy is administered for standard care.

In both treatment arms, lifestyle interventions for the background maintenance of S–K are also part of the management of HK. As described in Section B.1.3.5, historically this may have included low K^+ diets, but these are now considered not to be clinically effective and are associated with decreased patient QoL. The primary intervention in England for those with persistent HK with an S–K of ≥5.5–<6.0 mmol/L is modification of concomitant RAASi therapy, resulting in sub-optimal RAASi dosages that negatively impact a patient's clinical outcomes.

B.3.3 *Clinical parameters and variables*

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

The key clinical efficacy data for SZC come from ZS-004 for standard care versus SZC, and ZS-005 for long-term use of SZC.[127, 139] These studies have previously been evaluated as part of TA599 and as discussed in Table 29, the synthesis of evidence to inform changes in S–K in the SZC and standard care arm is aligned with the EAG preferred approach in TA599.[3] Changes in S–K levels were reported for the first 28 days in ZS-004 and 52 weeks for ZS-005, therefore the changes in S–K levels for those with a S–K of ≥5.5–<6.0 mmol/L at baseline are based on a pooled analysis of ZS-004 and ZS-005 for the first 28 days, and on ZS-005 only for day 29 to week 12.[127, 139] As both the ZS-004 and ZS-005 trials have patients treated with SZC in the correction phase, the placebo arm of ZS-003 was used to inform the changes in S–K levels in the correction phase of the standard care arm. The maximum duration of treatment in the model is three cycles (12 weeks), which is shorter than the trial period of 52 weeks in ZS-005. This is considered to be more aligned with clinical practice as validated by Market Research and expert clinical opinion.[23, 160]

Elevated S–K is linked to an increased risk of a number of adverse clinical outcomes including mortality, MACE and hospitalisation. As the clinical trials ZS-004 and ZS-005 did not measure the relationship between S–K and these long-term clinical outcomes, in the original appraisal (TA599), literature sources were identified to provide model inputs for this relationship.[3] However, uncertainties regarding the use of literature data were raised by the committee. In TA599, outcomes from an observational study conducted using data from CPRD, Luo *et al.* was used to model the relationship between S–K and MACE, mortality, and hospitalisation.[81] However, IRRs linking S–K and these long-term clinical outcomes did not adjust for RAASi usage, and thus the observed relationships may represent an overestimation of the benefits of SZC. In addition, unmeasured confounders led to further uncertainty in the measured outcomes.

To address these uncertainties, SPARK, an observational cohort study conducted using data from CPRD has been conducted by AstraZeneca to further evaluate the relationship between S–K and long-term outcomes (Section B.2.3.1). SPARK investigates the relationship between S–K and hospitalisation, MACE, and mortality, stratified by S–K levels and eGFR. In line with the NICE RWE framework, the SPARK study took steps to minimise the risk of bias, and adjusted by an additional 30+ confounders than the studies used to

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inform TA599 including co-medications, comorbidities and RAASi usage.[67] In addition to explore the likely effect of any residual confounding, e-values were calculated to quantify the strength of the unmeasured confounder needed to reverse the observed relationships.

Another source of uncertainty raised during the appraisal for TA599 was that the clinical evidence provided did not provide adequate evidence that SZC usage allows HK patients to maintain guideline RAASi dosage irrespective of S–K levels.[3] Instead, clinical expert opinion was used to inform this relationship.[3] To address this uncertainty, ZORA, a re-analysis of the multi-national observational study analysing data extracted from health registers and medical records from the US and Japan was used to compare the likelihood of maintained optimised RAASi therapy at six months following an incident HK among patient treated with SZC or standard care, stratified by S–K levels (Section B.2.3.2). An additional analysis of data from the ZORA study was conducted to specifically investigate the increased odds of patients maintaining RAASi within the decision problem population (persistent HK patients with an S–K of ≥5.5–<6.0 mmol/L, comorbid with CKD or HF) to provide evidence that SZC usage directly improves RAASi optimisation and maintenance. According to interviews conducted with UK clinical experts for the management of CKD to support the partial reappraisal of TA599, experts were all in agreement that whilst these data are not specific to the UK, results are generalisable to the UK population and the results reflect their clinical experience.[23]

Costs and clinical outcomes are not extrapolated beyond the trial period as the longest consecutive period that any patient can be on SZC in the model is 12 weeks, which is reflective of UK clinical practice.[23, 160] However, as patients in the model can have multiple re-treatments, an assumption is made that the efficacy of the drug seen in the trials remains the same for each repeat treatment. This assumption is justified as there is no evidence from the trials that a previous HK event affects response to SZC, and this evidence is extended to make the same assumption about standard care treatment. This assumption was previously considered appropriate in TA599.[3]

Costs of underlying medical conditions (such as HF and CKD) are extrapolated beyond the trial period using a literature source aligned with the original appraisal TA599 as identified in the economic SLR to estimate long-term costs and clinical outcomes.[3] The HCRU of the underlying medical conditions were sourced from Kent *et al.*[169] and Ford *et al.*[177] for CKD and HF disease states, respectively, and inflated to the current cost year using the NHSCII or the PSS Pay & Prices Index.[171]

B.3.3.2 *Transition probabilities*

B.3.3.2.1 Baseline demographics

To reflect the population for which the efficacy of SZC has been derived, baseline characteristics were based on results from ZS-004 and ZS-005, where possible.[127, 139] Table 34 provides the baseline characteristics of patients entering the model which could be derived from ZS-004 and ZS-005.[127, 139] While direct trial data was preferred where available, in line with the NICE reference case,[178] not all demographic data used in the model was available from ZS-004 and ZS-005.[127, 139]

Table 35 provides the baseline characteristics of patients entering the model which could not be derived from ZS-004 and ZS-005.[127, 139] As such, retrospective, observational studies in

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CKD and HF patients from the British Society for Heart Failure National Heart Failure Audit, CPRD (an English NHS observational data and interventional research service for primary care) and the PRAISE study (a large trial in over 1,000 HF patients), which were identified in a clinical SLR, were used. These sources were selected as they were the largest and most nationally representative data available.

Patients simulated in the model are split by CKD ([redacted]%) and HF ([redacted]%) based on the observed split between patients in the observational study SPARK.[29] Baseline characteristics for each patient entering the model are calculated by simulating using the weighted mean of HF and CKD inputs described in Table 34 and Table 35.

All patients are assumed to be eligible for RAASi therapy in the model. This is aligned to the current persistent HK recommendation in TA599 that SZC is recommended only if, because of HK, people are not taking an optimised dosage of RAASi.[3]

Table 34. Baseline demographics of CKD and HF cohorts entering the model

Patient characteristic	CKD cohort		HF cohort		Distribution	Source
	Mean	SE	Mean	SE		
Proportion with CKD	1.00*	N/A	0.00	N/A	N/A	Pooled from ZS-004 and ZS-005[1,139]
Proportion with HF	0.00	N/A	1.00*	N/A	N/A	
Age (years)	63.56	N/A	65.07	N/A	Normal	
Proportion female	0.37	N/A	0.37	N/A	Beta	
Weight (kg)	89.44	0.95	82.23	0.95	Normal	
SBP (mmHg)	141.20	0.83	132.13	0.83	Normal	
Hb (g/dL)	11.79	0.08	13.25	0.08	Normal	
WBC count (109/L)	7.28	0.10	7.66	0.10	Normal	
Lymphocytes (103/µL)	1.72	0.03	2.04	0.03	Normal	
Sodium (mEq/L)	137.71	0.13	137.55	0.13	Normal	

Footnotes: *These proportions are for the CKD only and HF only base case analyses. In the mixed CKD and HF population, the proportion of patients with CKD is [redacted] and the proportion of patients with HF is [redacted] based on the observed split between patients in the SPARK study.[29]
Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; Hb: haemoglobin; HF: heart failure; SBP: systolic blood pressure; SE: standard error; WBC: white blood cell.

Table 35. Baseline demographics of cohort entering the model (other sources)

Patient characteristic	CKD			HF			Dist.
	Mean	SE	Source	Mean	SE	Source	
Morbidity profile							
Duration of disease (years)	0	0	Assumption	0	0	Assumption	N/A
eGFR, (mL/min/1.73 m^2)	[redacted]	[redacted]	SPARK[29]	68.14	N/A	Pooled from ZS-004 and ZS-005[127,139]	N/A
Ejection fraction (mL)	N/A	N/A	N/A	21	0.18	PRAISE[174]	Normal
Ischaemic aetiology (%)				0.64	0.01		Beta

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Patient characteristic	CKD			HF			Dist.
	Mean	SE	Source	Mean	SE	Source	
NYHA Class I (%)				10	N/A	British Society for Heart Failure National Heart Failure Audit, 2015/16[179]	N/A
NYHA Class II (%)				10			
NYHA Class III (%)				43			
NYHA Class IV (%)				37			
Comorbidity/clinical history (proportion)							
Diabetes	0.146	0.0008	CPRD[180]	0.149	0.0008	CPRD[180]	Beta
Cancer	0.092	0.0007		0.098	0.0007		
Metastatic tumour	0.022	0.0003		0.017	0.0003		
PVD	0.024	0.0003		0.030	0.0003		
Dementia	0.025	0.0004		0.023	0.0004		
MACE	0.077	0.0006		0.213	0.0006		
Rheumatologic disease	0.033	0.0004		0.026	0.0004		
CPD	0.096	0.0007		0.136	0.0007		
Modifiable risk factors							
Proportion of smokers	0.161	0.002	CPRD[180]	0.226	0.002	CPRD[180]	Beta
BMI (kg/m^2)	28.836	2.88	Assumption**	28.836	2.88	Assumption**	Normal
Total cholesterol (mg/dL)*	193.860	0.166	CPRD[180]	168.920	0.166	CPRD[180]	
Uric acid (mg/dL)	N/A	N/A	N/A	8.9	0.078	PRAISE[174]	
Concomitant therapies (proportion, unless otherwise stated)							
RAASi (%)	100%	N/A	Assumption	100%	N/A	Assumption	N/A
K^+ sparing diuretics	N/A	N/A	N/A	0.030	0.005	PRAISE[174]	Beta
Diuretics	0.402	0.001	CPRD	0.402	0.001	CPRD[180]	Beta
Beta blocker	N/A	N/A	N/A	0.448	0.003		Beta
Calcium channel blocker	0.275	0.001	CPRD[180]	N/A	N/A	N/A	Beta

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Patient characteristic	CKD			HF			Dist.
	Mean	SE	Source	Mean	SE	Source	
Statin	N/A	N/A	N/A	0.415	0.0034	CPRD[180]	Beta
Proportion of RAASi users on ACE				0.819	0.003	CPRD[180]	Beta
Proportion of RAASi users on ARB				0.190	0.004	CPRD[180]	Beta
Allopurinol				0.100	0.009	PRAISE[174]	Beta
ICD				0.000	0.000		Beta
BICD				0.000	0.000		Beta
Diuretic dose (mg/kg)				1.450	0.040		Normal

Footnotes: *Total cholesterol measurements converted as follows: 1 mmol/L = 38.67 mg/dL. **BMI is calculated based on an assumed height of 1.75m.
Abbreviations: ACE: angiotensin-converting-enzyme; ARB: angiotensin II receptor blocker; BICD: biventricular implantable cardioverter defibrillator; BMI: body mass index; CKD: chronic kidney disease; CPRD: Clinical Practice Research Datalink; ICD: implantable cardioverter defibrillator; Dist.: distribution; HF: heart failure; K^+: potassium cation; N/A: not applicable; NYHA: New York Heart Association; PVD: peripheral vascular disease; RAASi: renin-angiotensin-aldosterone system inhibitor; SE: standard error.

B.3.3.3 *S–K profile*

S–K levels are important in the model as they are associated with long-term outcomes such as MACE and mortality. S–K levels are taken directly from trial data (see Appendix O), and the relationship between S–K and long-term clinical outcomes is informed by the RWE study SPARK (see Section B.2.3.1 for the SPARK study). Sections B.3.3.7 and B.3.3.8 detail the inputs derived from SPARK used to model the relationship between S–K and the risk of hospitalisation, MACE, and mortality in CKD and HF patients, respectively. These relationships are well supported by clinical literature.[31, 34, 70, 78, 81, 83-86]

The approach taken to model S–K levels with and without SZC treatment has previously been evaluated in TA599 and considered appropriate for decision-making.[3] The EAG preferred approach is used and described below, with data from those with an S–K of ≥5.5–<6.0 mmol/L. This is consistent with the EAG preferred approach which in TA599 preferred to only use those with an S–K of ≥6.0 mmol/L.

S–K levels fluctuate over time, with each patient exhibiting a unique S–K trajectory (representative example shown in Figure 13). To reflect this within the model, patient-specific profiles are simulated based using mixed effects regression models, which are based upon the S–K trajectories observed within the ZS-004,[127] ZS-005,[139] and ZS-003[132] clinical trials. These models comprise a fixed effect representing a time-varying, population-averaged mean level of S–K and a random effect representing patient-specific mean S–K levels that may be systematically higher or lower than the population-averaged mean level.

The fixed effect therefore represents the improvement in S–K levels that occurs across the whole population, and importantly captures the treatment effect of SZC in reducing S–K. The random effect is used to obtain estimates of S–K variability that occurs from patient to patient and to acknowledge unobserved heterogeneity in the patient population. This

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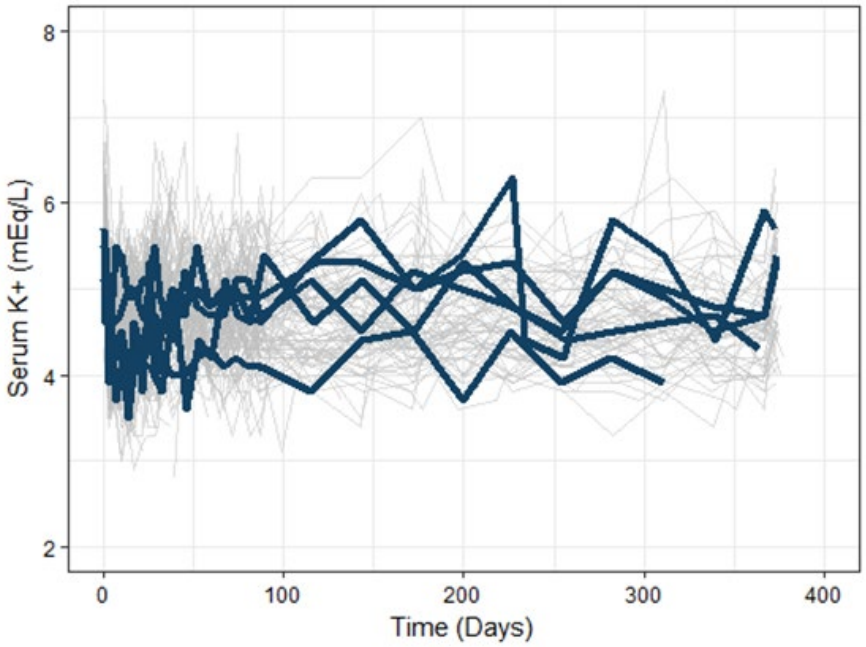
ensures that measurements taken from the same patient are more likely to be similar than measurements taken from different patients. The inclusion of patient-specific random effects increases the accuracy of the models, ensuring that key statistical assumptions are satisfied, and validity of inferences obtained from the models.

Figure 13. Illustrative patient-level S–K trajectories



Abbreviations: S–K: serum potassium; K^+: potassium cation.

Table 36 and Table 37 show the parameters associated with the mixed effect models used in the cost-effectiveness model for SZC and standard care respectively.

For SZC, parameters were estimated from pooled data from the ZS-004 and ZS-005 trials in order to take all the relevant evidence into account for patients who received doses of up to 10 g OD in the maintenance phase as per the SmPC,[7] see Section B.2.2.1 for details.[127, 139] Only the S–K trajectories of the subpopulation with S–K of ≥5.5–<6.0 mmol/L from the ZS-004 and ZS-005 trials is included in the model, in-line with the decision problem population.[127, 139]

Pooled data were used as patients in ZS-005 received the same treatment as those in ZS-004 for the first 28 days, therefore the first 28 days could be pooled across both trials. Patients included in the analysis received the same as per protocol dose of SZC in this initial correction phase (i.e. 10 g TID for 1–3 days: 2 days in ZS-004 and 1–3 days in ZS-005) and in the maintenance phase (5 g or 10 g OD for 28 days in ZS-004 and 5 g once every other day, OD or 10 g OD for up to 12 months).[127, 139]

For the correction phase of the standard care arm, S–K trajectories were derived from the placebo arm of the ZS-003 trial for the subpopulation with S–K of ≥5.5–<6.0 mmol/L. The 48 h absolute reduction observed in ZS-003 was applied to day 2 of the S–K trajectory, and linearly extrapolated to day 3 as per the EAG preferred approach in TA599, as this represents a more conservative approach because almost all patients with an initial S–K of ≥5.5–<6.0 mmol/L would have exited the acute phase after two days of treatment with SZC.[3]

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The maintenance phase trajectory was assumed to remain constant from day >4 onwards after the correction phase.

Table 36. Pre-defined S–K profile for SZC: mixed-effects model parameters

	Fixed component	Time-dependent component	Patient component (SD)	Observation component (SD)	Source
Day 0–3	[redacted]	[redacted]	[redacted]	[redacted]	Pooled data from ZS-004 and ZS-005[127, 139]
Day 4–14	[redacted]	[redacted]	[redacted]	[redacted]	
Day 15–28	[redacted]	[redacted]	[redacted]	[redacted]	
Day >28	[redacted]	[redacted]	[redacted]	[redacted]	

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

Table 37. Pre-defined S–K profile for standard care: mixed effects model parameters

	Fixed component	Time-dependent component	Patient component (SD)	Observation component (SD)	Source
Day 0–3	[redacted]	[redacted]	[redacted]	[redacted]	Control arm of ZS-003[132]
Day 4–14	[redacted]	[redacted]	[redacted]	[redacted]	
Day 15–28	[redacted]	[redacted]	[redacted]	[redacted]	
Day >28	[redacted]	[redacted]	[redacted]	[redacted]	

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

Patients receiving SZC enter the model at day 0 with an S–K of [redacted] mmol/L based on the mean S–K value of the patient cohort with an S–K ≥5.5–<6.0 mmol/L within the ZS-004 and ZS-005 trials. Patients receiving standard care will enter at the same S–K level, with plus a random draw based on the patient component (mean [redacted] and SD of [redacted]) prior to entering the model.

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

- The cohort-averaged mean S–K level in that time period, associated with the global time trend. This is fixed, depending on the time since HK event.
- A patient-specific component, obtained as a random draw from a normal distribution with mean 0 and a standard deviation taken from the pooled ZS-004 and ZS-005 trial data. This is randomly drawn at each HK event, and again at day 4 following an HK event.[127, 139]
- An observation-specific component, obtained as a random draw from a normal distribution with mean 0 and a standard deviation taken from the pooled ZS-004 and ZS-005 trial data.[127, 139] This is randomly drawn each cycle.

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

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Patients receiving SZC can discontinue treatment based on reaching ESRD (commencing RRT), reaching the end of the 3-month treatment period, and discontinuation based on any-cause (see Section B.3.3.9). Should SZC be discontinued for any reason, the S–K profile for each cycle reverts to day >28 of the standard care profile.

Patients that have discontinued SZC can be re-treated should S–K levels return to ≥5.5 mmol/L, upon which the patient S–K profile will follow the same trajectory as the initial treatment at day 0. Discontinuation and re-treatments can occur until the patient reaches an absorbing state such as ESRD (commencing RRT) and death.

Patients undergo RAASi status change (see Section B.3.3.4) as S–K changes throughout the simulated cycles. The down-titration and discontinuation of RAASi are assumed to be associated with an S–K change of −0.115 and −0.23 mmol/L, respectively, in line with EAG preferences in original appraisal TA599.[3] This should be considered a conservative assumption, as the S–K changes from TA599 are for those in the acute setting where the magnitude of S–K change upon RAASi down-titration/discontinuation is expected to be greater.

B.3.3.4 *RAASi status change*

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

- RAASi “max” – RAASi use in line with guidelines.[50]
- RAASi “sub-max” – RAASi use in line with the mean dose at baseline observed in the CPRD cohort,[181] intended to represent imperfect RAASi use.
- No RAASi use.

All patients simulated in the model are assumed to be eligible for RAASi at baseline. A limitation of the model is that all patients will initiate the model on RAASi at “max”, with discontinuing and down titrating of RAASi occurring at the first cycle. This is a conservative assumption as there is evidence that without SZC patients may already be on a sub-optimal dose of RAASi due to the fear of triggering an HK event (section B.1.3.3.2).[35, 38-40].

At any stage of the model, patients can discontinue RAASi. In addition, patients can down-titrate from “max” to “sub-max” and up-titrate from “none” or “sub-max” to “max”. The process for RAASi change is illustrated in Figure 14.

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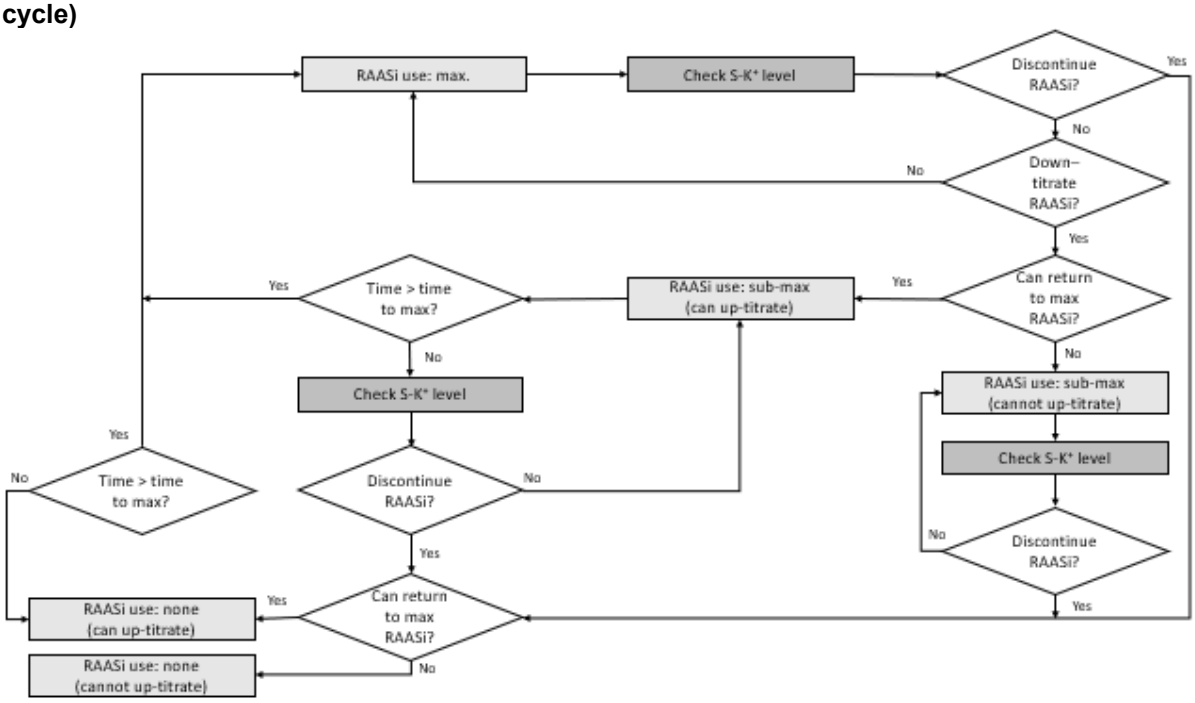
Figure 14. Logical process followed to model changes in RAASi use (up to one change per cycle)



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

Table 38 describes the proportion of patients discontinuing and down-titrating RAASi. These proportions depend on the S–K level and RAASi state.

The proportion of patients discontinuing, and down-titrating depends on whether the patient begins the cycle at “max” or “sub-max” RAASi. The proportion of patients at “max” RAASi that discontinue or down-titrate depends on their S–K levels and whether they are treated with SZC. If the patient is at “sub-max” RAASi then down-titration is already occurring and will continue. The proportions of patients discontinuing or down-titrating from “max”, or down-titrating from “sub-max” RAASi at each 0.5 mmol/L increment of S–K are based upon the an additional subgroup analysis of the multi-national observational study ZORA (see Section B.2.3.2 for more details).[135]

It is possible to return to max RAASi in the maintenance setting only; returns occur in 49.7% of eligible cycles for both treatment arms. This is justified based on Luo *et al.*[81] This paper contains data for CKD up-titration following discontinuation only, so an assumption is made that all HF and CKD up-titration following down-titration probabilities will be the same. It is assumed that a patient is eligible to return to “max” RAASi if they are in the chronic setting, have not left the model due to death or RRT and at least three cycles (12 weeks) have elapsed from the discontinuation / down-titration and the current cycle. The timing requirement is based on published literature,[182] and the value for the timing requirement itself (three cycles) is based on clinical expert input.[183] The modelling of RAASi re-continuation in terms of the time to return to max-RAASi dose and the proportion of patients reinitiating in each cycle is reflective of the committee preferred assumptions from TA599.

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Table 38. RAASi discontinuation and down-titration, by S–K category

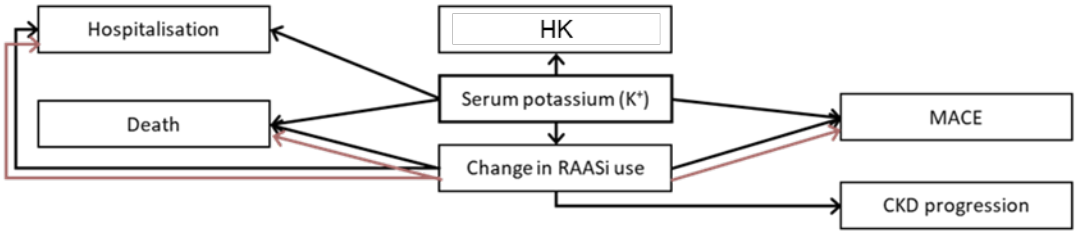
S–K category (mmol/L)	SZC				Standard care				Dist.	Source
	Proportion of patients discontinuing		Proportion of patients down-titrating		Proportion of patients discontinuing		Proportion of patients down-titrating			
	Mean	SE	Mean	SE	Mean	SE	Mean	SE		
<5.0	[redacted]								Beta	Assumption
5.0–5.5	[redacted]								Beta	ZORA subgroup analysis (Section B.2.3.2.6)
5.5–5.9	[redacted]								Beta	
≥6.0	[redacted]								Beta	

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

B.3.3.5 *Adverse events*

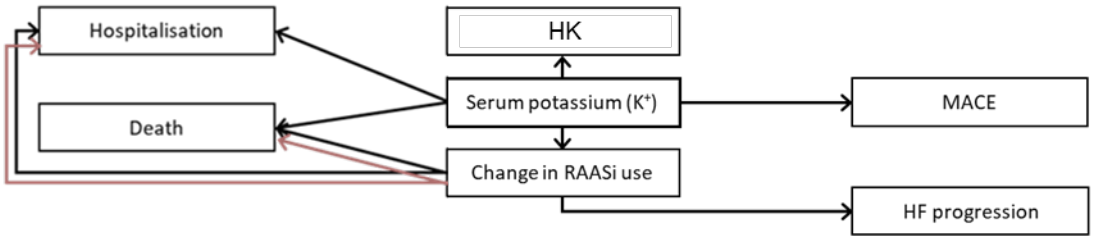
Over the course of the simulation, patients experience changes in S–K and RAASi profile which affect the probabilities of key clinical events including HK events, MACE, hospitalisation and death (see Figure 15 and Figure 16).

Figure 15. Modelled relationships between S–K levels, RAASi use and events in the CKD population



Footnotes: Red arrows represent relationships that may be modelled according to level of RAASi use (maximum versus sub-maximum. Black arrows represent modelled relationships between outcomes and variables.
Abbreviations: CKD: chronic kidney disease; CPRD: Clinical Practice Research Datalink; K^+: potassium cation; MACE: major adverse cardiac event; RAASi: renin-angiotensin-aldosterone system inhibitor; S–K: serum potassium.

Figure 16. Modelled relationships between S–K levels, RAASi use and events in the HF population



Footnotes: Red arrows represent relationships that may be modelled according to level of RAASi use (maximum versus sub-maximum. Black arrows represent modelled relationships between outcomes and variables.
Abbreviations: CKD: chronic kidney disease; CPRD: Clinical Practice Research Datalink; K^+: potassium cation; MACE: major adverse cardiac event; RAASi: renin-angiotensin-aldosterone system inhibitor; S–K: serum potassium.

B.3.3.6 *HK events*

Treatment-related adverse events

AEs are included in the model based on events recorded in the ZS-005 trial with an incidence of ≥5% in either arm.[139] The proportion of the treatment arm experiencing these

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events is taken from the ZS-005 trial. It was not possible to use the proportion of the standard care arm experiencing AEs from the trial, as treatment for the first 3 days of the trial was non-randomised and therefore unrepresentative of the standard care arm modelled. As such, a conservative approach was taken in which patients in the standard care arm did not experience AEs. Table 39 shows the proportion of AEs that patients in the treatment arm will experience.

The ZS-005 CSR distinguishes between treatment-related AEs (TRAEs) and treatment - emergent AEs (TEAEs).[139] As a conservative assumption, it is assumed that all AEs with an incidence of ≥5% in either arm are TRAEs for the purposes of modelling. As AEs are assumed to be treatment related, they can occur only when treatment is being given. For standard care, no TRAEs are experienced. For SZC, the proportion of patients experiencing TRAEs is shown in Table 39.

Table 39. Proportion of cohort experiencing adverse events

Adverse event	SZC (while on treatment)		Distribution	Source
	Mean	SE		
Oedema	0.116	0.012	Beta	ZS-005[139]
Worsening hypertension	0.109	0.011	Beta	
Constipation	0.064	0.009	Beta	
Diarrhoea	0.044	0.007	Beta	
Nausea	0.075	0.010	Beta	
Hypomagnesaemia	0.012	0.004	Beta	
Hypokalaemia	0.015	0.004	Beta	
UTI	0.079	0.010	Beta	

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

B.3.3.7 *CKD risk equations*

In the CKD cohort, eGFR decline is related to RAASi use (see Table 40). It was not possible to estimate annual eGFR decline from the trials, as the trials were ongoing for only 52 weeks. Therefore, Evans *et al.* was used.[101] RRT is initiated if eGFR ≤8.5 mL/min/1.73 m^2, which is the recommended level according to the Renal Association.[184]

Table 40. Natural history of eGFR decline in CKD

Health state	Annual eGFR decline (mL/min/1.73 m^2)			Justification
	Mean	SE	Distribution	
CKD; RAASi “max” or “sub-max”	2.34	0.023	Normal	Evans *et al.* 2012, as per placebo months 24–48[101]
CKD; no RAASi use	3.52	0.035	Normal	Evans *et al.* 2012, as per irbesartan months 24–48[101]

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

Event risk in CKD is related to eGFR/ CKD stage (Table 41), S–K (Table 42) and RAASi use status (Table 43). It was not possible to use the trials for these data because the trials were S–K based, not eGFR based, and therefore were not powered to detect AEs associated with

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eGFR levels. Therefore, literature sources identified in the SLR (see Appendix D) and outcomes from the observational study SPARK (see section B.2.3.1) conducted by AstraZeneca was used to provide this information. In the study Go *et al.*[185] (Table 41) the cardiovascular AE is defined in a slightly different way to that within the SPARK study (Table 42).[29] Therefore, it is assumed the increase in risk due to S–K levels for MACE is the same as for cardiovascular events, and that the increase in risk due to eGFR levels for cardiovascular events is the same as for MACE. This is justified as the definition of cardiovascular events in Go *et al.*,[185] is very similar to the definition of MACE used in the SPARK study (see section B.2.3.1).[29]

Table 41. Baseline cardiovascular, hospitalisation and mortality event rate in CKD patients, by CKD stage

Event	CKD subgroup – mean annual event rate (SE)					Dist.	Source
	1–2	3 a	3b	4	5		
Cardiovascular event*	0.0211 (0.0012)	0.0365 (0.0012)	0.1129 (0.0012)	0.218 (0.0024)	0.366 (0.0048)	Normal	Go *et al.*[185]
Hospitalisation	0.1354 (0.0045)	0.1722 (0.0045)	0.4526 (0.0067)	0.8675 (0.0090)	1.4461 (0.0090)	Normal	
Mortality (all-cause)	0.0076 (0.0002)	0.0108 (0.0004)	0.0476 (0.0007)	0.1136 (0.0018)	0.1414 (0.0031)	Normal	

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

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Table 42. Incidence rate ratio for MACE, hospitalisation and mortality in CKD patients, by S–K subgroup

Event	S–K subgroup – incidence risk ratio (SE)							Dist.	Source
	<3.5	≥3.5–<4.0	≥4.0–<4.5	≥4.5–<5.0	≥5.0–<5.5	≥5.5–<6.0	≥6.0		
MACE								Normal	SPARK[29]
Hospitalisation (eGFR <30 mL/min/1.73 m^2)								Normal	
Hospitalisation (eGFR 30–40 mL/min/1.73 m^2)								Normal	
Hospitalisation (eGFR 40–50 mL/min/1.73 m^2)								Normal	
Hospitalisation (eGFR 50–60 mL/min/1.73 m^2)								Normal	
Mortality (all-cause)								Normal	

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

Table 43. Odds ratios for RAASi use risk relating to event risk in CKD patients

Parameter	Odds ratio mean	Standard error	Distribution	Source
Mortality – "max" RAASi vs no RAASi	0.870	0.069	Normal	Xie *et al.*[94]
Mortality – "sub-max" RAASi vs no RAASi	0.935	0.069	Normal	Assumption – 50% of impact of "max" RAASi with same standard error
Cardiovascular event – "max" RAASi vs no RAASi	0.820	0.054	Normal	Xie *et al.*[94]
Cardiovascular event – "sub-max" RAASi vs no RAASi	0.910	0.054	Normal	Assumption – 50% of impact of "max" RAASi with same standard error
Hospitalisation – "max" RAASi vs no RAASi	1	0	Normal	Assumption – no literature source identified so null value used
Hospitalisation – "sub-max" RAASi vs no RAASi	1	0	Normal	Assumption – no literature source identified so null value used

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

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B.3.3.8 *HF risk equations*

NYHA classification transition probabilities are unrelated to RAASi use (see Table 44). It was not possible to use the trials for these data because the trials were S–K based, not NYHA-based, and therefore were not powered to detect AEs associated with NYHA levels. Therefore, literature sources were identified in the SLR and selected based on containing the most relevant information. In keeping with the hierarchy of evidence, observational datasets were only used where there was no appropriate literature source, which in the HF cohort was the risk equations for death, taken from the Seattle Heart Failure Model (SHFM), as shown in Table 47.

Table 44. Probabilities of changes in NYHA classification per cycle

	NYHA I	NYHA II	NYHA III	NYHA IV	Source
NYHA I	0.7956	0.1245	0.0738	0.0061	Yao *et al.*[186]
NYHA II	0.0710	0.8448	0.0765	0.0077	
NYHA III	0.0047	0.0893	0.8845	0.0216	
NYHA IV	0.0000	0.1064	0.1064	0.7872	

Abbreviation: NYHA: New York Heart Association

Event risk for the heart failure population depends on RAASi use and NYHA stage for hospitalisation (Table 45), and S–K levels.[29] The observed data from SPARK as described in Table 46 inform the risk of hospitalisation, MACE and mortality depending on S–K profile.[29] Unlike CKD patients, the hospitalisation risk in HF patients by S–K is independent of eGFR levels. As such the incidence risk ratios pooled across all eGFR levels were reported.

Table 45. Per-cycle probability of hospitalisation for heart failure and mortality in HF patients

	Mean	SE	Distribution	Source
Hospitalisation – NYHA I	0.015	0.000	Normal	Ford *et al.*[177]
Hospitalisation – NYHA II	0.024	0.000	Normal	
Hospitalisation – NYHA III	0.024	0.000	Normal	
Hospitalisation – NYHA IV	0.154	0.000	Normal	
Hospitalisation – Odds ratio RAASi vs no RAASi	0.670	0.000	Normal	Flather *et al.*[144]
Hospitalisation – Odds ratio "sub-max" RAASi vs no RAASi use	0.882	0.000	Normal	Assumption based on ATLAS,[53] which recorded 24% fewer hospitalisations for heart failure with high dose vs low dose lisinopril
Mortality – Odds ratio RAASi vs no RAASi	0.230	0.092	Normal	Chen *et al*.[65] – Conservative assumption as publication OR applies to max-RAASi dose versus sub-max RAASi dose, whilst in the model

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				this is applied for max-RAASi versus no RAASi
Mortality –Odds ratio “sub-max” RAASi vs no RAASi use	0.615	0.092	Normal	Assumption – 50% of impact of “max” RAASi with same standard error

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

Table 46. Incident rate ratio for MACE, hospitalisation and mortality in HF population by S–K levels

Event	S–K subgroup – incidence risk ratio (SE)							Dist.	Source
	<3.5	≥3.5–<4.0	≥4.0–<4.5	≥4.5–<5.0	≥5.0–<5.5	≥5.5–<6.0	≥6.0		
MACE								Normal	SPARK[29]
Hospitalisation (All eGFR)								Normal	
Mortality (all-cause)								Normal	

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

Finally, mortality risk for HF patients is estimated from the implementation of the SHFM.[174] This is a multivariate Cox model for survival among HF patients. Coefficients for this model are given in Table 47. These HRs modify the all-cause mortality risk.

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Table 47. SHFM hazard ratios for survival in HF patients

Parameters	Mean	SE	Distribution	Source
Age (parameter is age divided by 10)	1.090	0.0561	Normal	Levy *et al.*, 2006[174]
Male gender	1.089	0.1467	Normal	
NYHA (1–4)	1.600	0.3806	Normal	
100/Ejection fraction	1.030	0.0102	Normal	
Ischaemic aetiology (No/Yes)	1.354	0.1615	Normal	
SBP (parameter is mmHg divided by 10)	0.877	0.0286	Normal	
Diuretic dose (mg/kg)	1.178	0.0431	Normal	
Allopurinol use (No/Yes)	1.571	0.2395	Normal	
Statin use (No/Yes)	0.630	0.1449	Normal	
If sodium <138, 138–sodium	1.050	0.0235	Normal	
Cholesterol (100/mg/dL)	2.206	0.9212	Normal	
If haemoglobin <16, 16-haemoglobin	1.124	0.0375	Normal	
If haemoglobin >16, haemoglobin-16	1.336	0.1931	Normal	
Lymphocytes (%/5)	0.897	0.0523	Normal	
Uric acid (mg/dL)	1.064	0.0219	Normal	
ACE use (No/Yes)	0.770	N/A	Normal	
Beta blocker use (No/Yes)	0.660	N/A	Normal	
ARB use (No/Yes)	0.850	N/A	Normal	
K-sparing diuretic use (No/Yes)	0.740	N/A	Normal	
ICD (No/Yes)	0.730	N/A	Normal	
BICD (No/Yes)	0.790	N/A	Normal	

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

B.3.3.9 *Discontinuation*

In the base case, patients on SZC will discontinue this treatment after a treatment duration of 12 weeks or the initiation of RRT. In addition, patients may discontinue for other reasons not directly accounted for in the model. The annual discontinuation rate is 0.375 as observed from the ZS-005 clinical trial.[139]

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Other-cause mortality

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

Other-cause mortality is included, based on ONS life tables, which estimate general all-cause mortality for England and Wales by each year of age, from birth to 100.[187] A random number generator is used to determine the probability of death during each cycle.

It is unlikely but possible that the probability of death due to comorbidities is lower than the probability of death due to all-cause mortality; if this occurs, the probability of all-cause mortality is applied to retain clinical plausibility.[183]

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

B.3.3.10 *Clinical expert assessment of applicability of clinical parameters*

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

Results from this expert engagement are included in the reference pack, and referenced where applicable in this document.[188]

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B.3.4 *Measurement and valuation of health effects*

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

No HRQoL data were collected in the ZS-004[127] and ZS-005[139] studies; therefore, utility data were sourced from published literature.

B.3.4.2 *Mapping*

No HRQoL data were collected in the ZS-004[127] and ZS-005[139] studies to map onto a generic outcome measure; therefore, utility data were sourced from published literature.

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

Of the 80 publications that met the eligibility criteria across all economic review questions, 17 studies reported utility/disutility values and were considered for supporting the decision problem. A summary of the health-state utility values extracted for relevant health states from 12 of the 17 identified studies in the SLR are presented in Table 48. A detailed summary of the identified studies is provided in Appendix H. Five of the 17 articles identified were HTAs with two being NICE technology appraisals (TA599, TA623) for SZC vs standard care or patiromer vs standard care. Both of which applied utility and disutility values obtained from literature. The remaining HTAs were identified across Scotland (SMC), Canada (CADTH/CDA), or Australia (PBS).

In the original appraisal TA599,[3] utility scores for HF were obtained from a study by Göhler *et al.*,[168] which used EuroQol-5D (EQ-5D) data from the eplerenone post-acute MI HF efficacy and survival study trial to estimate utilities as a function of NYHA classification. For CKD, utility scores for stages stage 3 to 5 were sourced from Eriksson *et al.*;[189] the EAG criticised the company for using data for patients without anaemia, and preferred alternative parameters assuming independence between anaemia and CKD stage and performing a weighted average due to the absence of granular data. The studies Chay *et al.*,[190] Gonzalez-Juanatey *et al.*,[191] Kim *et al.*,[192] Ward *et al.*,[165] and Bakhai *et al.*[164] identified in the SLR also used the same literature sources for assigning utilities for CKD and HF stages. Utilities used in the economic model were aligned with the EAG-preferred values from TA599[3] and Göhler *et al.*[168] and are reported in the summary table in section B.3.4.5.

Of the 17 studies reporting HRQoL data, 9 of the 17 studies in the SLR presented disutility values for AEs used in the economic model. A summary of the disutility values extracted from those studies are presented in Table 49. As with health state utility values for CKD and HF, disutility values from the original appraisal TA599 are considered appropriate for the decision problem,[3] and was included in the economic model (see Section B.3.4.5).

Overall, no significant differences were identified between the trial data and the data identified in the literature.

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Table 48. Health state utility values identified in the literature (n=12 of the 17 publications)

Health state/event	CKD Stage 3a	CKD Stage 3b	CKD Stage 4	CKD Stage 5 (pre-RRT)	NYHA Class I	NYHA Class II	NYHA Class III	NYHA Class IV
Chay 2024;[190] Gonzalez-Juanatey 2022a;[191] Kim 2022;[192] Ward 2022;[165] Bakhai 2018[164]	0.870 (SE: 0.034)	0.870 (SE: 0.034)	0.850 (SE: 0.029)	0.570 (SE: 0.057)	0.855 (SE: 0.005)	0.771 (SE: 0.005)	0.673 (SE: 0.006)	0.532 (SE: 0.027)
NICE TA599[3]	0.85 (SD: 0.21); EAG 0.80 (SE: 0.02)	0.85 (SD: 0.21); EAG 0.80 (SE: 0.02);	0.81 (SD: 0.22); EAG 0.74 (SE: 0.02);	0.74 (0.29); EAG 0.71 (SE: 0.02);	0.855 (SE: 0.005)	0.771 (SE: 0.005)	0.673 (SE: 0.006)	0.532 (SE: 0.027)
NICE TA623[15]	0.80 (95% CI: 0.69–1.0)	0.80 (95% CI: 0.68–1.0)	0.74 (95% CI: 0.62–0.85)	NR	NR	NR	NR	NR
Shaeen 2022;[193] PBS 2019/20[194]	0.80 (95% CI: 0.69–1.0)	0.8 (95% CI: 0.68–1.0)	0.74 (95% CI: 0.62–0.85)	0.73 (95% CI: 0.62–1.0)				
Tian 2023[195]	0.84 (SE: 0.084)	0.84 (SE: 0.084)	0.77(SE: 0.077)	0.65 (SE: 0.065)	0.73 (SE: 0.073)	0.78 (SE: 0.078)	0.72 (SE: 0.070)	0.66 (SE: 0.066)
SMC 2020[163]	0.85 (SE: 0.21)	0.85 (SE: 0.21)	0.81 (SE: 0.21)	NR	NR	NR	NR	NR
Little 2014[196]	0.87 (SD: 0.24)	0.87 (SD: 0.24)	NR			0.64 (SD: NR)	0.58 (SD: NR)	

Abbreviations: CKD: chronic kidney disease; EAG: Evidence Assessment Group; NICE: National Institute for Health and Care Excellence; NR: not reported; NYHA: New York Heart Association (classification); PBS: Pharmaceutical Benefits Scheme; RRT: renal replacement therapy; SD: standard deviation; SE: standard error; SMC: Scottish Medicines Consortium.

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Table 49: Health state/adverse event disutility values identified (n=9 of the identified 17publications)

Adverse event/disutility	Chay 2024;[190] Gonzalez-Juanatey 2022a;[191] Kim 2022;[192] Ward 2022; Tian 2023;[195] Bakahi 2018[164]	CADTH 2019[197]	NICE TA599[3]	Widen 2020[198]
Anorexia	NR	SZC: −0.0029 (SE: NR) SoC: −0.0368 (SE: NR)	−0.0029 (SE: 0.001)	
Constipation	−0.073 (SE: 0.009)	SZC: −0.0056 (SE: NR) SoC: −0.0727 (SE: NR)	−0.0056 (SE: 0.001)	Patiromer: −0.002 (SE: NR)
Diarrhoea	−0.010 (SE: 0.006)	SZC: −0.0008 (SE: NR) SoC: −0.0100 (SE: NR)	−0.0008 (SE: 0.001)	Patiromer: −0.002 (SE: NR)
Hospitalisation	−0.024 (SE: 0.007);	NR	−0.024 (SE: 0.007)	NR
Hypokalaemia	0.000 (SE: 0.000)	SZC: 0.0000 (SE: NR) SoC: 0.0000 (SE: NR)	NR	
Hypomagnesaemia	−0.010 (SE: 0.022)	SZC: −0.0028 (SE: NR) SoC: −0.0095 (SE: NR)	−0.0028 (SE: 0.002)	
Nausea	−0.048 (SE: 0.016)	SZC: −0.0037 (SE: NR) SoC: −0.04802 (SE: NR)	−0.0037 (SE: 0.001)	
Oedema (generalised and peripheral)	−0.038 (SE: 0.004)	SZC: −0.0029 (SE: NR) SoC: −0.0375 (SE: NR)	−0.0029 (SE: 0.000)	
Urinary tract infection	−0.005 (SE: 0.007)	SZC: −0.0004 (SE: NR) SoC: −0.0054 (SE: NR)	−0.0004 (SE: 0.001)	
MACE	−0.050 (SE: 0.040)	NR	−0.050 (SE: 0.040)	

Abbreviations: CADTH: Canadian Agency for Drugs and Technologies in Health; MACE: major adverse cardiac events; NICE: National Institute for Health and Care Excellence; NR: not reported; SE: standard error.

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B.3.4.4 *Adverse reactions*

No new sources of TRAEs were included compared to those previously evaluated in TA599.[3] Table 52 summarises these disutilities, and the associated probabilities are provided in B.3.4.5.

Disutilities related to AEs were applied by assigning a utility decrement to the baseline utility, conditional on experiencing any particular AE. The length of time a disutility was applied to a particular baseline utility depended on which AE was experienced. The total disutility experienced, however, is the same for the treatment and standard care arms – the reason for this modelling assumption is to allow for the possibility of multiple incidents of the same AE in the standard care arm as treatment in the standard care arm lasts significantly less than one cycle. This is the same approach as taken in TA599 and was considered appropriate for decision-making.[3]

It was not possible to use trial data to estimate the disutility of AEs in TA599, since the trial was designed to measure S–K levels and therefore not powered to detect the effect of an AE on utility above the confounding effect of HF and CKD progression. Consequently, utilities identified from the SLR or TLR have been included as estimates of the per cycle disutility of an event. Table 52 summarises these disutilities, which remain unaltered from those presented in TA599.[3]

B.3.4.5 *Health-related quality of life data used in cost-effectiveness analysis*

Patients' QoL in each health state depends on expected baseline utility in the general population, which varies by age and sex (Table 50) and a condition-specific utility score, which varies by NYHA in the HF population and CKD stage in the CKD population (Table 51). The patient's health state utility is defined as their baseline utility multiplied by their condition-specific utility, less adverse event disutility. The risk of events of importance to patients (death, MACE, hospitalisation) is predicted by S–K levels and their disease progression (see Sections B.3.3.6 to B.3.3.8), but SZC does not affect the progression of the underlying HF or CKD.

As per the approach taken in TA599, other than utility decreasing over time due to age, utility is assumed to be constant over the course of the disease for a given disease state. Disease-specific health state utility values have been adjusted to account for baseline utility. The patient's health state utility in the model is defined as their baseline utility multiplied by their condition-specific utility. No health effect with a prevalence of >5% in the literature or trials was excluded from the economic model.

A conservative assumption was made, that despite the fact that SZC would prevent the requirement for a low potassium diet, no disutilities were applied to standard care for this lifestyle management despite significant literature and clinical expert opinion suggesting that this diet impacts patient QoL negatively.[199]

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

Age	Male mean	Male SE	Female mean	Female SE	Distribution	Source
0	0.000	0.007	0.000	0.007	Normal	Szende *et al.*[200]
1–24	0.934	0.007	0.934	0.007	Normal	
25–34	0.922	0.005	0.922	0.005	Normal	
35–44	0.905	0.005	0.905	0.005	Normal	
45–54	0.849	0.010	0.849	0.010	Normal	
55–64	0.804	0.010	0.804	0.010	Normal	
65–74	0.785	0.010	0.785	0.010	Normal	
75–100	0.734	0.013	0.734	0.013	Normal	

Abbreviation: SE: standard error

Table 51. Summary of utility values for disease-specific utility for cost-effectiveness analysis

Health state	Utility	SE	Distribution	Source
NYHA I	0.855	0.005	Beta	Göhler *et al.*[168]
NYHA II	0.771	0.005	Beta	
NYHA III	0.673	0.006	Beta	
NYHA IV	0.532	0.027	Beta	
CKD 3 a	0.800	0.080	Beta	TA599[3]
CKD 3b	0.800	0.080	Beta	
CKD 4	0.740	0.074	Beta	
CKD 5 (pre-RRT)	0.710	0.071	Beta	

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

Table 52. Summary of AE disutilities

Health state	No. cycles applied for	Utility	SE	Dist.	Source
Oedema	13 (1 year)	−0.0029	0.000	Beta	Sullivan *et al.*[201]
Constipation	13 (1 year)	−0.0056	0.001	Beta	Sullivan *et al.* [201]
Diarrhoea	13 (1 year)	−0.0008	0.001	Beta	Kristiansen *et al.*[202]
Nausea	13 (1 year)	−0.0037	0.001	Beta	Nafees *et al.*[203]
Hypomagnesaemia	13 (1 year)	−0.0028	0.002	Beta	Sullivan *et al.* [201]
Anorexia	13 (1 year)	−0.0029	0.001	Beta	Sullivan *et al.* [201]
Hypokalaemia	13 (1 year)	0.0000	0.000	Beta	Assumption – no study identified
UTI	13 (1 year)	−0.0004	0.001	Beta	Sullivan *et al.* [201]
MACE event	1	−0.050	0.040	Beta	Kent *et al.*[204]
Hospitalisation	1	−0.024	0.007	Beta	Göhler *et al.*[168]

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

B.3.4.6 *Clinical expert assessment of applicability of health state utility values*

See Section B.3.3.10 for details.

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

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

From the most recent SLR update (18th June 2024), a total of 62 studies were identified as containing cost and/or resource use data. Of these, eight studies reported resource use from a UK/ Irish perspective. A detailed summary of the identified studies is provided in Appendix I. A summary of the cost parameters identified in the published literature and used to estimate cost-effectiveness is presented in Table 53. Additional details are provided in Appendix I.

Table 53. Summary of cost parameters used in the cost-effectiveness model

Parameter	Annual cost (mean)	Cost (SE)	Source (primary source)	Cross-reference
CKD stage 3a	£1,354.02	£59.04	Kent *et al.*[169]	Appendix I and Table 58
CKD stage 3b	£1,354.02	£59.04		
CKD stage 4	£4,741.00	£107.81		
CKD stage 5 (pre-RRT)	£16,623.00	£237.43		
HF NYHA I	£106.89	£10.69	Ford *et al.*[177]	Appendix I and Table 58
HF NYHA II	£123.15	£12.31		
HF NYHA II	£159.72	£15.97		
HF NYHA IV	£170.46	£17.05		
HK event “Less severe”	£379.931	£37.99	Clinical expert input[23]	Appendix I and Table 63
Emergency HK “Severe” - SZC	£2,749.39	£274.74	Clinical expert input[23]	Appendix I and Table 63
Emergency HK “Severe” - SoC	£3611.87	£361.19	Clinical expert input[23]	Appendix I and Table 63
MACE	£5,817.39	£822.37	Kent *et al.*[169]	Appendix I and Table 68
Hospitalisation	£2,962.16	£296.22	Colquitt *et al.*[176, 205, 206]	Appendix I and Table 68

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

As many sources retrieved in the SLR used a different cost-year to the model and submission, all costs retrieved in the SLR were inflated to the current cost year using the NHSCII and PSS Pay & Prices index.[171]

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

NHS Reference Costs are appropriate for costing discrete events that occur on the HK treatment pathway, for example AE costs (Table 67) and resource use during an emergency HK event (Table 63 and Table 64). However, NHS Reference Costs and Payment-by-Results tariffs are not appropriate for costing the time-in-state costs associated with HF and CKD, since they are not associated with a single event or intervention undertaken by the NHS. For these costs, literature values have been sought and included in the model as per the hierarchy of evidence adopted in the model (see Section B.3.5.5).

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B.3.5.3 *Clinical expert assessment of applicability of cost and healthcare resource use values from TA599*

In TA599, clinical expert opinion was used to estimate healthcare resource use. As a micro-costing approach was adopted for several parameters, clinical estimates of the required resources for each setting were required as there was no plausible published literature identified in either the systematic literature search or ad-hoc searches to populate the model. See Section B.3.3.10 for details. This approach was accepted for use in decision making within TA599.[3] Table 54 identifies all parameters where clinical expert opinion was sought regarding resource use.

Table 54. Parameters where clinical expert opinion was sought

Parameter	Estimated cost / resource use	Standard error	Distribution	Reference
Costs of a SZC treatment cycle	£[redacted] (correction phase) – based on micro-costing, see reference £[redacted] (4-weeks maintenance phase) – based on micro-costing, see reference	£[redacted] (correction phase) £[redacted] (4- weeks maintenance phase)	Gamma	Table 56
RAASi class distributions used in treatment	Varies depending on population – based on micro-costing, see reference	N/A	N/A	Table 59 to Table 62
Resource use of HK event	£379.93 – based on micro-costing, see reference	£37.99	Gamma	Table 64

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

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

Costs for SZC and standard care per day are summarised in Table 55 and described in more detail below. No therapy is administered for standard care, so the treatment cost is assumed to be nil.

As low K^+ diets are now considered not to be clinically effective and are not routinely used in clinical practice, no costs were included for low K^+ diet intervention. As such, the cost of standard care may be underestimated.

Table 55. Cost per day for SZC and standard care

Day	SZC cost / day	Standard care (lifestyle advice) cost / day
1	[redacted]	£0.00
2	[redacted]	£0.00
3	[redacted]	£0.00
4+	[redacted]	£0.00

Abbreviation: SZC: sodium zirconium cyclosilicate.

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The cost for a 5 g sachet of SZC is £5.20. The cost for a 10 g sachet is £10.40. The cost of a course of SZC was the cost per sachet multiplied by the actual doses given over the first 84 days of the ZS-005 trial specifically for patients with an S–K of ≥5.5–<6.0 mmol/L.[139] The actual drug cost per day therefore varied, but on average on day 4+ was calculated to be [redacted]. The breakdown of the costs of SZC per day based on the dosing schedule in ZS-005 is given in Table 56.

Table 56. Dosing schedule for SZC in model-based on actual doses given in ZS-005 trial

Day	5 g daily	10 g daily	10 g three times a day	Cost / day
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
Day	**5 g every other day**	**5 g daily**	**10 g daily**	**Cost / day**
4+	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: SZC: sodium zirconium cyclosilicate.

The total cost for each course of treatment is given in Table 57. For a treatment course of SZC, the costs are made up of the correction phase (days 1–3), and the maintenance phase (days 4–28 of cycle 1, followed by two further four-week cycles). The correction phase treatment is only given to patients at the start of the model. In subsequent re-treatments, the maintenance phase treatment only is given. The wastage assumption of 2 days per 28 days is only applied to the maintenance phase. In the model base case, the cost of the correction phase is [redacted] and the cost of the maintenance phase for one four-week cycle is [redacted], with the wastage assumption applied. No costs are directly associated with the prescription of SZC, as the costs considered to be included within the initial management costs following an HK event.

Table 57. Total costs for one treatment cycle in the model with and without a wastage assumption, based on treatment arm

Scenario	SZC	Standard care
No wastage assumption	[redacted]	£0.00
Wastage assumption	[redacted]	£0.00

Footnotes: The total treatment cost of one cycle is made up of the correction phase, and the maintenance phase of three four-week cycles.
Abbreviations: HK: hyperkalaemia; SZC: sodium zirconium cyclosilicate.

B.3.5.5 *Health state costs and resource use*

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

As the trials were not designed to identify the effect of CKD and HF stage above the impact of HK generally, it was not possible to use the trials to estimate costs for time-in-state. Consequently, existing NICE guidelines or other national body guidelines are used in the estimation of these values, in keeping with the model's hierarchy of evidence. It was not possible to use these values for the parameter RAASi therapy time-in-state costs ("sub-max"

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level), and no literature was found to support parameterisation, and so the CPRD dataset was used to give estimated values.

B.3.5.5.1 CKD and HF costs

Costs associated with each stage of CKD and HF are taken from Kent *et al.* and Ford *et al.* respectively, as described in Table 58.[169, 177] The costs of CKD and HF management identified in the studies have been inflated to the current cost year using the PSS Pay & Prices Index.[171]

Table 58. Time-in-state costs

State	Annual cost (mean)	Annual cost (SE)	Distribution	Source
CKD stage 3a	£1,354.02	£59.04	Gamma	Kent *et al.*[169]
CKD stage 3b	£1,354.02	£59.04	Gamma	
CKD stage 4	£4,741.00	£107.81	Gamma	
CKD stage 5 (pre-RRT)	£16,623.00	£237.43	Gamma	
HF NYHA I	£106.89	£10.69	Gamma	Ford *et al.*[177]
HF NYHA II	£123.15	£12.31	Gamma	
HF NYHA II	£159.72	£15.97	Gamma	
HF NYHA IV	£170.46	£17.05	Gamma	
S–K, all levels of S–K	£0.00	£0.00	N/A	Assumption – no literature source found so conservative assumption made

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

B.3.5.5.2 RAASi therapy costs

The main costs associated with ongoing RAASi therapy are the use of ACEi, ARBs and MRA drugs. The effectiveness of RAASi therapy is estimated assuming no MRA use (the source their effectiveness is based on, Xie *et al.*,[94] did not consider MRA use, see Section B.3.3.2, Table 43), but the cost of RAASi includes an MRA component as a conservative assumption and to better reflect national guidelines and research databases. In the model these drugs can be prescribed at two levels, corresponding to “max” and “sub-max” levels referred to elsewhere. The weighted annual cost is therefore calculated as £46.48 for “max” RAASi (Table 59) and £25.16 for “sub-max” RAASi (Table 60) in the CKD population, and £55.79 for “max” (Table 61) and £33.47 for “sub-max” (Table 62) in the HF population. In the base case of the model the weighted average annual “max” cost is £49.16 and the weighted average annual “sub-max” cost is £27.45, based on the proportions of CKD and HF patients identified in the SPARK study (see Section B.3.3.2.1).[29]

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

Event	Percentage of cohort	Average daily dose (mg)	Cost per mg	Source
ACEi (assumed to be ramipril for costing)	90%	10.00	£0.0058	ESC recommendations[50]
ARB (assumed to be candesartan cilexetil for costing)	10%	32.00	£0.0036	ESC recommendations[50]
MRA (assumed to be spironolactone for costing)	50%	50.00	£0.0026	ESC recommendations[50]

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

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

Event	Percentage of cohort	Average daily dose (mg)	Cost per mg	Source
ACEi (assumed to be ramipril for costing)	90%	5.99	£0.0058	CPRD mean dose at baseline [181]
ARB (assumed to be candesartan cilexetil for costing)	10%	10.06	£0.0036	CPRD mean dose at baseline [181]
MRA (assumed to be spironolactone for costing)	30%	44.59	£0.0026	CPRD mean dose at baseline [181]

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

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

Event	Percentage of cohort	Average daily dose (mg)	Cost per mg	Source
ACEi (assumed to be ramipril for costing)	90%	10.00	£0.0058	ESC recommendations[50]
ARB (assumed to be candesartan cilexetil for costing)	10%	32.00	£0.0036	ESC recommendations[50]
MRA (assumed to be spironolactone for costing)	70%	50.00	£0.0026	ESC recommendations[50]

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

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Table 62. RAASi therapy time-in-state costs ("sub-max" level, HF population)

Event	Percentage of cohort	Average daily dose (mg)	Cost per mg	Source
ACEi (assumed to be ramipril for costing)	90%	5.99	£0.0058	CPRD mean dose at baseline [181]
ARB (assumed to be candesartan cilexetil for costing)	10%	10.06	£0.0036	CPRD mean dose at baseline [181]
MRA (assumed to be spironolactone for costing)	50%	44.59	£0.0026	CPRD mean dose at baseline [181]

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

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

B.3.5.6.1 HK event costs

HK events are triggered once S–K goes above 5.5 mmol/L and require the immediate re-initiation of treatment without any hospital admission.

A micro-costing approach was adopted to more accurately describe the cost of an HK event. The mixture of resource use of an HK event was derived from clinical expert opinion, summarised in Table 63 and described in detail in Table 64. Nationally representative value sets such as NHS references costs and PSSRU are used for all costings.[207, 208] All costs derived from treatment guidelines have been inflated to the current cost year using the PSS Pay & Price index.[171]

The costing for the HK event is based on estimates of resource use rates validated by clinical expert opinion. The clinicians described how only an outpatient visit would be relevant in that situation, and therefore that the cost of HK events would be minimal.[23] The price estimated by the micro-costing approach for an HK event is £379.93 and equal across the SZC and standard care arms.

Table 63. Summary of cost of HK event

Event	SZC		Standard care			
	Cost (mean)	Cost (SE)	Cost (mean)	Cost (SE)	Dist	Source
HK event	£379.93	£37.99	£379.93	£37.99	Gamma	Table 64

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

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Table 64. HK event costs

Event	Cost (mean)	Source	Resource use (SZC)	Resource use (standard care)	Source
ECG	£155.69	NHS reference costs 2022-2023[207]	1	1	Clinical expert input[23]
U&E test	£7.24	NICE NG45[209]	1	1	
Outpatient visit	£217.00	PSSRU 2023[208]	1	1	

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

B.3.5.6.2 RAASi alteration costs

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

Assumptions around what resource use is needed at each stage are listed in Table 65 and Table 66, and were validated by clinical experts' opinion.[183] Expert opinion was that up-titration would happen exclusively in primary care, but that down-titration and discontinuation could happen in either primary care or secondary care. To represent this, clinical expert opinion confirmed that a 50% primary and 50% secondary split would be appropriate as an assumption.[183] When care occurred in a secondary setting, it was further assumed that no inpatient services were used, as per the preferred committee assumptions in TA599.[3] Care costs comprise of initial care and follow-up care. Nationally representative sources of costs are used for all values, in line with the discussion in Section B.3.5.2. The calculated weighted costs are £280.48 for a discontinuation, £168.72 for a re-continuation and £420.72 for a down-titration.

Table 65. RAASi alteration event costs in primary care

Event	Annual cost (mean)	Source	Down-titration of RAASi		Discontinuation of RAASi		Return to max RAASi	
			Patients affected	Resource use for these patients	Patients affected	Resource use for these patients	Patients affected	Resource use for these patients
Primary care - Initial								
GP visit	£49.00	PSSRU 2023[208]	100%	1.00	100%	1.00	100%	1.00
U&E test	£7.24	NICE NG45[209]	100%	1.00	100%	1.00	100%	1.00
Primary care - Follow-up								
GP visit	£49.00	PSSRU 2023[208]	100%	2.00	100%	1.00	100%	2.00
U&E test	£7.24	NICE NG45[209]	100%	2.00	100%	1.00	100%	2.00

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

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Table 66: RAASi alteration event costs in secondary care

Event	Annual cost (mean)	Source	Down-titration of RAASi		Discontinuation of RAASi		Return to max RAASi	
			Patients affected	Resource use for these patients	Patients affected	Resource use for these patients	Patients affected	Resource use for these patients
Secondary care - Initial								
U&E test	£7.24	NICE NG45[209]	100%	1.00	100%	1.00	100%	1.00
Outpatient visit	£217.00	PSSRU 2023[208]	100%	1.00	100%	1.00	100%	1.00
Inpatient day	£857.00	PSSRU 2023[208]	0%	1.00	0%	1.00	0%	0.00
Secondary care - Follow-up								
U&E test	£7.24	NICE NG45[209]	100%	2.00	100%	1.00	100%	2.00
Outpatient visit	£217.00	PSSRU 2023[208]	100%	2.00	100%	1.00	100%	2.00
Inpatient day	£857.00	PSSRU 2023[208]	0%	2.00	0%	1.00	0%	2.00

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

B.3.5.6.3 Adverse-event costs

The proportions of patients expected to experience each AE (Section B.3.4.4) are used in conjunction with AE costs, to derive an average per-patient cost associated with treatment-related AEs for SZC and the comparators. The model inputs are defined as the annual cost of AEs, conditional on experiencing that event. All costs are obtained from the latest cost year of NHS reference costs (2022–2023) and are summarised in Table 67. The cost of adverse events is assumed to be equal across treatment arms.

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Table 67. Adverse-event costs

Event	Cost (mean)	Cost (SE)	Dist	Source
Oedema (generalised and peripheral)	£292.17	£29.22	Gamma	Day Case: DZ20E, DZ20F. Pulmonary Oedema without Interventions, with different CC scores
Worsening hypertension	£358.47	£35.85	Gamma	Day Case: EB04Z. Hypertension
Constipation	£560.74	£56.07	Gamma	Day Case: FZ91K/FZ91L/FZ91M. Non-Malignant Gastrointestinal Tract Disorders without Interventions, with different CC scores
Diarrhoea	£560.74	£56.07	Gamma	Day Case: FZ91K/FZ91L/FZ91M. Non-Malignant Gastrointestinal Tract Disorders without Interventions, with different CC scores
Nausea	£280.37	£28.04	Gamma	Day Case: FZ91K/FZ91L/FZ91M. Non-Malignant Gastrointestinal Tract Disorders without Interventions, with different CC scores
Hypomagnesaemia	£390.89	£39.09	Gamma	Day Case: KC05J/KC05K/KC05L/KC05M/KC05N. Fluid or Electrolyte Disorders, without Interventions, with different CC scores
Anorexia	£410.34	£41.03	Gamma	Day Case: FZ49F/FZ49G/FZ49H. Nutritional Disorders without Interventions, with different CC scores
Hypokalaemia	£390.89	£39.09	Gamma	Assumption – same as hypomagnesaemia
Urinary tract infection	£353.63	£35.36	Gamma	Day Case: LA04S/LA04R/LA04Q/LA04P. Kidney or Urinary Tract Infections, without Interventions, with different CC scores

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

B.3.5.6.4 Other event costs

Event costs not otherwise described are shown in Table 68. Each event cost applies only to the cycle in which it occurs and, does not have any associated ongoing cost.

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It was not possible to identify the cost of these events from the trial, and existing national body guidance did not give values which were applicable to the HK population. Consequently, values were taken from the SLR for the cost of hospitalisation and MACE (Table 53 and Appendix I).

Table 68. Other event costs

Event	Annual cost (mean)	Annual cost (SE)	Distribution	Source
MACE	£5,817.39	£822.37	Gamma	Kent *et al.*[204]
Hospitalisation	£2,962.16	£296.22	Gamma	Colquitt *et al.*[206]

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

B.3.5.7 *Miscellaneous unit costs and resource use*

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

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

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

A summary of thresholds related to decisions and events related to SZC treatment of HK is summarised in Table 69. Table 70 summarises the variables which are constant across all base-case model scenarios (mixed CKD and HF population, HF only and CKD only) and varied individually in sensitivity analyses. Table 71 summarises variables that are specific to the HF only and CKD only analyses.

Table 69. Summary of SZC treatment-related parameters

Parameter	Value	Source
Maximum duration of initial treatment	3 days (correction phase) + 12 weeks (maintenance phase)	Market Research and clinical expert input[23, 160]
Maximum duration of repeat treatment	12 weeks	Clinical expert input[23]
S–K threshold to initiate treatment (mmol/L)	5.5*	Clinical expert input[23]
S–K threshold to initiate re-treatment (mmol/L)	5.5*	
S–K threshold defining "Less severe" HK event	5.5*	
Annual probability of SZC discontinuation	0.375*	ZS-005 trial[139]

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

Table 70. Summary of structural parameters which are constant across all base-case model scenarios

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Time horizon	Sooner of 80 years or initiation of RRT	N/A		Fixed	Section B.3.2.2, Table 33
Cycle length	28 days	N/A		Fixed	Section B.3.2.2, Table 33
Cohort size	60,000	N/A		Fixed	N/A
Discount rate (costs)	3.5%	0.0%	6.0%	Fixed	Section B.3.2.2, Table 33
Discount rate (benefits)	3.5%	0.0%	6.0%	Fixed	Section B.3.2.2, Table 33
Threshold for low HK event	5.50	4.95	6.05	Fixed	Section B.3.3.6 Table 56

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Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Proportion of patients CKD*	71.2%	N/A	N/A	Fixed	Section B.3.3.2.1, Table 34
Proportion of cohort female	0.37	0.00	1.00	Beta	
Age at baseline*	63.99	57.60	70.39	Normal	
eGFR at baseline*	[redacted]	[redacted]	[redacted]	Normal	
eGFR threshold for RRT initiation	8.60	7.74	9.46	Normal	
Proportion RAASi use	1.00	0.00	1.00	Beta	

Footnotes: These values are for the mixed CKD and HF population base case analysis. In the CKD only base case analysis, the proportion of patients with CKD is 100%, the age at baseline is 63.56 and eGFR at baseline is [redacted]. In the HF only base case analysis, the proportion of patients with CKD is 0%, the age at baseline is 65.07 and eGFR at baseline is 68.14.
Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; OWSA: one-way sensitivity analyses; PSA: probabilistic sensitivity analysis; RAASi: renin-angiotensin-aldosterone system inhibitor; RRT: renal replacement therapy.

Table 71: Summary of parameters that differ across the modelled populations

Parameter	Value		OWSA (CKD)		OWSA (HF)		Within the PSA varied by	Reference to section in submission
	CKD	HF	Lower bound	Upper bound	Lower bound	Upper bound		
Age at baseline (years)	63.56	65.07	57.20	69.92	58.56	71.58	Normal	Section B.3.3.2.1, Table 34
eGFR at baseline (ml/min/1.73 m^2)	[redacted]	68.14	[redacted]	[redacted]	61.33	74.95	Normal	Section B.3.3.2.1, Table 34
Statin usage at baseline (%)	0%	41%	N/A	N/A	N/A	N/A	Fixed	Section B.3.3.2.1, Table 35
Sodium at baseline (mEq/L)	137.71	137.55	N/A	N/A	N/A	N/A	Fixed	Section B.3.3.2.1, Table 34
Cholesterol at baseline (mg/dL)	193.86	168.92	N/A	N/A	N/A	N/A	Fixed	Section B.3.3.2.1, Table 35
Haemoglobin at baseline (g/dL)	11.790	13.250	N/A	N/A	N/A	N/A	Fixed	Section B.3.3.2.1, Table 35
Lymphocytes at baseline (10^3 cells/µL)	1.72	2.04	N/A	N/A	N/A	N/A	Fixed	Section B.3.3.2.1, Table 34

Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure; OWSA: one-way sensitivity analyses; PSA: probabilistic sensitivity analysis.

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Table 72. Summary of transitional probabilities which are constant across all base-case model scenarios

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Proportion NYHA I	0.10	Not varied within OWSA		Beta	Section B.3.3.2.1, Table 44
Proportion NYHA II	0.10			Beta	
Proportion NYHA III	0.43			Beta	
Proportion NYHA IV	0.37			Beta	
Proportion of treated patients: oedema (generalised and peripheral)	0.116			Beta	Section B.3.3.5, Table 39
Proportion of treated patients: constipation	0.064			Beta	
Proportion of treated patients: diarrhoea	0.044			Beta	
Proportion of treated patients: nausea	0.075			Beta	
Proportion of treated patients: hypomagnesaemia	0.012			Beta	
Proportion of treated patients: anorexia	0.000			Beta	
Proportion of treated patients: hypokalaemia	0.015			Beta	
Proportion of treated patients: urinary tract infection	0.079			Beta	
Weeks to return to RAASi max, if returning	12.0			Normal	Section B.3.3.3
Proportion RAASi max that discontinue: S–K ≥5.5–<6.0 mmol/L – SZC arm	[redacted]	Proportions vary from 90% to 110%		Beta	Section B.3.3.4, Table 38
Proportion RAASi max that discontinue: S–K ≥5.5–<6.0 mmol/L – Standard care	[redacted]			Beta	
Proportion RAASi max that down-titrate: S–K ≥5.5–<6.0 mmol/L – SZC arm	[redacted]			Beta	
Proportion RAASi max that down-titrate: S–K ≥5.5–<6.0 mmol/L – Standard care	[redacted]			Beta	
Proportion RAASi sub-max that discontinue: S–K ≥5.5–<6.0 mmol/L – SZC arm	[redacted]			Beta	
Proportion RAASi sub-max that discontinue: S–K ≥6.0 mmol/L – Standard care	[redacted]			Beta	

Abbreviations: NYHA: New York Heart Association; OWSA: one-way sensitivity analyses; PSA: probabilistic sensitivity analysis; RAASi: renin-angiotensin-aldosterone system inhibitor.

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Table 73. Summary of utility parameters which are constant across all base-case model scenarios

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Health state utility: CKD 3a	0.80	0.72	0.88	Beta	Section B.3.4, Table 51
Health state utility: CKD 3b	0.80	0.72	0.88	Beta	
Health state utility: CKD 4	0.74	0.67	0.81	Beta	
Health state utility: CKD 5 (pre-RRT)	0.71	0.64	0.78	Beta	
Health state utility: NYHA I	0.86	0.77	0.94	Beta	
Health state utility: NYHA II	0.77	0.69	0.85	Beta	
Health state utility: NHYA III	0.67	0.61	0.74	Beta	
Health state utility: NYHA IV	0.53	0.48	0.59	Beta	
Disutility: MACE event	−0.050	Not varied within the OWSA		Beta	Section B.3.4.4
Disutility: hospitalisation	−0.02			Beta	
Disutility: oedema	-0.0029			Beta	
Disutility: constipation	−0.0056			Beta	
Disutility: diarrhoea	−0.0008			Beta	
Disutility: nausea	−0.0037			Beta	
Disutility: hypomagnesaemia	−0.0028			Beta	
Disutility: anorexia	−0.0029			Beta	
Disutility: hypokalaemia	0.0000			Beta	
Disutility: urinary tract infection	−0.0004			Beta	

Abbreviations: CKD: chronic kidney disease; MACE: major adverse cardiac event; NYHA: New York Heart Association; OWSA: one-way sensitivity analyses; PSA: probabilistic sensitivity analysis; RAASi: renin-angiotensin-aldosterone system inhibitor; RRT: renal replacement therapy.

Table 74. Summary of cost parameters which are constant across all base-case model scenarios

Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Cost of SZC	See reference	N/A	N/A	Fixed	Section B.3.5.4, Table 56

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Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Cost of standard care	See reference	N/A	N/A	Fixed	
Cost of initial treatment with SZC	[redacted]	[redacted]	[redacted]	Fixed	
Cost of repeat treatment with SZC	[redacted]	[redacted]	[redacted]	Fixed	
Event cost: HK event	£379.93	Not varied within OWSA		Gamma	Section B.3.5.6, Table 64
Annual cost of RAASi: maximum dose	£49.16			Gamma	Section B.3.5.5, Table 59
Annual cost of RAASi: sub-maximum dose	£27.56			Gamma	Section B.3.5.5, Table 60
Event cost: RAASi discontinuation	£280.48			Gamma	Section B.3.5.6.2, Table 65
Event cost: RAASi down-titration	£420.72			Gamma	Section B.3.5.6.2, Table 65
Event cost: return to maximum RAASi use	£168.72			Gamma	Section B.3.5.6.2, Table 65
Event cost: MACE event	£5,817.39			Gamma	Section B.3.5.6.2, Table 67
Event cost: Oedema	£292.17			Gamma	Section B.3.5.6.3, Table 67. Adverse-event costs
Event cost: Constipation	£560.56			Gamma	
Event cost: Diarrhoea	£560.74			Gamma	
Event cost: Nausea	£280.37			Gamma	
Event cost: Hypomagnesaemia	£390.89			Gamma	
Event cost: Anorexia	£410.34			Gamma	
Event cost: Hypokalaemia	£390.89			Gamma	
Event cost: Urinary tract infection	£353.63			Gamma	
Annual cost CKD 3a	£1,354.02			Gamma	Section B.3.5.5.1, Table 58
Annual cost CKD 3b	£1,354.02			Gamma	
Annual cost CKD 4	£4,741.00			Gamma	

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Parameter	Value	OWSA		Within PSA varied by	Reference to section in submission
		Lower bound	Upper bound		
Annual cost CKD 5 (pre-RRT)	£16,623.00			Gamma	

Abbreviations: CKD: chronic kidney disease; HK: hyperkalaemia; MACE: major adverse cardiac event; OWSA: one-way sensitivity analyses; PSA: probabilistic sensitivity analysis; RAASi: renin-angiotensin-aldosterone system inhibitor; RRT: renal replacement therapy; SZC: sodium zirconium cyclosilicate.

Table 75. Summary of clinical parameters which are constant across all base-case model scenarios

Parameter		Value	OWSA		Within PSA varied by	Reference to section in submission
			Lower bound	Upper bound		
IRR mortality CKD	<3.5 mmol/L	[redacted]	[redacted]	[redacted]	Normal	Section B.3.3.7, Table 42
	≥3.5–<4.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥4.0–<4.5 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥4.5–<5.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥5.0–<5.5 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥5.5–<6.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥6.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
IRR MACE CKD	<3.5 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥3.5–<4.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥4.0–<4.5 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥4.5–<5.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥5.0–<5.5 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥5.5–<6.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥6.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
IRR hospitalisation CKD (eGFR <30 mL/min	<3.5 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥3.5–<4.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥4.0–<4.5 mmol/L	[redacted]	[redacted]	[redacted]	Normal	

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Parameter		Value	OWSA		Within PSA varied by	Reference to section in submission
			Lower bound	Upper bound		
/1.73 m²)	≥4.5–<5.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥5.0–<5.5 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥5.5–<6.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥6.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
IRR hospitalisation CKD (eGFR 30–40 mL/min /1.73 m²)	<3.5 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥3.5–<4.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥4.0–<4.5 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥4.5–<5.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥5.0–<5.5 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥5.5–<6.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥6.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
IRR hospitalisation CKD (eGFR 40–50 mL/min /1.73 m²)	<3.5 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥3.5–<4.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥4.0–<4.5 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥4.5–<5.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥5.0–<5.5 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥5.5–<6.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥6.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
IRR hospitalisation (eGFR 50–60 mL/min	<3.5 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥3.5–<4.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥4.0–<4.5 mmol/L	[redacted]	[redacted]	[redacted]	Normal	

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Parameter		Value	OWSA		Within PSA varied by	Reference to section in submission
			Lower bound	Upper bound		
/1.73 m²)	≥4.5–<5.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥5.0–<5.5 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥5.5–<6.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥6.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
IRR mortality HF	<3.5 mmol/L	[redacted]	[redacted]	[redacted]	Normal	Section B.3.3.8, Table 46
	≥3.5–<4.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥4.0–<4.5 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥4.5–<5.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥5.0–<5.5 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥5.5–<6.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥6.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
IRR MACE HF	<3.5 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥3.5–<4.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥4.0–<4.5 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥4.5–<5.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥5.0–<5.5 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥5.5–<6.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥6.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
IRR hospitalisation HF (all eGFR)	<3.5 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥3.5–<4.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥4.0–<4.5 mmol/L	[redacted]	[redacted]	[redacted]	Normal	

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Parameter		Value	OWSA		Within PSA varied by	Reference to section in submission
			Lower bound	Upper bound		
	≥4.5–<5.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥5.0–<5.5 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥5.5–<6.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	
	≥6.0 mmol/L	[redacted]	[redacted]	[redacted]	Normal	

Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HF, heart failure; IRR: incident rate ratio; MACE: major adverse cardiac event.

B.3.6.2 *Summary of scenario analysis*

A summary of the scenario analyses performed on the base-case is provided in Table 76.

Table 76. Summary of scenario analysis inputs

Parameter	Purpose	Base-case	Scenarios	Reference to section in submission
Population split	To assess the impact of the population mix of HF and CKD as seen in the ZS clinical trial data compared to UK RWE	Population split as per SPARK data – [redacted] HF, [redacted] CKD	Population split as per pooled ZS-004 and ZS-005 trial data – 35.70% HF, 64.30% CKD	Section B.3.3.2.1
CKD patients starting at stage 3a	To assess the cost-effectiveness if CKD patients were to start treatment at an earlier CKD stage than currently recommended by NICE in TA599	[redacted] CKD patients, starting eGFR of CKD patients is [redacted]	100% CKD patients, starting eGFR of CKD patients is 52	Section B.3.3.2.1
RAASi discontinuation assumptions	Clinicians indicate they would primarily use SZC to enable up-titration of RAASi therapy and SZC would allow them to maintain RAASi for those with HK	Based on the ZORA re-analysis: [redacted] discontinue, [redacted] down-titrate when S–K is ≥5.5–<6.0 mmol/L [redacted] discontinue, [redacted] down-titrate when S–K is ≥5.0–<5.5 mmol/L	No patients in the SZC arm discontinue RAASi with an S–K of <6.0 mmol/L	Section B.3.3.4

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Parameter	Purpose	Base-case	Scenarios	Reference to section in submission
	and an S–K of ≥5.5–<6.0 mmol/L.[23] This scenario assesses the impact if SZC enabled all patients to reach and maintain RAASi usage.			
Impact of RAASi on long term outcomes	To assess the impact using TA599 committee preferred assumption of RAASi impact on long term outcomes	Mortality odds ratio RAASi vs no RAASi for HF patients: 0.23, as informed by Chen *et al.* (2023)[65]	No mortality odds ratio for RAASi vs no RAASi in HF patients.	Section B.3.3.8
Treatment dosage	Clinicians indicated that they would initiate all patients with persistent HK and an S–K of ≥5.5–<6.0 mmol/L on 5 g of SZC once a day[23]	Treatment pattern is based upon the dosage distribution observed for the ≥5.5–<6.0 subgroup within the ZS-005 trial, as summarised in Table 56	The dosage schedule is 5 g of SZC once a day for the entire treatment duration (correction phase and maintenance phase)	Section B.3.5.4
Wastage assumption	To assess the impact of removing the wastage assumption . This would be relevant were patients to keep SZC sachets between HK events, or if more tailored prescriptions were available	Wastage assumption of 2-days per 28 days	No wastage assumption	Section B.3.5.4
2 day S–K trajectory for SoC	In TA599, the Committee preferred an approach whereby the 48 h absolute reduction	The 48 h absolute reduction observed in ZS-003 was applied to day 2 of the S–K trajectory, and linearly extrapolated to day 3	All patients exit the acute phase by day 2	Section B.3.3.3

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Parameter	Purpose	Base-case	Scenarios	Reference to section in submission
	observed in ZS-003 was applied to day 2 of the S–K trajectory, and linearly extrapolated to day 3. As this represents a more conservative approach because almost all patients with an initial S–K of ≥5.5–<6.0 mmol/L would have exited the acute phase after two days of treatment with SZC, a scenario was explored where all patients exit the acute phase by day 2			

Abbreviations: eGFR: estimated glomerular filtration rate; HK, hyperkalaemia; S–K, serum potassium; RAASi, renin-angiotensin-aldosterone system inhibitor; SZC, sodium zirconium cyclosilicate.

B.3.6.3 *Assumptions*

Table 77 contains a list of all assumptions made in the de novo economic model along with justifications.

Table 77. Model assumptions and justifications

Assumption	Justification
Time horizon	
The model ends at renal replacement therapy	Assumption has remained consistent with TA599. Whilst SZC is now licenced in patients who are receiving chronic haemodialysis,[5] this population was not considered in TA599 as SZC did not have a license for this population and these patients were not included in the ZS clinical trial programme.[3] The current clinical data on the use of SZC in dialysis patients is limited to the DIALIZE and ADAPT studies.[6, 125] Whilst these studies demonstrate that SZC is safe and efficacious at reducing S–K in patients receiving chronic haemodialysis, there are still a paucity of data reporting on the association between S–K and long-term health or resource use outcomes in this population, as such they were not included in the decision problem. Furthermore,

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	appropriate cost-effectiveness modelling of SZC amongst patients in receipt of haemodialysis is complicated as RRT and transplantation are not cost-effective treatments.[175, 176] As an adaptation of the model structure would simulate patients receiving RRT as separate health states within the patient population, the inherent lack of cost-effectiveness associated with RRT and transplantation potentially negatively impacts the overall cost-effectiveness of SZC, thus obscuring the decision problem and targeted nature of this partial update, that is expanding the current positive guidance for those with persistent HK to a those with S–K ≥5.5–<6.0 mmol/L. It should be noted that SZC has been previously incorporated into the emergency COVID-19 guidelines for the management of dialysis patients in the NICE guidelines (NG160) as a holding measure to allow a delay in dialysis until COVID-19 test results are known.[126] The guidelines also recommended the prescription of K^+ binders to allow the frequency of dialysis to be reduced, and reduce the risk of transferring patients undergoing dialysis to a hospital without dialysis facilities.[126] Therefore, SZC has demonstrated value within the NHS in the dialysis population.
Duration of disease before model commences equal to 0 years	Assumption has remained consistent with TA599. No other available evidence to inform this assumption
Patients cannot age past 100	Assumption has remained consistent with TA599. Standard modelling assumption.
An other-cause mortality is applied in addition to condition-specific mortality	Assumption has remained consistent with TA599. Standard modelling assumption. As a significant fraction of all-cause mortality is due to cardiovascular disease this assumption is likely unfavourable to treatment
Clinical progression of disease	
There is no general factor of eGFR decline in HF population	Assumption has remained consistent with TA599. Clinical expert input[183]
No difference in costs, utilities and outcomes between first and subsequent HK events	Assumption has remained consistent with TA599. Those included in the trial may already have had an HK event, therefore if there is a relationship between number of HK events and outcomes this should already be accounted for in the data based on the trial
Adverse events last 13 cycles on SZC (at 1/13 of the utility decrement per cycle) and are not applied on standard care	As patients can have up to one HK event per cycle it is possible for a patient experiencing an adverse event from the treatment of a prior HK event to randomly be assigned to the same adverse event on their next event. As there is no literature on how – for example – nausea might compound, it is more appropriate to ensure that patients do not experience multiple copies of the same adverse event at the same time. Adverse events occur only on treatment which greatly favours standard care
Condition-specific utility assumed to be constant	Assumption has remained consistent with TA599. The model contains transition probabilities driving movement from less-severe to more-severe disease states,

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	therefore it is likely that condition-specific decline of utility is already correctly accounted for
Cost of S–K levels assumed to be 0 for all levels	Assumption has remained consistent with TA599. Based on an assumption in Bennett *et al.* (a)[205] but thought to be conservative as SZC should lower S–K levels below standard care
RAASi use	
Resource use associated with down-titration, discontinuation and return to max RAASi	Assumption has remained consistent with TA599. Data on resource use associated with RAASi dose alteration were not available. Expert opinion was that up-titration would happen exclusively in primary care, but that down-titration and discontinuation could happen in either primary care or secondary care.[183] To represent this, clinical expert opinion confirmed that a 50% primary and 50% secondary split would be appropriate as an assumption.[183] When care occurred in a secondary setting, it was further assumed that no inpatient services were used, as per the preferred committee assumptions in TA599[3]
Mix of drugs used in RAASi therapy assumed to be only Ramipril, Candesartan cilexetil, and Spironolactone	Assumption has remained consistent with TA599. There is no source for actual mix of drugs used in the UK, but these three drugs are representative of ACEi, ARB and MRA drugs respectively, for which there is data. This assumption is likely to have a minimal impact on results, and is thought to be representative of clinical practice
Proportion of drugs used on RAASi therapy in sub-max RAASi use compared to max RAASi use	Assumption has remained consistent with TA599. Based on CPRD mean dose[181]
Odds ratio for sub-max RAASi vs no RAASi contributing to mortality assumed to be 50% of max RAASi vs sub-max RAASi in CKD and HF population	While there are strong literature sources supporting (Xie *et al.* and Chen *et al.* 2023)[65, 94] the max vs no RAASi scenario, there is no literature supporting the sub-max vs no RAASi scenario and therefore plausible assumption was made based on other associations observed and clinical judgement
Odds ratio for sub-max RAASi vs no RAASi contributing to CV event assumed to be 50% of max RAASi vs sub-max RAASi in CKD population	While there is a strong literature source supporting (Xie *et al.* and Chen *et al.*)[65, 94] the max vs no RAASi scenario, there is no literature supporting the sub-max vs no RAASi scenario and therefore plausible assumption was made based on other associations observed and clinical judgement
Odds ratio for RAASi use of any sort contributing to hospitalisation in CKD population	Assumption has remained consistent with TA599. Assumed to be 1 as there is no literature source and this is the most conservative assumption which is still clinically plausible
Odds ratio for “sub-max” RAASi use vs no RAASi use contributing to hospitalisation in HF population	Assumption has remained consistent with TA599. Assumed to be 0.882 based on a trial in an HF but not HK population in the absence of any direct evidence.
All patients initiate model at “max” RAASi	A limitation of the model is that all patients will initiate the model on RAASi at “max” with discontinuing and down titrating of RAASi occurring at the first cycle. This is a conservative assumption as there is evidence that

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	without SZC patients may already be on a sub-optimal dose of RAASi due to the fear of triggering an HK event
Treatment costs and disutilities	
No cost associated with prescribing SZC	Assumption has remained consistent with TA599. Cost is included for secondary care hospital appointment, which is assumed to cover the cost of prescribing the drug
No cost for low K^+ diet	Assumption has remained consistent with TA599. The treatment cost for standard care can be considered conservative as low potassium diet costs (and lifestyle advice) are not included
All adverse events assumed to only possibly occur on treatment	Assumption has remained consistent with TA599. This is a conservative assumption as there is no data identified on the adverse events of lifestyle interventions (for example, a low potassium diet)
Costs and utility of death state assumed to be 0	Assumption has remained consistent with TA599. Standard modelling assumption
Disutility of HK event assumed to be 0	Assumption has remained consistent with TA599. HK events are assumed to generate disutility through an increased risk of hospitalisation, death and MACE. Therefore, this assumption avoids double counting
Disutility of hypokalaemia assumed to be 0	Assumption has remained consistent with TA599. No study was identified describing the disutility of hypokalaemia, so zero was selected as a Schelling point. Low K^+ levels are associated with some adverse outcomes in the general population, but it is unclear how well these data generalise to the HK population
Disutility of low K^+ diet assumed to be 0	Assumption has remained consistent with TA599. Conservative assumption in light of no other data to inform disutility; despite the fact it is well documented that quality of life is negatively affected by low K^+ diets
Cost of hypokalaemia assumed to be equal to hypomagnesaemia	Assumption has remained consistent with TA599. No reference cost was identified giving the cost of hypokalaemia, therefore it was assumed to be equivalent to the other metabolic disorder adverse event, hypomagnesaemia

Abbreviations: ACEi: angiotensin-converting enzyme inhibitor; AE: adverse event; ARB: angiotensin II receptor blocker; CKD: chronic kidney disease; CPRD: Clinical Practice Research Datalink; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; HF: heart failure; HK: hyperkalaemia; ICER: incremental cost-effectiveness ratio; K^+: potassium cation; MACE: major adverse cardiac event; MRA: mineralocorticoid receptor antagonist; RAASi: renin-angiotensin-aldosterone system inhibitor; RRT: renal replacement therapy; S–K: serum potassium; SZC: sodium zirconium cyclosilicate.

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B.3.7 *Base-case results*

B.3.7.1 *Base-case incremental cost-effectiveness analysis results*

Base-case results are presented in Table 78 for the mixed CKD & HF population, in Table 79 for the CKD population, and in Table 80 for the HF population.

Over a lifetime horizon, the mixed CKD & HF cohort receiving SZC accrued 4.128 QALYs at a cost of £45,546. Patients receiving standard care accrued 3.703 QALYs at a cost of £40,234. Therefore, SZC has an ICER of £12,495 compared with standard care.

Over a lifetime horizon, the CKD cohort receiving SZC accrued 3.466 QALYs at a cost of £54,241. Patients receiving standard care accrued 3.194 QALYs at a cost of £49,669. Therefore, the ICER for SZC vs standard care is £16,833.

Over a lifetime horizon, the HF cohort receiving SZC accrued 3.906 QALYs at a cost of £24,224. Patients receiving standard care accrued 3.187 QALYs at a cost of £17,719. Therefore, the ICER for SZC vs standard care is £9,053

Table 78. Base-case results for the mixed CKD & HF population

Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
SZC	£45,546	6.938	4.128	£5,312	0.728	0.425	£12,495
Standard care	£40,234	6.210	3.703	-	-	-	-

Abbreviations: ICER: incremental cost-effectiveness ratio; Inc.: incremental; LYG: life-years gained; QALYs: quality-adjusted life years; SZC: sodium zirconium cyclosilicate.

Table 79. Base-case results for the CKD population

Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
SZC	£54,241	5.796	3.466	£4,572	0.441	0.272	£16,833
Standard care	£49,669	5.354	3.194	-	-	-	-

Abbreviations: ICER: incremental cost-effectiveness ratio; Inc.: incremental; LYG: life-years gained; QALYs: quality-adjusted life years; SZC: sodium zirconium cyclosilicate.

Table 80. Base-case results for the HF population

Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
SZC	£24,224	6.985	3.906	£6,506	1.295	0.719	£9,053
Standard care	£17,719	5.690	3.187	-	-	-	-

Abbreviations: ICER: incremental cost-effectiveness ratio; Inc.: incremental; LYG: life-years gained; QALYs: quality-adjusted life years; SZC: sodium zirconium cyclosilicate.

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B.3.7.2 *Clinical outcomes from the model and disaggregated results of the base-case analysis*

A summary of the clinical outcomes and disaggregated results of the base-case incremental cost-effectiveness analysis for the three populations can be found in Table 81. Note that the definition of 'hospitalisation' excludes hospitalisations during HK events in order to disaggregate this result. Note also that the potentially counterintuitive result of increased MACE, hospitalisation events, and RAASi down-titration/discontinuation in the SZC arm of the model is explained by increased life-expectancy, allowing for more S–K-unrelated medical events.

Table 81. Disaggregated clinical outcomes per patient for the base case populations

Events	Cumulative events per patient					
	Mixed CKD & HF		CKD		HF	
	SZC	Standard care	SZC	Standard care	SZC	Standard care
HK event	12.141	16.621	10.252	14.314	12.096	14.764
MACE	1.194	1.129	1.238	1.218	0.929	0.768
Hospitalisation	4.652	4.378	4.978	4.749	3.260	2.799
RAASi discontinuation/ down-titration	2.720	2.451	2.576	2.431	2.732	2.426
Mortality within 5 years of first HK event	0.272	0.329	0.341	0.381	0.380	0.506

Abbreviations: CKD: chronic kidney disease; HF: heart failure; HK: hyperkalaemia; MACE: major adverse cardiac event; SZC: sodium zirconium cyclosilicate.

B.3.8 *Sensitivity analysis*

Sensitivity analyses were conducted to explore the level of uncertainty in the model results. All results presented are for the mixed CKD and HF population.

B.3.8.1 *Probabilistic sensitivity analysis*

Probabilistic sensitivity analysis (PSA) was performed to explore the uncertainty around key model inputs. In the base case of the model patients are generated probabilistically, but in the PSA all values are drawn from a distribution at the beginning of each simulated cohort in order to vary parameters that would otherwise remain fixed in the deterministic case. One hundred PSA iterations were run in order to obtain a stable estimate of the mean model results. The number of runs was selected based on analysis of the speed and durability of ICER convergence, which is shown in Figure 17.

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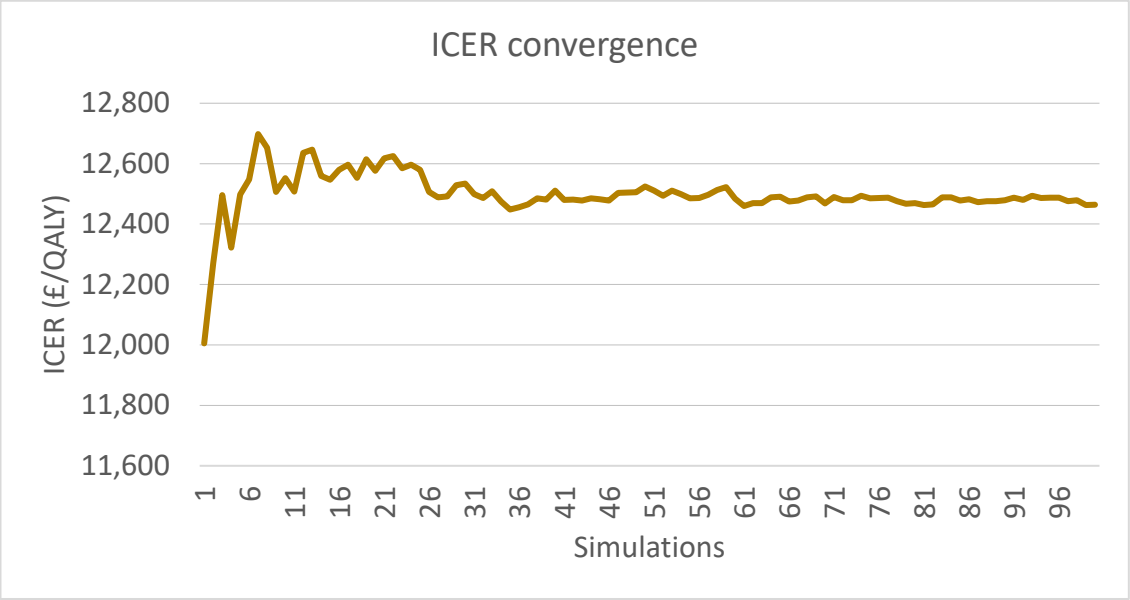
Figure 17. ICER convergence in PSA runs



Abbreviations: ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life-year.

As shown in Table 70, the following parameters were kept fixed in the PSA: maximum length of initial treatment, maximum length of subsequent treatment, discount rate for costs and benefits, time horizon, S–K thresholds (for treatment, repeat treatment, “Less Severe” HK event, “Severe” HK event) and all transition probabilities derived from CPRD regression equations.

Mean incremental results were recorded and illustrated through an incremental cost-effectiveness plane (ICEP). In addition, a cost-effectiveness acceptability curve (CEAC) is plotted.

PSA results of SZC vs standard care are presented in Table 82. The mean PSA results lie close to the deterministic base-case results (Table 78). The population receiving SZC accrued 4.126 QALYs at a cost of £45,596. Patients receiving standard care accrued 3.703 QALYs at a cost of £40,321. Therefore, SZC has a mean ICER of £12,417 compared with standard care.

The ICEP showing the PSA results is presented in Figure 18. The CEAC is presented in Figure 19. In all simulations, the cost-effectiveness of the pairs lie below the WTP threshold of £20,000.

Table 82. PSA results

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
SZC	£45,596	6.933	4.126	£5,276	0.423	£12,417
Standard care	£40,321	6.209	3.703	-	-	-

Abbreviations: ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensibility analysis; QALYs: quality-adjusted life years.

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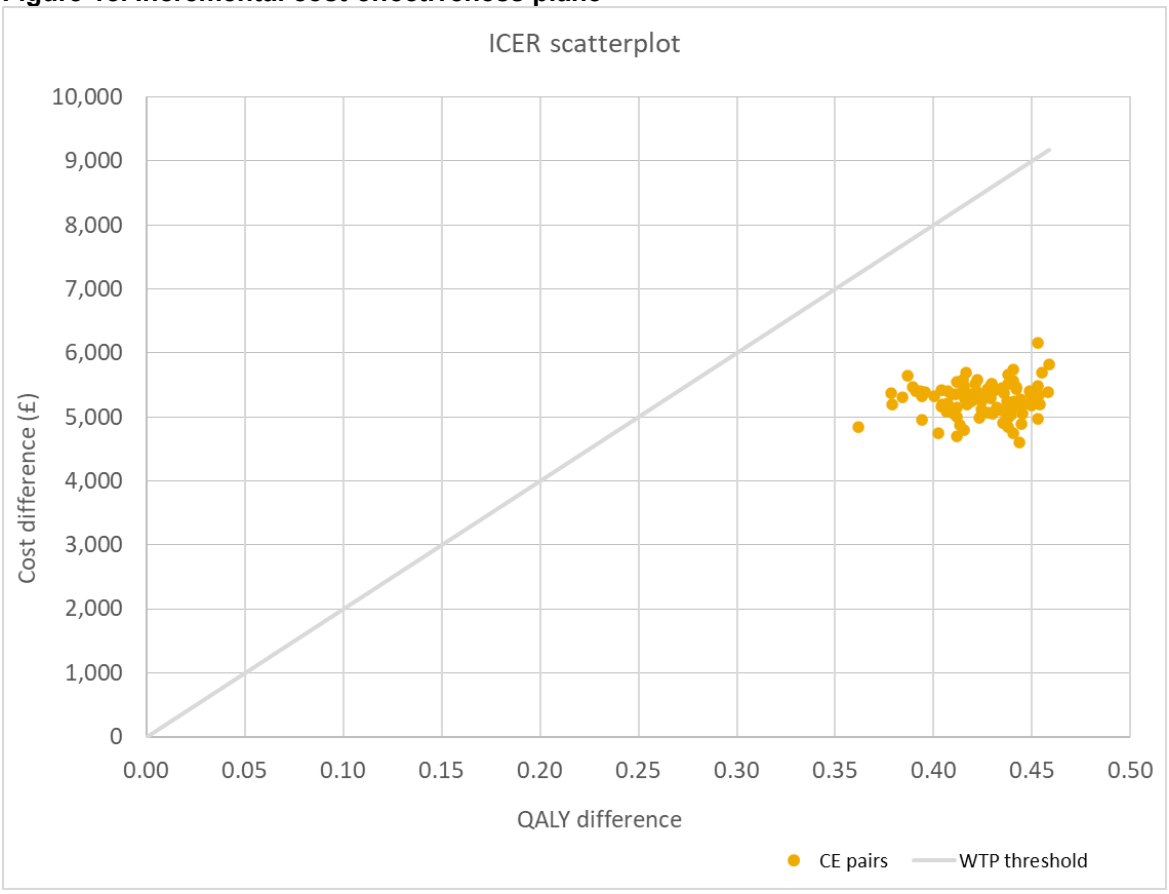
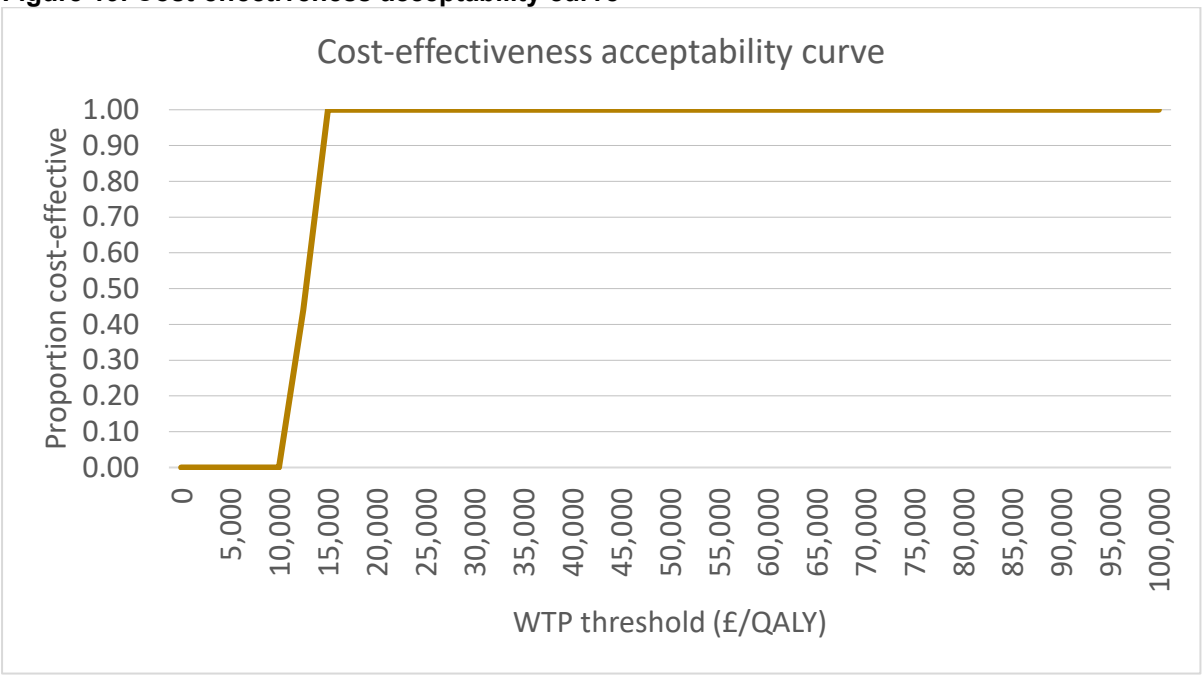
Figure 18. Incremental cost-effectiveness plane



Abbreviations: CE: cost-effectiveness; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; WTP: willingness to pay.

Figure 19. Cost-effectiveness acceptability curve



Abbreviations: QALY: quality-adjusted life-year; WTP: willingness to pay.

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B.3.8.2 *Deterministic sensitivity analysis*

One-way sensitivity analysis (OWSA) was performed to assess the impact of individual parameters on the model results. OWSA considered upper and lower CIs sourced from literature in the first instance or calculated from the pre-specified probabilistic distributions assigned to each parameter as an alternative. Where the standard error was unavailable to calculate upper and lower CIs, this was assumed to be 10% of the mean value. The upper and lower bounds for the parameters included in the OWSA are shown in Table 72.

A tornado diagram is presented in Figure 21 to illustrate the level of uncertainty over the ICER inherent in each parameter, and varying some parameters as groups to represent correlation between certain groups of parameters (for example, if the annual rate of death is higher than estimated in earlier CKD stages it is likely to be higher in later CKD stages too).

The most sensitive parameters are the S–K threshold for repeat treatment, the discount rate for costs, and the threshold for a low-severity HK event to start SZC treatment. Outside of these parameters, the variation of other parameters was less significant to overall results, since no variation led to SZC being anything but cost-effective under a WTP threshold of £20,000/QALY (excluding the S–K threshold for repeat treatment).

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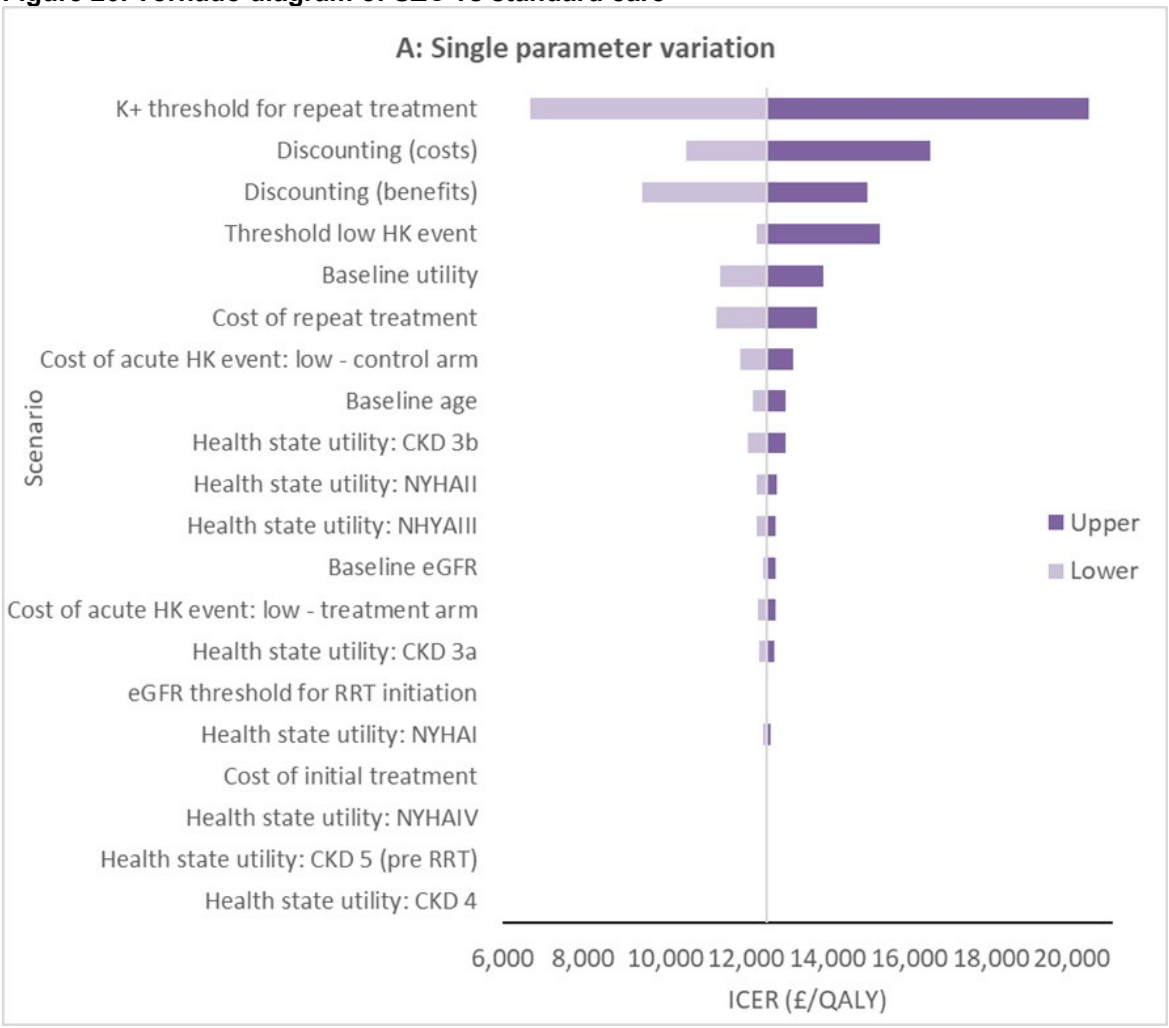
Figure 20. Tornado diagram of SZC vs standard care



Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HK: hyperkalaemia; ICER: incremental cost-effectiveness ratio; NYHA: New York Heart Association; QALY: quality-adjusted life-year; RAASi: renin-angiotensin-aldosterone system inhibitor; RRT: renal replacement therapy; SZC: sodium zirconium cyclosilicate.

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Table 83. OWSA results of SZC vs standard care

Parameter	ICER		
	Lower bound (£)	Upper bound (£)	Difference (£)
Health state utility: CKD 4	£12,491	£12,499	£8
Health state utility: CKD 5 (pre RRT)	£12,475	£12,516	£41
Health state utility: NYHAIV	£12,467	£12,523	£56
Cost of initial treatment	£12,463	£12,527	£65
Health state utility: NYHAI	£12,393	£12,599	£205
eGFR threshold for RRT initiation	£12,556	£12,601	£45
Health state utility: CKD 3a	£12,309	£12,687	£379
Cost of acute HK event: low - treatment arm	£12,279	£12,712	£433
Baseline eGFR	£12,402	£12,723	£321
Health state utility: NHYAIII	£12,268	£12,731	£463
Health state utility: NYHAII	£12,247	£12,753	£506
Health state utility: CKD 3b	£12,050	£12,974	£924
Baseline age	£12,158	£12,975	£817
Cost of acute HK event: low - control arm	£11,838	£13,152	£1,314
Cost of repeat treatment	£11,269	£13,721	£2,452
Baseline utility	£11,359	£13,884	£2,524
Threshold low HK event	£12,254	£15,288	£3,034
Discounting (benefits)	£9,432	£14,973	£5,541
Discounting (costs)	£10,521	£16,505	£5,984
K^+ threshold for repeat treatment	£6,705	£20,421	£13,716

Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HK: hyperkalaemia; ICER: incremental cost-effectiveness ratio; K^+: potassium cation; NYHA: New York Heart Association; OWSA: one-way sensitivity analysis; RAASi: renin-angiotensin-aldosterone system inhibitor; RRT: renal replacement therapy; SZC: sodium zirconium cyclosilicate.

B.3.8.3 *Scenario analyses*

Scenario analyses were conducted to assess alternate model settings and structural uncertainty of the model as described in Table 76.

As shown in Table 84, base-case results were most sensitive to the assumptions around the impact of RAASi on long-term outcomes and the proportion of CKD patients starting at stage 3a.

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Table 84. Scenario analysis results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Base case							
SZC	£45,546	6.938	4.128	£5,312	0.728	0.425	£12,495
Standard care	£40,234	6.210	3.703	-	-	-	-
35.70% HF, 64.30% CKD population split (Pooled ZS-004 and ZS-005 trial data)[127, 139]							
SZC	£43,568	7.173	4.253	£5,418	0.782	0.453	£11,955
Standard care	£38,150	6.391	3.799	-	-	-	-
CKD patients starting at stage 3a (CKD population only)							
SZC	£56,502	8.240	5.023	£5,042	0.524	0.319	£15,797
Standard care	£51,460	7.716	4.703	-	-	-	-
No RAASi discontinuation/ down-titration with S–K of <6.0 mmol/L in the SZC arm							
SZC	£54,499	8.787	5.172	£14,266	2.577	1.469	£9,712
Standard care	£40,234	6.210	3.703	-	-	-	-
TA599 assumptions for impact of RAASi on long term outcomes							
SZC	£44,571	6.622	3.951	£4,517	0.478	0.285	£15,836
Standard care	£40,054	6.143	3.665	-	-	-	-
SZC treatment dosage is 5 g SZC daily							
SZC	£44,347	6.938	4.128	£4,113	0.728	0.425	£9,676
Standard care	£40,234	6.210	3.703	-	-	-	-
No wastage assumption							
SZC	£45,198	6.938	4.128	£4,964	0.728	0.425	£11,678
Standard care	£40,234	6.210	3.703	-	-	-	-
2 day S-K trajectory for SoC							
SZC	£48,737	6.775	4.034	£5,288	0.795	0.464	£11,402
Standard care	£43,449	5.980	3.570	-	-	-	-

Abbreviations: CKD: chronic kidney disease; HF: heart failure; HK: hyperkalaemia; ICER: incremental cost-effectiveness ratio; LYG: life-year gain; QALY: quality-adjusted life-year; RAASi: renin-angiotensin-aldosterone system inhibitor; SZC: sodium zirconium cyclosilicate.

B.3.8.4 *Summary of sensitivity analyses results*

OWSA results concluded that, all results resulted in SZC remaining cost-effective at a threshold of £20,000/QALY, excluding one extreme parameter variation which resulted in lower and upper bounds of £6,705/QALY–£20,421/QALY, respectively. The most sensitive parameters were the S–K threshold for repeated treatment and the discount rate for costs; all other varied parameters resulted in SZC remaining cost-effective at a threshold of £20,000/QALY.

Mean PSA results provided the same conclusion as the deterministic base-case results, such that SZC is likely to be cost-effective at willingness-to-pay thresholds of around £20,000.

B.3.8.5 *Subgroup analysis*

No subgroup analyses were explored in the cost-effectiveness analysis.

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B.3.9 *Benefits not captured in the QALY calculation*

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are treatments that can be prescribed to CKD and HF patients in addition to RAASi therapies to lower the risk of MACE, hospitalisation for HF, CV events and death, improve QoL, and slow the progression of kidney disease.[210] SGLT-2 inhibitors were not used in the management of HF during the Committee's previous decision-making for TA599. However, these treatment have since become a commonly used therapy for patients with HF, and evidence from the National Heart Failure Audit shows that in 51% of HFrEF patients were prescribed an SGLT2 on discharge from hospital in England and Wales from 2022–2023.[211] In a retrospective analysis of 44 patients with HFrEF with a history of HK who were receiving SZC to enable prescription of RAASi therapy, it was found that the use of SGLT-2 inhibitors increased from 66% prior to the SZC prescription to 84% after the prescription of SZC.[212] Data on SGLT-2 use were not captured in the clinical trials for SZC and therefore the impact of SZC treatment on SGLT-2 use was not included in the economic model. However, data from the retrospective analysis highlight the potential benefit of SZC for patients eligible for SGLT-2 inhibitor treatment.

CKD and HF are common comorbid conditions. For example, a nested case-control study within an incident HF cohort of 50,114 patients with 12-years follow-up found that the prevalence of CKD in the HF community was 63%.[213] Patients with CKD and HF simultaneously would be expected to have an even greater need for optimised RAASi usage, and therefore would be at a greater risk of developing HK compared with those with CKD or HF only.[2] Therefore, the approach taken to model the CKD only and HF only populations may be conservative.

In the economic model, a conservative assumption was made that no disutilities were applied to standard care for a low K^+ diet. This is despite significant literature and clinical expert opinion suggesting that this diet impacts patient QoL negatively.[199] SZC would prevent the requirement for a low K^+ diet and therefore the QoL benefits associated with SZC treatment may be underestimated in the model.

Another conservative assumption made is that all patients initiate the model on "max" RAASi, with discontinuing and down-titrating of RAASi occurring at the first cycle. This is a conservative assumption as there is evidence that without SZC patients may already be on a sub-optimal dose of RAASi due to the fear of triggering an HK event (section B.1.3.3.2),[35, 38-40] and this modelling approach does not allow for the benefit of SZC in facilitating RAASi dose up-titration, as shown in the ZORA study (section B.2.3.2.6), to be captured in the model.

B.3.10 *Validation*

B.3.10.1 *Validation of de novo cost-effectiveness analysis*

The model has undergone thorough internal and external validation, to ensure it is reflective of the natural disease progression and complexities of HK and its management. The model was initially developed by an external health economics consultancy and the current version incorporates most of the committee preferred assumptions resultant from the appraisal in TA599, [3] with additional data derived from RWE and updated clinical validation used to inform previous evidence gaps and accurately reflect current clinical practice. During the development stage, AstraZeneca sought input from health economists. Professor Ben van Hout, Professor of Health Economics, suggested the underlying structure of natural disease progression in HF and CKD, on top of which S–K and its management is overarching. This model structure was considered appropriate to capture the complexity of HK management in patients with CKD or HF, while enabling the modification of RAASi therapies, including down-titration or discontinuation, and was previously considered appropriate by

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the committee as per the prior appraisal TA599.[3] The use of recognised published literature and risk equations was considered appropriate to model the benefits of SZC. Another external health economics consultancy then reviewed the approach and methodology and provided suggestions for improvement. Clinical trial data underpinning the decision-tree section of the model has been taken directly from the ZS-004[127] and ZS-005[139] trials. Assumptions were ratified by external UK clinical experts with relevant expertise. All feedback obtained by internal and external ratification went into the final model and this written submission.

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B.3.10.2 *Interpretation and conclusions of economic evidence*

Treatment options for patients not reaching this threshold with persistent HK (i.e. patients with S–K ≥5.5–<6.0 mmol/L treated in an outpatient setting) are limited. Current treatment is limited to down-titration or discontinuation of RAASi therapies. However, the current NICE guidance is no longer aligned with updated international guidelines, which have updated the standard care for this population since the introduction of the K^+ binders such as SZC. These updated guidelines include KDIGO 2024 guidance, which recommends initiating K^+ binders at an S–K level of ≥5.5 mmol/L.[13]

SZC is currently recommended for use by NICE in patients with life-threatening emergency HK and persistent HK if patients have comorbid CKD (stage 3b–5) or HF with an S–K of ≥6.0 mmol/L, as appraised in the original submission TA599.[3] In T599, uncertainties were raised by NICE and the EAG which meant that the cost-effectiveness of SZC in the treatment of patients with persistent HK and an S–K of ≥5.5–<6.0 mmol/L could not be established.[3] Following the regulatory approval and reimbursement of SZC for the treatment of HK in the UK and internationally, it has been possible to collect real-world data on SZC usage to further investigate these uncertainties. To this end, two RWE studies were conducted by AstraZeneca to specifically address the uncertainties raised in TA599: SPARK[29] and a re-analysis of the ZORA study.[135, 136] An additional SLR update was also conducted to identify RCT evidence on RAASi treatment in CKD and HF to address the RAASi treatment-related uncertainties raised in TA599.[3]

Using a similar approach to that previously accepted in TA599 supplemented with the recently collated data described above, the cost-effectiveness of SZC has been assessed for the chronic setting for patients with an S–K of ≥5.5–<6.0 mmol/L. In this setting, SZC is more effective and more costly than standard care, resulting in an ICER below the range usually considered by NICE to be the threshold for cost-effectiveness (£20,000–30,000). The ICER can also be considered a conservative estimate due to a range of benefits that could not be captured in the model such as the population of patients co-morbid with CKD and HF, the potential for lower doses of SZC needed to maintain patients at an S–K level of <5.5 mmol/L, and the potential benefit of SZC for patients eligible for SGLT-2 inhibitor treatment (section B.3.9). Furthermore, sensitivity and scenario analyses show that the results are robust to altering parameter values and assumptions underpinning the model. As such, it can be concluded that SZC is a cost-effective use of NHS resources for patients with persistent HK with an S–K of ≥5.5–<6.0 mmol/L.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

[ID6439]

Summary of Information for Patients (SIP)

January 2025

File name	Version	Contains confidential information	Date
ID6439_SZC_SIP_Final Version	V1.0	No	7th January 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Sodium zirconium cyclosilicate (SZC)
Brand name: Lokelma®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

In this submission, NICE will be appraising the use of SZC for adults with **persistent hyperkalaemia** with a **blood potassium** concentration of equal to or greater than 5.5 and less than 6.0 mmol/L, when these people also have **chronic kidney disease stage 3b to stage 5**, and/or **heart failure**. These terms are explained in detail in Section 2a.

Sodium zirconium cyclosilicate (SZC) is already recommended by NICE for use in England and Wales for patients with a blood potassium level of greater than 6.0 mmol/L with chronic kidney disease stage 3b to 5 or heart failure.[1]

The purpose of this submission is to provide people with persistent hyperkalaemia with a potassium level of greater than or equal to 5.5 to less than 6.0 mmol/L (for simplicity, described as “between 5.5 and 6.0 mmol/L” throughout the rest of this document) access to treatment.

Please note: Further explanations for the words and phrases highlighted in **black bold text** are provided in the glossary (Section 4b). Cross-references to other sections or documents are highlighted in orange.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Marketing authorisation is a licence required to place a medicinal product on the market, and sets out the conditions for use of a drug based on evidence of its safety and clinical effectiveness.

SZC has received marketing authorisation by the **European Medicines Agency (EMA)** and the **Medicines and Healthcare products Regulatory Agency (MHRA)** for the treatment of hyperkalaemia in adult patients. The EMA governs treatments in the European Union and the MHRA governs treatments in the UK. SZC was originally approved on 22nd March 2018 and the licence was updated to allow SZC to be used in patients receiving **haemodialysis** (28th April 2020 by the via the EMA centralised procedure).[2, 3]

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

AstraZeneca UK does engage the following patient groups relevant to this medicine with the aims of strengthening patient insights and responding to requests for information:

Kidney Care UK

Kidney Research UK

National Kidney Federation

Pumping Marvellous Foundation

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

SZC is intended to treat hyperkalaemia

What is hyperkalaemia?

Potassium is needed within the body to help control the balance of fluids in cells, and to ensure that the heart works properly.[4] However, having too much or too little potassium in the blood can cause problems. Persistent hyperkalaemia is a life-limiting and potentially life-threatening condition that occurs when a person has a higher-than-normal level of potassium in the blood over a sustained period of time.[5]

In clinical practice in the UK, a blood potassium level of more than 5.0 mmol/L (the unit used to measure concentration) is considered hyperkalaemia, but treatment is not recommended until this level reaches 5.5 mmol/L or above.[1, 5, 6]

What are the signs and symptoms of hyperkalaemia?

Hyperkalaemia can often have no symptoms at all, or non-specific symptoms, which makes it hard to diagnose. Due to this, hyperkalaemia is most often spotted during routine medical tests where blood potassium levels are measured.[7] People with hyperkalaemia may experience symptoms such as:[8, 9]

- Diarrhoea
- Feeling sick and being sick
- Trouble breathing
- Stomach pain
- Muscle pain
- Weakness
- Paralysis in rare cases

Even if the symptoms of hyperkalaemia start off mild, blood potassium levels can continue to increase when not treated and lead to serious problems like **respiratory failure** (when the lungs cannot get enough oxygen into the blood), irregular heartbeats, heart attack, and sudden death. It is therefore very important to start treatment for hyperkalaemia as soon as possible. Doing so helps to bring potassium levels back to normal and can prevent serious health problems from occurring.

What causes hyperkalaemia?

Hyperkalaemia mainly happens in people who are already experiencing kidney problems and/or heart issues.[10, 11] Potassium levels within the blood are regulated by the kidneys, which filter out excess potassium.[5] Kidney disease affects the function of the kidneys which means that less potassium is filtered out of the blood, leading to hyperkalaemia.[5] Chronic kidney disease is divided into 6 stages, and stages 3b to stage 5 are the more severe cases of disease.[12] People with heart failure can often have low blood pressure, because their hearts cannot pump blood as strongly as needed. This means that less blood flows through the kidneys, resulting in less potassium being filtered out of the blood, which can also lead to hyperkalaemia.

Some medications, particularly those used to treat heart failure or kidney disease (like certain blood pressure medicines) can also raise potassium levels by making it harder for the body to remove potassium, and because of this raise the risk of hyperkalaemia.[13-17]

One class of drugs that can raise potassium levels are the **renin-angiotensin-aldosterone system inhibitors (RAASi)**.[16, 17] These medications are vital for treating heart and kidney diseases, but they can make it harder for the body to remove potassium.[13-15] RAASi drugs work by stopping the renin-angiotensin-aldosterone system from working properly.[18] This system typically helps to control potassium levels in the blood through aldosterone, a hormone that promotes the removal of potassium by the kidneys.[18] When RAASi medications inhibit this system, aldosterone production is reduced. This can lead to reduced removal of potassium from the blood and can result in hyperkalaemia.[18]

How many people get hyperkalaemia?

At any one time, hyperkalaemia affects about 6 out of every 100 adults globally, but it is more common in people with health issues such as chronic kidney disease and/or heart failure.[10] In the UK, many people with certain medical conditions have higher potassium levels. About 40–50% of people with advanced chronic kidney disease, who have received a kidney transplant, or who are treated with RAASi medications experience hyperkalaemia.[19]

Can you get hyperkalaemia more than once?

Many people with chronic kidney disease and/or heart failure taking RAASi treatments get hyperkalaemia more than once.[15, 20] Often, doctors will adjust or stop RAASi treatments when people experience hyperkalaemia.[21] The more often people get hyperkalaemia, the more likely it is that people will have the amount of RAASi medication that they take reduced or stopped.[21] Reducing or stopping RAASi treatment because of hyperkalaemia can make it more likely that a person will experience complications relating to their underlying disease.[22-30]

What is the impact of hyperkalaemia (disease burden)?

Hyperkalaemia can have considerable impacts on individuals, families, and society as a whole. For those people living with hyperkalaemia, the condition can lead to a higher risk of serious health events, such as heart problems and hospital visits.[31-35] If left untreated, hyperkalaemia is associated with an increased risk of death compared with people without hyperkalaemia.[31-36]

Additionally, hyperkalaemia often requires ongoing disease management, including changes to RAASi medications and sticking to strict diets which are low in potassium. These lifestyle changes can be stressful and challenging, affecting the **quality of life** of people with hyperkalaemia and creating a constant reminder of their illness.[37-40] In a study of people with chronic kidney disease who were undergoing dietary and fluid management, people reported that these dietary restrictions caused challenges for them socially, left them feeling deprived and led them to experience difficulties navigating change, frequently fighting the temptation to enjoy food.[41]

Taking care of someone with hyperkalaemia is not just hard for the individual themselves. Their family members and caregivers often have to help with meal planning, which can be

difficult.[38] Giving this level of support can be stressful and take a lot of time, which can impact the lives and wellbeing of family members and caregivers.

Managing hyperkalaemia can impact the ability of people to work and can affect people's personal finances. People with hyperkalaemia often need to visit the doctor regularly, and sometimes stay in hospital.[42, 43] This can result in lost income if they need to take time off work and can put a financial strain on individuals.

Managing hyperkalaemia also comes with costs to the healthcare system. In particular, people with hyperkalaemia often require regular and extended visits to hospital. For example, a study in the UK showed that people with hyperkalaemia had higher rates of admission to hospital (around 71%) compared with people without the condition (around 54%).[44]

As described above, doctors have to adjust or stop RAASi treatments when people experience hyperkalaemia.[21] Research shows that maintaining the right dosage of RAASi treatments is important for people with heart and kidney diseases. Studies have found that reducing or stopping RAASi medications is associated with an increased risk of serious health problems, such as heart failure, irregular heartbeats, and even death.[11, 45, 20, 23, 46] Additionally, people on a reduced RAASi dose or who stop taking the medication are associated with a higher risk of heart and kidney issues compared with those on the ideal dose.[47, 48] Therefore, it is important that potassium levels can be managed for these people to make sure that they can continue on the right dose of RAASi treatment and avoid these unwanted problems.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How is hyperkalaemia diagnosed?

Diagnosing hyperkalaemia often happens by chance when potassium is measured during routine blood tests, as early symptoms (if present) can be general and hard to notice.[7-9] People with kidney disease and heart failure undergo regular blood tests to check their potassium levels.[49, 50] During these tests, hyperkalaemia would be suspected if the test showed high levels of potassium.[49] Sometimes a second test is required to check that the potassium level was measured correctly, and that the result was not an error.[49]

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For

example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What are the goals of treating hyperkalaemia?

The goal of hyperkalaemia treatment is to reduce potassium levels to within the normal range.[1] Currently, treatment options for people with hyperkalaemia with potassium levels between 5.5 and 6.0 mmol/L aim to limit the amount of potassium that people consume and to reduce or stop treatments which may be impacting their potassium levels, such as RAASi therapies.[1]

What are the current treatment options for hyperkalaemia?

People with persistent hyperkalaemia are typically treated by specialist kidney and/or heart doctors who routinely manage patients with conditions such as chronic kidney disease and/or heart failure.[39] Of these patients, around 80% will be on medicines to treat their heart or kidney condition such as RAASi therapies which means that their potassium levels will be regularly monitored.[39]

For people with persistent hyperkalaemia with a blood potassium level more than 6.0 mmol/L with chronic kidney disease stage 3b to 5 or heart failure, SZC is recommended for use in England and Wales.[1] In the initial assessment of SZC, the NICE committee concluded that “SZC treatment reduced serum potassium level from baseline”,[1] however, there were some limitations in the available evidence which meant that the NICE committee could not be certain that SZC could deliver value for money for people with hyperkalaemia with potassium levels of between 5.5 and under 6.0 mmol/L.[1] Therefore, NICE were unable to make a recommendation for SZC for this group of people with hyperkalaemia.[1]

For people with persistent hyperkalaemia with potassium levels between 5.5 and 6.0 mmol/L, current standard care involves decreasing the dosage (**down-titrating**) or stopping (discontinuing) RAASi therapy. However, these recommendations are no longer in line with international guidelines which have been updated since treatments like SZC were introduced.[5, 12, 51] These international guidelines now recommend the use of SZC to allow patients to benefit from RAASi therapies.[5, 12, 51] In the past, patients with hyperkalaemia were also encouraged to eat a diet which is low in potassium, however, this is now considered to not work and be unhealthy, and so doctors no longer advise this.[52]

As such, there are limited treatment options for the management of patients with hyperkalaemia with potassium levels between 5.5 and 6.0 mmol/L. NICE guidelines for the management of chronic kidney disease recommend:[53]

- Patients should not be routinely offered RAASi if their potassium level before treatment is greater than 5.0 mmol/L
- RAASi therapy should be stopped if a patient's potassium level increases to 6.0 mmol/L or more and other drugs which are known to cause hyperkalaemia have been stopped

UK experts and local clinical guidelines suggest that diagnosis of hyperkalaemia should be made and treatment should be started when potassium levels are greater than or equal to 5.5 mmol/L.[5, 54] According to UK clinical experts, doctors would begin reducing the dose (down-titrating) of RAASi treatments for patients with potassium levels greater than or equal to 5.5 mmol/L, and they would stop (discontinue) RAASi treatments if levels increased to greater than or equal to 6.0 mmol/L.[39]

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Hyperkalaemia from the patient perspective

Hyperkalaemia affects everyday life and can lead to serious health issues such as heart problems, more hospital visits, and increased risk of death. Studies using data collected from a real-world programme for people with chronic kidney disease have shown that people with chronic kidney disease who also have hyperkalaemia have a lower quality of life overall compared with those who have normal potassium levels.[55-56] This can be due to the physical toll of the disease, the mental effects of hyperkalaemia, and how much the disease impacts daily life.[55, 57]

There are not many treatment options for people with persistent hyperkalaemia with potassium levels between 5.5 and 6.0 mmol/L. The main treatment involves changing or stopping RAASi medications and following a strict diet that limits how much potassium you consume. This diet can be especially challenging because it often means cutting back on fruits and vegetables, which are often high in potassium. This means that people with hyperkalaemia give up the benefits of a healthy diet, and sticking to this diet to manage hyperkalaemia can be hard for many people.[37, 39, 40] The diet can affect people's daily routines, social lives, and enjoyment of food.[38-40] People with hyperkalaemia report that they often feel like they are always reminded of their illness and have to make tough choices about what they eat and drink.[38-40] A review of 46 studies investigated how people with hyperkalaemia view diet and drink restrictions.[41] It found that some people find the diet confusing and hard to stick to because it feels like they are giving up healthy foods

they previously enjoyed.[41] Some people have said they feel left out at social events because they cannot eat or drink the same things as everyone else.[41]

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

SZC is a medication used to lower high potassium levels in the blood. It does not get absorbed into the body but works to remove potassium through the digestive system.[58-60] SZC binds to potassium in the digestive system, stopping it from entering the bloodstream and meaning that the potassium is removed in faeces.[58-60] SZC is already used for the treatment of people with hyperkalaemia with potassium levels greater than or equal to 6.0 mmol/L and in the emergency setting.[1]

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

SZC is not intended to be used with any other treatment for hyperkalaemia. However, it may be used alongside RAASi treatments for the management of chronic kidney disease and/or heart failure to manage hyperkalaemia associated with RAASi therapy.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

How is SZC taken?

SZC comes as a sachet of powder which should be added to a glass with around 45 mL of water in it.[58] The liquid is stirred and should be drunk straight away. SZC can be taken with or without a meal, but should be taken at the same time each day if possible.[58]

When starting SZC treatment, the usual dose is 10 g taken by mouth with 45 mL of water three times a day.[58] After a maximum of three days, the dose is typically reduced to 5 g once a day if potassium levels have returned to normal.[58] Depending on the person's needs, the dose can be adjusted to up to 10 g once a day or 5 g every other day to keep potassium levels stable.[58] The maximum dose for ongoing treatment is 10 g daily.[58] If potassium levels have not returned to normal within three days, an alternative treatment may be needed.[58]

For people undergoing haemodialysis (often known as dialysis), SZC should only be taken on days when the person is not having dialysis.[58] The starting dose is usually 5 g once a day and the dose can be adjusted based on potassium levels before dialysis, up to a maximum of 15 g on non-dialysis days.[58] Potassium levels should be checked weekly while adjusting the dose and regularly once levels are stable.[58]

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Studies investigating SZC as a treatment for hyperkalaemia

Five key clinical trials provide **clinical evidence** for SZC in hyperkalaemia: ZS-002, ZS-003, ZS-004, ZS-004E and ZS-005. The main clinical evidence for SZC comes from ZS-004 and ZS-005.[58, 61-67]

These trials investigated the ability of SZC to reduce potassium levels to a normal range (**normokalaemia**) (i.e., its efficacy). The trials also investigated the safety and tolerability of SZC. In ZS-004, SZC was compared to a **placebo**. A summary of the key information about each trial is provided in Table 1.

Table 1. Clinical trials investigating SZC

Details	ZS-004 (NCT02088073)	ZS-005 (NCT02163499)
Trial design	Phase 3	Phase 3
Study location	United States, Australia and South Africa	United States, Australia, Germany, United Kingdom, The Netherlands, and South Africa

Population	Adult patients with a potassium level of greater than or equal to 5.1 mmol/L	Adult patients with hyperkalaemia (defined as a potassium level of greater than or equal to 5.1 mmol/L)
Treatment	• 10 g of SZC three times a day for two days, then • Either 5 g, 10 g or 15 g of SZC once a day	• 10 g of SZC three times a day for one to three days depending on the patient's potassium levels, then • 5 g of SZC once a day for up to 12 months, then • Dose adjusted based on the patient's potassium levels
Comparator	Placebo	None

The efficacy and safety of SZC in the treatment of hyperkalaemia has already been assessed by NICE in TA599.[1] SZC is currently recommended for use by NICE in patients with life threatening emergency hyperkalaemia and persistent hyperkalaemia if patients have chronic kidney disease stage 3b–5 or heart failure with a potassium level of greater than or equal to 6.0 mmol/L.[1] In the original appraisal, the NICE committee concluded that the clinical evidence for SZC shows that it can return potassium levels to normal,[1] however, there were some limitations in the available evidence which meant that the NICE committee could not be certain that SZC could deliver value for money for people with hyperkalaemia with potassium levels between 5.5 and under 6.0 mmol/L.[1] These were:[1]

- The clinical evidence did not clearly show a relationship between potassium levels and long-term health outcomes like survival rates, hospital visits, or major heart issues (**major adverse cardiac events**)
- The clinical evidence did not clearly show that using SZC can allow people to restart, increase, or maintain the right dosage of RAASi medications
- The clinical evidence did not clearly show how the RAASi dosage affects long-term health outcomes

Studies addressing the limitations from the previous appraisal of SZC for hyperkalaemia

As SZC has already been shown to be effective at returning potassium levels to normal in the original NICE appraisal (TA599), no new clinical evidence has been presented for the efficacy of SZC in this submission.[1] This reappraisal focuses on providing additional clinical evidence to address the areas of uncertainty described above.[1] Additional evidence from studies among people with hyperkalaemia in the real-world setting is presented to demonstrate the benefit of widening the population of patients who can receive SZC to include patients with hyperkalaemia with potassium levels between 5.5 and 6.0 mmol/L.

The SPARK study was a study conducted by AstraZeneca to specifically investigate the relationship between potassium levels and long-term health outcomes. This includes hospital visits, and major heart issues (major adverse cardiac events) and risk of death.[68] It was a **retrospective**, **observational** study which means that the study looked back at data that had already been collected, and the researchers observed any trends without making changes to people's routine medical care. The study was **longitudinal,** meaning

that the study followed people's health outcomes over a period of time, rather than looking at a single snapshot in time.

The ZORA study was a study conducted by AstraZeneca which looked at how treatment with SZC affects the use of RAASi medications in the real-world for people with chronic kidney disease and/or heart failure who have hyperkalaemia.[69] ZORA was a It was an observational, longitudinal study that looked at patients in the US, Japan, and Spain. Patients from the UK could not be used to investigate this outcome, as SZC is not recommended for treatment of HK in patients with an potassium levels of <6.0 mmol/L. Although ZORA did not include UK patients, experts have stated that the results are relevant for patients in the UK.[70]

A summary of the key information about the SPARK and ZORA studies is provided in Table 2.

Table 2. Real-world evidence studies with SZC

Details	SPARK	ZORA
Trial design	Retrospective, observational, longitudinal study	Observational, longitudinal cohort study
Study location	United Kingdom	United States, Japan and Spain
Population	Adult patients with a recorded potassium level, a diagnosis of hyperkalaemia, or a prescription of a potassium binder (a treatment like SZC)	Adult patients with a diagnosis of chronic kidney disease and/or heart failure, and a prescription for a RAASi medication within six months before the start of the study
Treatment	None	SZC
Comparator	None	No potassium binder medication

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

As mentioned in Section 3d, SZC has already been shown to be effective at treating hyperkalaemia in the original NICE appraisal (TA599).[1] Full details on the efficacy of SZC in the treatment of hyperkalaemia can be found in the NICE guidance for TA599.[1] This reappraisal focuses on providing additional clinical evidence to address the areas of uncertainty described in Section 3d.[1]

Clinical evidence linking potassium levels with long-term health results

The results of SPARK show that the risks of dying and being admitted to hospital are much higher for people with chronic kidney disease or heart failure with potassium levels between 5.5 and 6.0 mmol/L compared with people with normal potassium levels

(between 4.5 and 5.0 mmol/L).[68] People with chronic kidney disease with potassium levels between 5.5 and 6.0 mmol/L also have a much higher risk of major adverse cardiac events than people with normal potassium levels.[68]

The increased risk of being admitted to hospital for people with potassium levels of between 5.5 and 6.0 mmol/L compared with people with normal potassium levels is not dependent on how well a person's kidneys worked for people with chronic kidney disease or heart failure.[68]

Full results from the SPARK study are shown in **Document B 2.3.1.**

Clinical evidence showing that SZC helps people to restart, increase or maintain the right dose of RAASi medications

Results from the ZORA study show that the chance of being able to maintain the optimal RAASi dose after people experience hyperkalaemia is over twice as high for people treated with SZC compared with those not treated with SZC.[69] People were also less likely to stop (discontinue) RAASi treatment if they were treated with SZC than people who were not treated with SZC.[69] Similar results were found when looking only at people with chronic kidney disease, heart failure, and both chronic kidney disease and heart failure.[69]

Specifically among patients with a potassium level of between 5.5 and 6.0 mmol/L, it was found that treatment with SZC meant that people were less likely to stop (discontinue) RAASi treatment.[71]

Full results from the ZORA study are shown in **Document B 2.3.2.**

Clinical evidence showing how the RAASi dose affects long-term health

To investigate how RAASi dosage may impact a persons long term health, a review of published scientific studies was completed. This review identified studies which showed that in patients with chronic kidney disease stopping treatment with RAASi increased a persons risk of heart-related events including heart attack, and dying of any cause. There was no evidence for how switching to a lower dose of RAASi affected patients in the long term.[72, 73]

In patients with heart failure, the review identified a study which showed that showed stopping treatment with RAASi following an episode of hyperkalaemia was associated with a 31% increase in dying for any reason.[74] Stopping RAASi treatment was also associated with an increased risk of dying for any reason, dying due to heart-related issues, and being hospitalised due to heart failure.[75] In patients with HF, two studies showed that switching to a lower dose of RAASi increased a person's risk of dying for any reason.[76, 77]

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

No data on the impact of SZC on the quality of life of patients were collected in ZS-004 and ZS-005 so quality of life data used in the health economic model were taken from published studies.[61, 65]

Evidence on the impact of hyperkalaemia on people's quality of life can be found in Section 2d.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

As mentioned in Section 1b, the safety of SZC in the treatment of hyperkalaemia has already been assessed by NICE in TA599.[1] This reappraisal focuses on presenting evidence to address the uncertainties identified in TA599 as explained in Section 3e.[1]

Every medicine has **side effects** and the same medicine can produce different reactions in different people.

In the **Phase 3** clinical trials, SZC was well tolerated, with very few serious side effects. The most common side effects that occurred after treatment was started were **gastrointestinal disorders** (problems related to the stomach and intestines), but all were considered mild.[61, 65, 78] In the trials assessing SZC treatment over a year, the most common side effects (of all grades) that occurred after treatment were **hypertension** (high blood pressure) occurring in 11% of patients, **peripheral oedema** (swelling in extremities caused by the buildup of fluid in tissues) occurring in 9.7% of patients, and **urinary tract infections** occurring in 7.9% of patients.[67] In the ZS-004 trial, the rates of oedema were similar up to 28 days after people started treatment with placebo compared with those receiving SZC. Only one patient discontinued treatment due to oedema. Furthermore, there was no change in average blood pressure readings and nobody stopped treatment due to hypertension.[61, 65]

Information on other potential side effects is available in the Patient Information Leaflet, and results from the clinical trials for SZC can be found in the NICE guidance for TA599.[1, 58]

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Managing potassium levels improves long-term health results

According to real-world evidence, the risks of events like death and hospitalisation are much higher for people with chronic kidney disease or heart failure with potassium levels between 5.5 and 6.0 mmol/L than those with normal potassium levels.[68] Currently, people with potassium levels between 5.5 and 6.0 mmol/L are treated with standard care (decreasing the dosage or stopping RAASi therapy and adopting a low potassium diet). However, SZC is effective at managing potassium levels. Therefore, treating people with potassium levels between 5.5 and 6.0 mmol/L with SZC may reduce the risk of long-term health problems for people with hyperkalaemia. Furthermore, hyperkalaemia currently requires ongoing disease management, including medication adjustments and strict diets. These lifestyle changes can be stressful and challenging, affecting the quality of life of people and creating a constant reminder of their illness.[37-40] Effectively managing hyperkalaemia with SZC may reduce the burden of ongoing disease management and dietary restrictions on people with hyperkalaemia.

SZC can help to start, increase or keep the right dose of RAASi medications

When people have to reduce (down-titrate) or stop (discontinue) taking RAASi medicines after experiencing hyperkalaemia, it is associated with a higher chance of serious heart and kidney problems, and in some cases, even death.[11, 23, 45] RAASi medications can make it hard to manage health issues like chronic kidney disease and heart failure. Therefore, it is important to proactively treat high potassium levels so that people can continue taking the right amount of RAASi medication. This helps in preventing worsening kidney and heart conditions.[11, 23, 45]

Results from real-world use of SZC show that SZC increases the chances of being able to keep taking the optimal RAASi dose after people experience hyperkalaemia compared to not being treated with SZC.[69] People have also been shown to be less likely to stop (discontinue) RAASi treatment if they are treated with SZC than people who are not treated with SZC.[69] As such, SZC treatment could help patients to start, increase or keep the optimal dose of RAASi medications.

Not maintaining an optimal RAASi dose affects long-term health results

In people with chronic kidney disease, studies showed that stopping treatment with RAASi increased a person's risk of heart-related events including heart attack, and dying of any cause.[72, 73] Furthermore, in people with heart failure, the review identified a study which showed that showed stopping treatment with RAASi following an episode of hyperkalaemia was associated with a 31% increase in dying for any reason.[74] Stopping RAASi treatment was also associated with an increased risk of dying for any reason, dying due to heart-related issues, and being hospitalised due to heart failure.[75] In people with HF, two studies also showed that switching to a lower dose of RAASi increased a person's risk of dying for any reason.[76, 77] As such, treatment with SZC could help people to experience better long term health outcomes by enabling people with chronic kidney disease and/or heart failure to stay on RAASi treatment.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

SZC is generally well-tolerated and effective. However, like all existing hyperkalaemia treatments, it may not work for everyone. Also, some people may experience side effects while they are taking the treatment. The most common side effects include diarrhoea or constipation, swelling or fluid retention, and **electrolyte imbalances**. These are usually manageable, and most people do not need to stop treatment because of side effects.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Healthcare providers need to get the best value from their limited budgets. To achieve this, they have to decide if a new medication offers "good value for money" compared with current treatment options. They assess the costs of the new medication and the potential health benefits for people with hyperkalaemia who use it. The pharmaceutical company responsible for developing the medication supplies these data through a **health economic model**. This model is used to conduct an analysis that compares the benefits and costs of the new treatment (SZC) with the existing treatment or comparator (standard care).

How the model reflects hyperkalaemia

The economic model was designed to reflect the key features of hyperkalaemia and clinical practice in the UK. In order to compare the clinical benefits, costs and quality of life associated with people treated with SZC and standard care, a similar approach was taken to the original NICE appraisal of SZC for hyperkalaemia to calculate how the control of a person's potassium levels over a long period of time is related to health outcomes.[1] The model allows for the risks of multiple events to be accounted for at the same time, as well as how these events may effect each other.

Modelling the link between hyperkalaemia and patient outcomes

Clinical evidence for the impact of SZC on potassium levels from clinical trials was used to model the benefits of SZC compared with standard care for the management of hyperkalaemia. Clinical evidence gathered across the real-world studies summarised in **Section 3e** was then used to inform the impact of SZC and potassium levels on risk of a number of short- and long-term hyperkalaemia-related health events, including:

- Change in RAASi treatment usage
- Number of emergency hyperkalaemia events
- Number of major adverse cardiac events
- Number of hospitalisations
- Number of deaths

In this model, SZC was found to provide clinical benefit compared with standard care. This was driven by SZC being more effective in reducing potassium levels, which in turn was associated with more optimal use of RAASi treatment and a reduction in the risk of negative health events.

Modelling how much a treatment improves quality of life

Quality of life data from published studies were used to assess how treatment with SZC affected an individual's quality of life based on how it affected people's risks of adverse events related to their treatment, adverse events related to hyperkalaemia, and hyperkalaemia progression.

Modelling how the costs of treatment differ with the new treatment

Various costs are included in the model for SZC and standard care. These costs include:

- The cost to purchase SZC
- The costs associated with different stages of chronic kidney disease and heart failure
- The costs associated with RAASi treatments and changes to RAASi treatments (e.g. costs of medicines and clinician time, covering both the initial and follow-up check-ups)
- Costs associated with hyperkalaemia events (e.g. tests and treatments required and healthcare professional time to see the patient)

Model results indicated that SZC may result in higher costs for the NHS compared with standard care for people with hyperkalaemia and chronic kidney disease or heart failure

whose potassium level is between 5.5 and 6.0 mmol/L. The key reason for this is that SZC treatment costs money whereas standard care is assumed to be free.

Cost-effectiveness results

The model indicated that treatment with SZC was associated with higher costs than standard care but was more effective at managing hyperkalaemia and hyperkalaemia-related outcomes. Based on NICE's cost-effectiveness threshold, the model suggests that SZC could be considered a cost-effective use of NHS resources for people with hyperkalaemia and chronic kidney disease and/or heart failure whose potassium level is between 5.5 and 6.0 mmol/L. It should be noted that these results are based on company-preferred assumptions which will be considered by the NICE committee. However, most of the assumptions preferred by the committee during the original appraisal of SZC have stayed the same in this model. Any updates to assumptions have only been made to reflect the current treatment landscape for hyperkalaemia and the specific group of people being looked at in this appraisal.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

The company did not present any data on SZC being innovative.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

Some people with kidney failure are no longer able to filter waste products and excess fluids from the blood properly and they need a medical treatment to do this for them

(**dialysis**). People on dialysis can also experience hyperkalaemia.[2, 5] SZC has a marketing authorisation for patients who are receiving chronic haemodialysis.[2]

Evidence for the safety of SZC and how well it works as a treatment for hyperkalaemia for people who are on chronic dialysis comes from the DIALIZE study.[79] This study looked at how well SZC worked and how safe it was when given once a day to people on the days that they were not having dialysis.[79] Out of 97 people who were given SZC, 41.2% were able to maintain a potassium level of 4.0–5.0 mmol/L before they received dialysis compared with 1.0% of the 99 people who were given placebo.[79] This study found that the drug works well and is generally well-tolerated when treating high potassium levels before dialysis in people with severe kidney disease.[79] However, the study only followed people for 10 weeks and so it does not provide enough information to determine if the drug is cost-effective for those receiving long-term dialysis treatment.[79]

The ADAPT study looked at using SZC for people on long-term dialysis instead of using dialysis fluids with low potassium.[80] The study found that people who took the drug had fewer cases of irregular heartbeats and low potassium levels after dialysis compared with those treated with low potassium dialysis fluids.[80]

There is not much information available about the long-term effects of SZC in people receiving chronic dialysis, so dialysis patients were not included in the main decision-making process of the submission. SZC is considered to be safe and effective for people receiving chronic dialysis. Restricting access to SZC to exclude people who are receiving dialysis on the basis of a lack of data to demonstrate cost-effectiveness would preclude them from accessing a safe and effective treatment, and would result in inequitable access across the full group of people for which SZC has marketing authorisation.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Further information on hyperkalaemia:

- What is hyperkalaemia (high potassium)? Hyperkalaemia (high potassium) – Kidney Research UK
- Your kidneys and high potassium (hyperkalemia). Your kidneys and high potassium (hyperkalemia) – National Kidney Foundation
- High potassium levels (hyperkalaemia) and kidney disease. High potassium levels (hyperkalaemia) and kidney disease – Kidney Care UK
- Elevated Potassium levels (Hyperkalaemia). Elevated Potassium levels (Hyperkalaemia) – HeartFailureMatters.org

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

This glossary explains terms highlighted in **blue bold text** in this summary of information for patients. At times, an explanation for a term might mean you need to read other terms to understand the original terms

Blood potassium	The level (concentration) of potassium in your blood. Potassium is a mineral found in your blood that helps your muscles work, including the muscles that control your heart. It also helps with nerve function and balancing the water in your body.
Chronic kidney disease	A condition that happens when your kidneys, which filter waste from your

	blood, are not working as well as they should over a long period of time.
Clinical evidence	The results provided by a clinical trial/ clinical study.
Clinical trial	A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis or treatment of a disease. Also called a clinical study.
Concentration	How much of a certain substance is present in a specific amount of liquid or another medium.
Cost-effective	A treatment that is considered to provide good value for money.
Diabetes	A condition where the body either does not make enough insulin or cannot use it properly, leading to high levels of sugar in the blood. Insulin is a hormone that helps sugar from food get into cells to be used for energy.
Down-titrating	Gradually reducing the amount (dose) of a medication.
Electrolyte imbalance	When the levels of minerals in your blood, like sodium, potassium, or calcium, are too high or too low. These minerals help control important body functions, and an imbalance can cause problems like muscle weakness or irregular heartbeats.
European Medicines Agency (EMA)	The regulatory body that evaluates, approves and supervises medicines throughout the European Union.
External Assessment Group	A group of independent experts that carefully reviews information about medical technologies, like new tests or treatments, to help NICE make informed decisions and recommendations for patients and healthcare providers.
Gastrointestinal disorders	These are problems related to the stomach and intestines. Symptoms might include stomach pain, bloating, and changes in bowel habits
Health economic model	A way to predict the costs and effects of a technology over time or in patient groups not covered in a clinical trial.
Haemodialysis (also known as dialysis)	A treatment for people with kidney failure. It uses a machine to remove waste, salt,

	and extra water from your blood, doing the job that your kidneys can no longer do.
Heart failure	A condition that happens when the heart is not pumping blood as well as it should be.
Hypertension	The medical term for high blood pressure.
Longitudinal	A type of study in which people are followed over a period of time instead of looking at just one snapshot in time.
Major adverse cardiac events	Serious heart-related problems that can include heart attack, stroke, or death due to heart disease.
Marketing authorisation	The legal approval by a regulatory body that allows a medicine to be given to people in a particular country.
Medicines and Healthcare products Regulatory Agency (MHRA)	The regulatory body that evaluates, approves and supervises medicines throughout the United Kingdom.
Normokalaemia	A state when the level of potassium in the blood is normal.
Observational	In this type of study, researchers observe and collect data without trying to change anything. Patients are not given any treatments or interventions as part of the study, researchers simply record and analyse what happens.
Peripheral oedema	This is swelling caused by the buildup of fluid in tissues outside your central body, typically in the lower legs, ankles, or feet. It can happen for various reasons, including heart or kidney issues, and can make movement uncomfortable.
Persistent hyperkalaemia	A long-term condition where you have too much potassium in your blood.
Phase 3	This type of clinical trial that tests the safety and how well a new treatment works compared with a standard treatment. For example, it evaluates which group of patients has better survival rates or fewer side effects.
Placebo	A substance that appears to be a medicine, but has no actual therapeutic benefit. It is used in clinical trials to compare against the new treatment that is being developed.
Quality of life	An individual's physical, emotional, and social wellbeing. Many clinical trials

	assess the effects of a disease and its treatment on the quality of life of individuals. These studies measure aspects of an individual's sense of well-being and their ability to carry out activities of daily living.
Real-world evidence	Evidence that has come from routine clinical practice and not a clinical trial.
Renin-angiotensin-aldosterone system inhibitors (RAASi)	Medications that help to relax blood vessels and lower blood pressure, making it easier for your heart to pump blood. They are often used to treat heart and kidney conditions.
Respiratory failure	When lungs cannot get enough oxygen into the blood.
Retrospective	This type of clinical study looks back at data that has already been collected.
Side effects	An unexpected medical problem that arises during treatment. Side effects may be mild, moderate or severe.
Stages 3b–5	These stages describe the severity of chronic kidney disease. Stage 3b means moderate to severe kidney damage, and by stage 5, the kidneys have very little function left, which is often when dialysis or a kidney transplant is needed.
Urinary tract infection	This is an infection that affects any part of your urinary system, which includes the kidneys, bladder, ureters, and urethra.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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2. Medicines and Healthcare products Regulatory Agency. Summary of Product Characteristics for Lokelma. Available at: https://mhraproducts4853.blob.core.windows.net/docs/d0a9a0ced0712d1f3e9e6963009d5cc94ffe4e80. [Accessed: 24 September 2024], 2024.
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7. Campese V, Adenuga G. Electrophysiological and clinical consequences of hyperkalemia. Kidney International Supplements 2016;6:16-19.
8. Ben Salem C, Badreddine A, Fathallah N, et al. Drug-induced hyperkalemia. Drug Saf 2014;37:677-92.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Sodium zirconium cyclosilicate for treating hyperkalaemia (partial review of TA599) ID6439

Clarification questions

May 2025

File name	Version	Contains confidential information	Date
ID6439 SZC EAG clarification questions 04 June 2025_[REDACTED].docx	1.0	Yes	04 June 2025

Summary

Sodium zirconium cyclosilicate (SZC) has previously been evaluated by NICE in TA599, and was recommended as a treatment option for adults with life-threatening emergency hyperkalaemia (HK) and persistent HK in patients with comorbid chronic kidney disease (CKD; stage 3b–5) or heart failure (HF), if they:[3]

- Have a confirmed serum potassium (S–K) level of at least 6.0 mmol/L *and*
- Because of HK, are not taking an optimised dosage of renin-angiotensin-aldosterone system inhibitor (RAASi) *and*
- Are not on dialysis

As aligned with NICE at scoping and at the decision problem meeting, this appraisal is a partial review of TA599 aimed at appraising the clinical and cost effectiveness of expanding the recommendation for use of SZC within its marketing authorisation for treating persistent HK in adults with an S–K of ≥5.5–<6.0 mmol/L. As a partial review, the scope of this appraisal does not cover HK in adults with an S–K of >6.0 mmol/L as the clinical and cost effectiveness of this population has already been assessed in TA599. Therefore the methods and data sources used to establish the clinical and cost-effectiveness of SZC for patients with an S–K of ≥5.5–<6.0 mmol/L align with those accepted in the original appraisal, except where newly available real-world evidence can be used to reduce the uncertainties raised by NICE and the External Assessment Group (EAG) during their review of TA599, which ultimately resulted in the cost-effectiveness of SZC for the treatment of patients with persistent HK and an S–K of ≥5.5–<6.0 mmol/L not being established.[3] In other instances, the company have aligned to the committee preferred approaches from TA599. This ensures consistency, transparency, and alignment with NICE's expectations, with new evidence or methodological adjustments incorporated only where justified or requested.

Section A: Clarification on effectiveness data

SZC was previously evaluated in TA599, and was recommended for use in patients with life-threatening emergency HK and persistent HK if patients have comorbid CKD (stage 3b–5) or HF with an S–K of ≥6.0 mmol/L.[3]

The clinical effectiveness of SZC was established in TA599 on the basis of the ZS trials.[3] However, uncertainties were raised by NICE and the EAG which meant that the cost-effectiveness of SZC in the treatment of patients with persistent HK and an S–K of ≥5.5–<6.0 mmol/L could not be established.[3] The main uncertainties raised were:[3]

- A paucity of clinical data linking S–K levels and long-term clinical outcomes
- Uncertainty around SZC usage allowing reinitiation, up-titration or maintenance of optimum RAASi dosage
- Uncertainty around the relationship between RAASi dosage and long-term clinical outcomes

Aside from newly generated evidence which was developed to address these uncertainties, the approaches used to establish the clinical and cost effectiveness of SZC for patients with an S–K of ≥5.5–<6.0 mmol/L otherwise reflect those accepted in the previous appraisal.[3]

Changes since the publication of TA599

The association between elevated S–K and/or RAASi down-titration and adverse clinical outcomes, as well as the capacity of potassium (K^+) binder therapy to normalise S–K levels and enable optimised use of RAASi, is well accepted in clinical guidelines.[4-6] Following the regulatory approval and reimbursement of SZC for the treatment of HK in the UK and internationally, it has been possible to collect real-world data on SZC usage. To this end, two real-world evidence (RWE) studies were conducted by AstraZeneca to specifically address the uncertainties raised in TA599: SPARK[7] and a post-hoc analysis of the ZORA study.[8, 9]

SPARK

The SPARK study was initiated specifically to address the concerns raised by the committee in TA599.[7] This study adds to those conducted previously which have found a relationship between increased S–K levels and the incidence of long-term clinical outcomes by adjusting for multiple additional confounders, including RAASi usage which was raised as a key concern during decision-making in TA599, and exploring the potential impact of any remaining unknown confounders.[3]

ZORA

The ZORA study was used to address the concerns raised by the committee in TA599 that sufficient evidence for SZC facilitating the reinitiation, up-titration or maintenance of optimum RAASi dosage, irrespective of S–K levels, had not been presented.[3] This study investigated real-world usage of RAASi medication in patients with CKD and/or HF who are experiencing HK.[8] An additional subgroup analysis provided the proportions of persistent HK patients that down-titrate or discontinue RAASi dosage after 180 days since the incident HK event at each S–K level after receiving SZC treatment or standard care.[9]

RAASi systematic literature review (SLR)

An additional SLR update was conducted to identify randomised controlled trial (RCT) evidence on RAASi treatment in CKD and HF to address the RAASi treatment-related uncertainties raised in TA599.[3] This SLR update provides a comprehensive overview of the latest research relevant to the use of RAASi in patients with CKD or HF in terms of long-term effects on cardiovascular (CV) events, mortality, and hospitalisation and also markers of disease progression. Evidence on the impact of RAASi discontinuation or down-titration was also sought.

A1. Priority question. Clinical advice to the EAG, and results from an observational study [1] identified by the EAG, suggest that SGLT-2 inhibitors are effective at reducing the risk of hyperkalaemia and RAAS inhibitor discontinuation in patients with CKD and/or HF. Please comment on whether SGLT-2 inhibitors should be considered as part of standard care.

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are treatments that can be prescribed to patients with CKD and/or HF in addition to RAASi therapies to lower the risk of major adverse cardiac events (MACE), hospitalisation for HF, CV events and death, improve quality of life, and slow the progression of kidney disease.[10] The initiation of SGLT-2 inhibitors has not been shown to increase HK risk, and there is some evidence to suggest that SGLT-2 inhibitors are associated with a lower risk of HK among patients with diabetes, HF, or CKD. However, SGLT-2 inhibitors were excluded from the analysis in the current partial review of TA599 as data on SGLT-2 use were not captured in the clinical trials for SZC and to ensure a consistent approach with that taken in TA599.[3]

In the UK, SGLT-2 inhibitors are not indicated for HK and are not used by clinicians with the aim of lowering patient S–K levels. Furthermore, UK clinical guidelines state that patients should only initiate SGLT-2 inhibitors if they are in receipt of an optimised RAASi dose (angiotensin receptor blocker [ARB] or angiotensin converting enzyme [ACE] inhibitor).[11, 12] SZC facilitates maintenance of an optimised RAASi dosage,[9] meaning that SZC has the potential to enable more patients to be eligible for SGLT-2 inhibitors than standard care. For example, data from a retrospective analysis of 44 patients with heart failure with reduced ejection fraction with a history of HK who were receiving SZC to enable prescription of RAASi therapy found that the use of SGLT-2 inhibitors increased from 66% prior to the SZC prescription to 84% after the prescription of SZC.[13] As such, the benefits of SGLT-2 inhibitors will disproportionately favour the SZC arm and therefore the approach of excluding SGLT-2 inhibitors should be considered conservative.

A2. Priority question. It is unclear whether SPARK and ZORA study patient S-K levels fluctuate over the study period or remain stable. Please provide complete patient-level S-K data over the whole study period. If it is not

possible to provide these data, for each of the S-K ≥5.0 to <5.5, ≥5.5 to <6 and ≥6.0 groups, please provide:

- **the proportion of patients who, over the whole study period, a) had S-K levels that remained within their baseline S-K group; b) had S-K levels that, at least once, exceeded their baseline S-K group and c) had S-K levels that, at least once, fell below their baseline S-K group**

- **a histogram of the number of S-K level measurements over the study period**

SPARK

The information requested for the SPARK study is provided in Table 1 below and histograms illustrating the distribution of S–K level measurements are provided in Figure 1–Figure 3. The data show that the majority of patients in the overall cohort had S–K levels that at least once fell below their baseline S–K group or remained in their baseline S–K group. In the SPARK analysis, S-K levels were updated dynamically in outcome models using Generalized Estimating Equation (GEE) Poisson regression in a time-updated manner, which has taken into account fluctuations of S-K levels beyond baseline.

Table 1: S–K trajectories by baseline group in the SPARK study: patient-level trends and shifts over the study period

		All patients	Patients with ≥1 S-K measures (%*)				
Cohort	**Baseline S–K group**	**N**	**N**	**Remained**	**Exceeded**	**Fell below**	**Both exceeded and fell**
Overall	5.0–5.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5.5–6.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≥6.0	[redacted]	[redacted]	[redacted]		[redacted]	
Prior HF no CKD	5.0–5.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5.5–6.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≥6.0	[redacted]	[redacted]	[redacted]		[redacted]	
Prior CKD no HF	5.0–5.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5.5–6.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≥6.0	[redacted]	[redacted]	[redacted]		[redacted]	
Prior HF or CKD	5.0–5.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5.5–6.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≥6.0	[redacted]	[redacted]	[redacted]		[redacted]	

* Percentage with respect to patients with ≥1 S-K measures
Abbreviations: CKD: chronic kidney disease; HF: heart failure; S–K: serum potassium.

Figure 1: Histogram of S–K level measurements in the ≥5.0–<5.5 mmol/L baseline group in the SPARK study[1]

Patients with more than 30 measures (N=198, 0.04%) were truncated in the histogram.
Abbreviations: S–K: serum potassium.

Figure 2: Histogram of S–K level measurements in the ≥5.5–<6.0 mmol/L baseline group in the SPARK study

Patients with more than 30 measurements (N=27, 0.05%) were truncated in the histogram.
Abbreviations: S–K: serum potassium.

Figure 3: Histogram of S–K level measurements in the ≥6.0 mmol/L baseline group in the SPARK study

Patients with more than 30 measurements (N=6, 0.09%) were truncated in the histogram.
Abbreviations: S–K: serum potassium.

ZORA

The requested results for a) and b) are provided below. Additional context and results are provided to aid in the interpretation, considering the following aspects related to the study design and the nature of the data:

- S–K values are only available as recorded in routine clinical practice rather than consistently for all patients and at pre-specified time points. Analyses of S–K during the study period was not specified as an *a priori* analysis in the ZORA clinical study protocol.

- As previously demonstrated, the SZC cohort were more likely to remain on RAASi treatment compared to the no K^+-binder cohort, thereby increasing their risk of HK.
- By design, the SZC cohort were required to remain on continuous SZC treatment for at least 120 days, and some may have discontinued thereafter. Therefore, results are also provided separately for the two-time periods; the first 120 days and days 121–180. We have also provided plots of individual patient S–K values over time, in each cohort and strata.

Table 2: Changes in S–K levels during the ZORA study period

	S–K ≥5.0–<5.5		S–K ≥5.5–<6.0		S–K ≥6.0	
	SZC	**No K^+ binder**	**SZC**	**No K^+ binder**	**SZC**	**No K^+ binder**
US (N total)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any available S–K during study period (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S–K remained within baseline group during study period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S–K exceeded baseline group during study period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S–K below baseline group during study period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Japan (N total)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any available S–K during study period (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S–K remained within baseline group during study period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S–K exceeded baseline group during study period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S–K below baseline group during study period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HK: hyperkalaemia; K^+: potassium ion; S–K: serum potassium; SZC: sodium zirconium cyclosilicate.

The proportion of patients who, within the first 120 days, had S–K levels that, at least once, exceeded their baseline S–K group and had S–K levels that, at least once, fell below their baseline S–K group are presented in Table 3. During this time window, all patients in the Lokelma cohort were required to remain on continuous SZC treatment, according to the study design.

Table 3: Proportion of patients with S–K levels exceeding or falling below baseline S–K group at least once within the first 120 days of the ZORA study

First 120 days	S–K ≥5.0–<5.5		S–K ≥5.5–<6.0		S–K ≥6.0	
	SZC	No K^+ binder	SZC	No K^+ binder	SZC	No K^+ binder
US (N total)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Available S–K in first 120 days (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S–K exceeded baseline group during first 120 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S–K below baseline group during first 120 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Japan (N total)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Available S–K in first 120 days (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S–K exceeded baseline group during first 120 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S–K below baseline group during first 120 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HK: hyperkalaemia; K^+: potassium ion; S–K: serum potassium; SZC: sodium zirconium cyclosilicate.

The proportion of patients who, within days 121–180, had S–K levels that, at least once, exceeded their baseline S–K group and had S–K levels that, at least once, fell below their baseline S–K group are presented in Table 4. According to the study design, during this time window, patients were allowed to have discontinued SZC treatment.

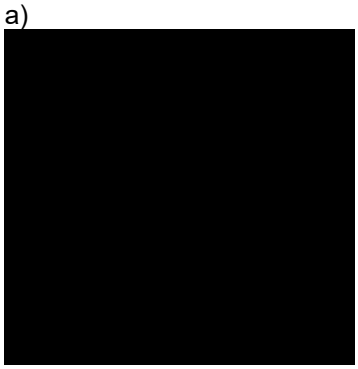
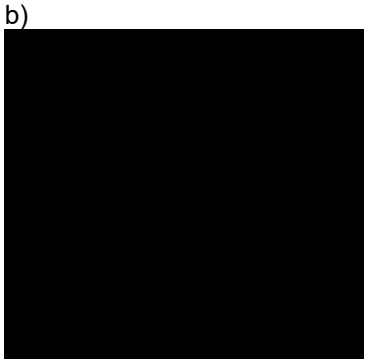
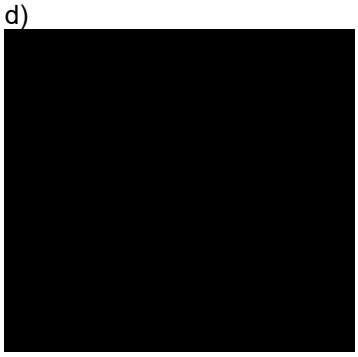
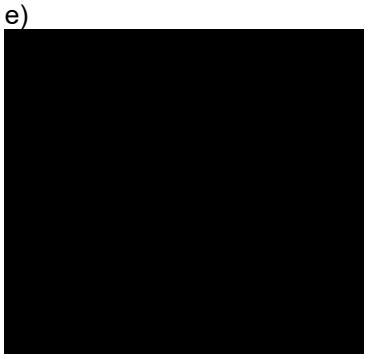
Table 4: Proportion of patients with S–K levels exceeding or falling below baseline S–K group at least once within days 121–180 of the ZORA study

Days 121-180	S–K ≥5.0–<5.5		S–K ≥5.5–<6.0		S–K ≥6.0	
	SZC	No K^+ binder	SZC	No K^+ binder	SZC	No K^+ binder
US (N total)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Available S–K within days 121–180 days (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S–K exceeded baseline group within days 121–180	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S–K below baseline group within days 121–180	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Japan (N total)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Available S–K within days 121–180 days (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S–K exceeded baseline group within days 121–180	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S–K below baseline group within days 121–180	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HK: hyperkalaemia; K^+: potassium ion; S–K: serum potassium; SZC: sodium zirconium cyclosilicate.

Plots of individual patient S–K values over the study period are presented for the US and Japan populations in Figure 4 and Figure 5, respectively.

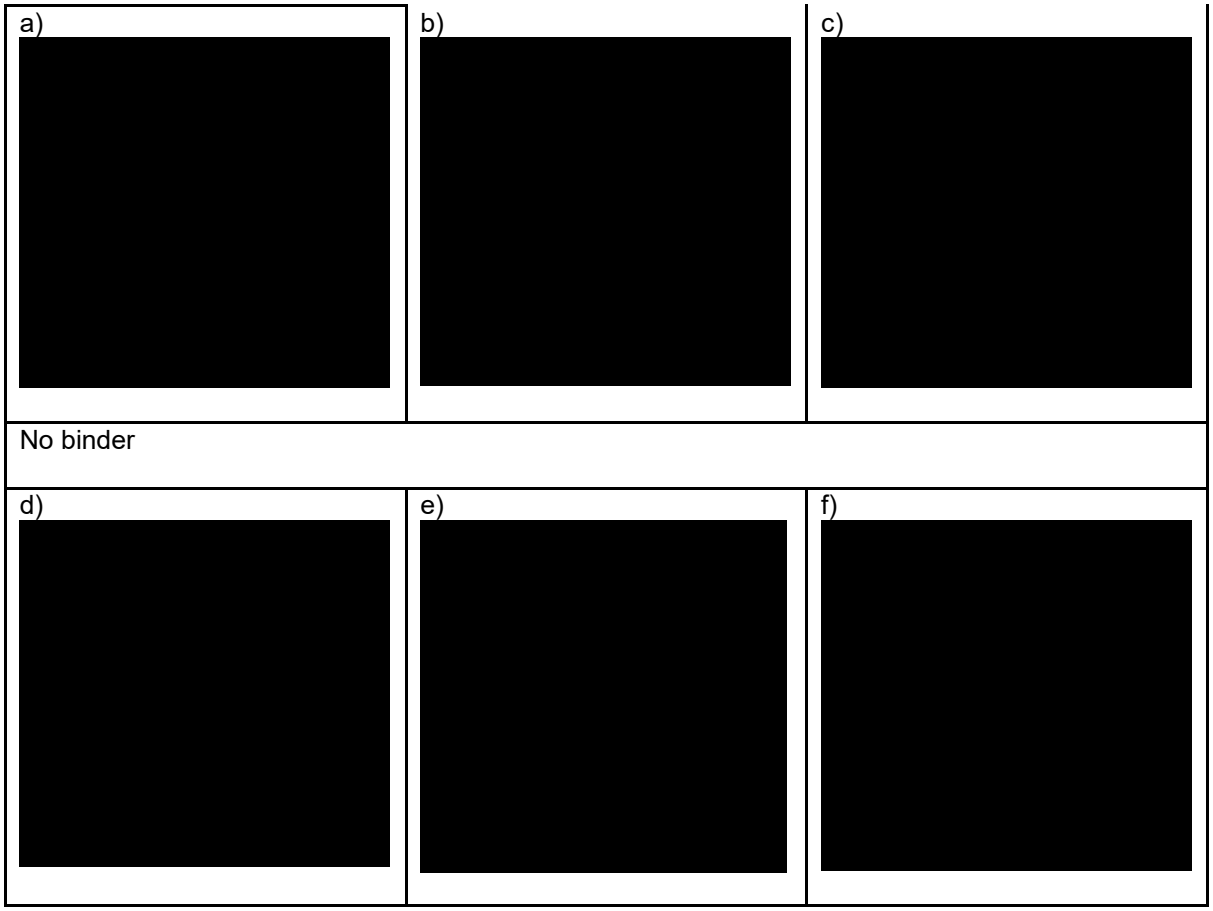
Figure 4: Plots of individual patient S–K values over the study period for the US ZORA population

S–K ≥5.0–<5.5	S–K ≥5.5–<6.0	S–K ≥6.0
SZC		
a) 	b) 	c)
No K^+ binder		
d) 	e) 	f)

Abbreviations: HK: hyperkalaemia; S–K: serum potassium; SZC: sodium zirconium cyclosilicate.

Figure 5: Plots of individual patient S–K values over the study period for the Japan ZORA population

S–K ≥5.0–<5.5	S–K ≥5.5–<6.0	S–K ≥6.0
SZC		



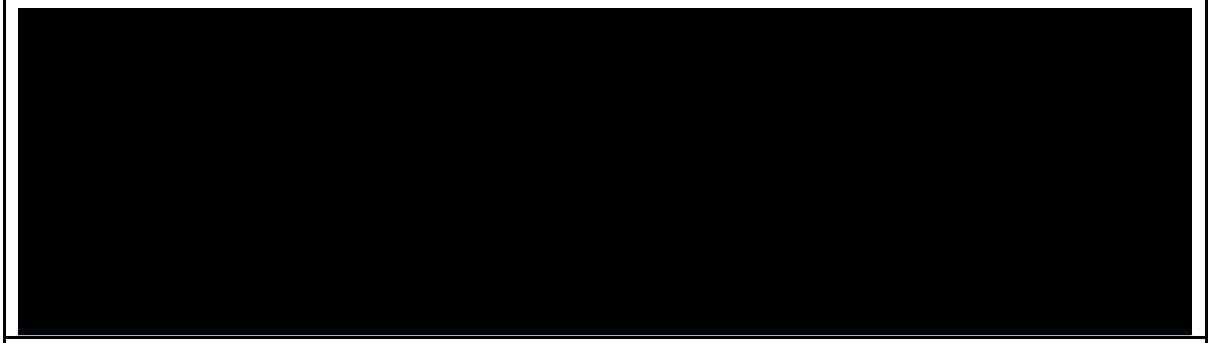
Abbreviations: HK: hyperkalaemia; S–K: serum potassium; SZC: sodium zirconium cyclosilicate.

Histograms of the number of S–K level measurements over the study period are provided in Figure 6 and Figure 7 for the US and Japan populations, respectively. In the diagrams, the x-axis shows number of S–K measurements over the 180-day study period while the y-axis shows percentage of patients with the respective number of S–K measurements.

Figure 6: Histograms of the number of S–K level measurements over the ZORA study period in the US population

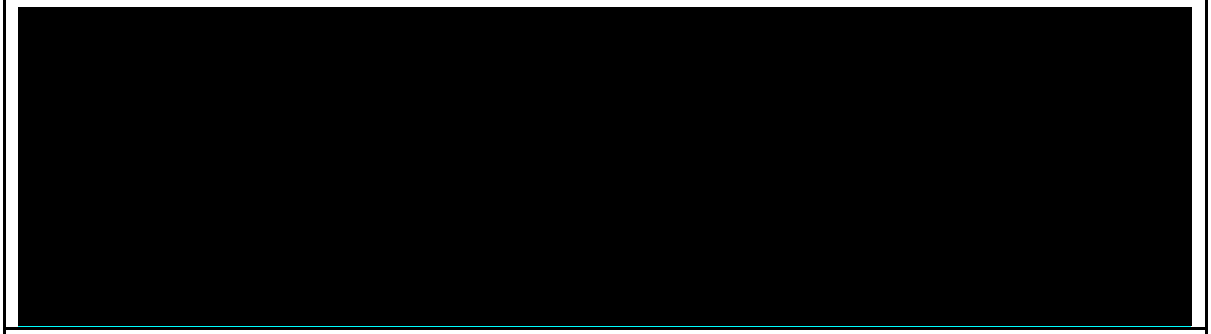
SZC – S–K ≥5.0–<5.5

SZC – S–K ≥5.5–<6.0



SZC – S–K ≥6.0

No K^+ binder – S–K ≥5.0–<5.5



No K^+ binder – S–K ≥5.5–<6.0

[redacted]

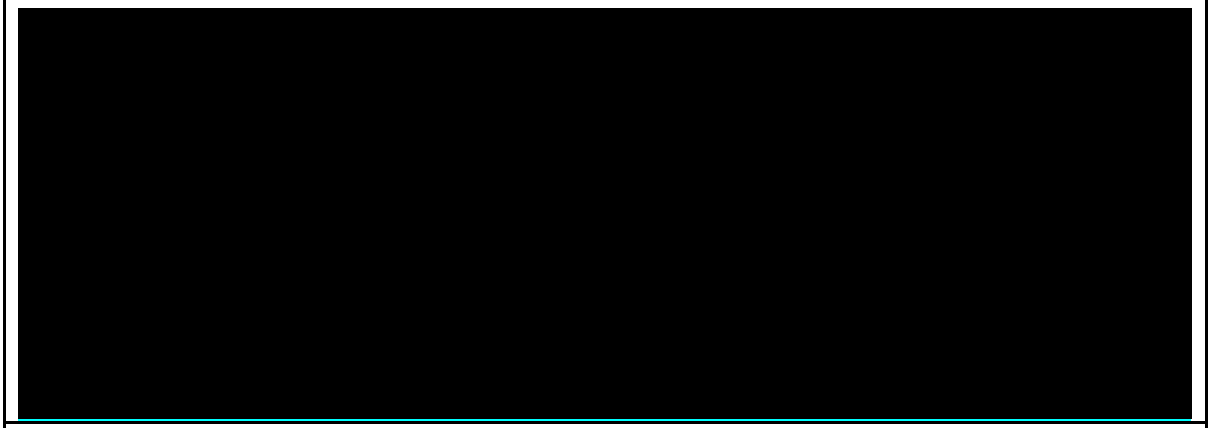
No K^+ binder – S–K ≥6.0

[redacted]

Abbreviations: HK: hyperkalaemia; S–K: serum potassium; SZC: sodium zirconium cyclosilicate.

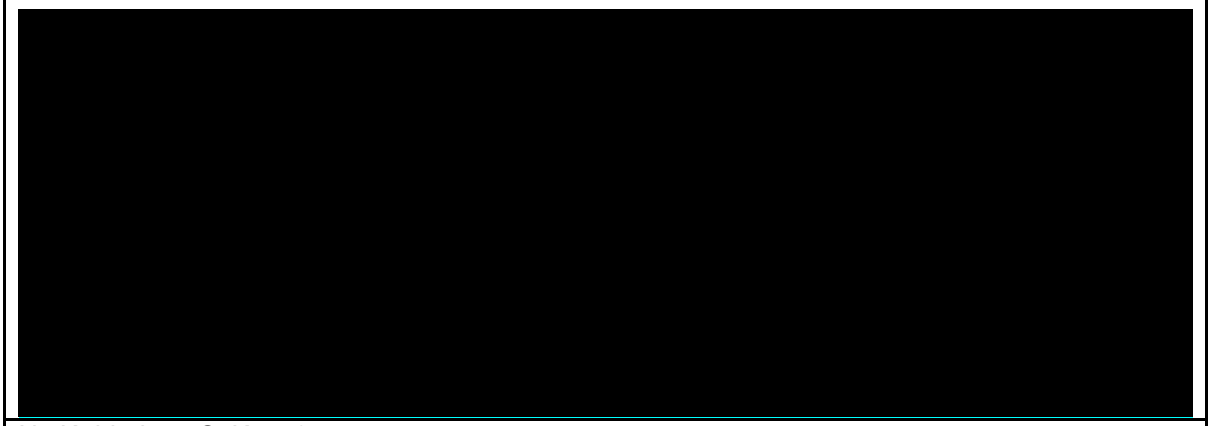
Figure 7: Histograms of the number of S–K level measurements over the ZORA study period in the Japan population

SZC – S–K ≥5.0–<5.5

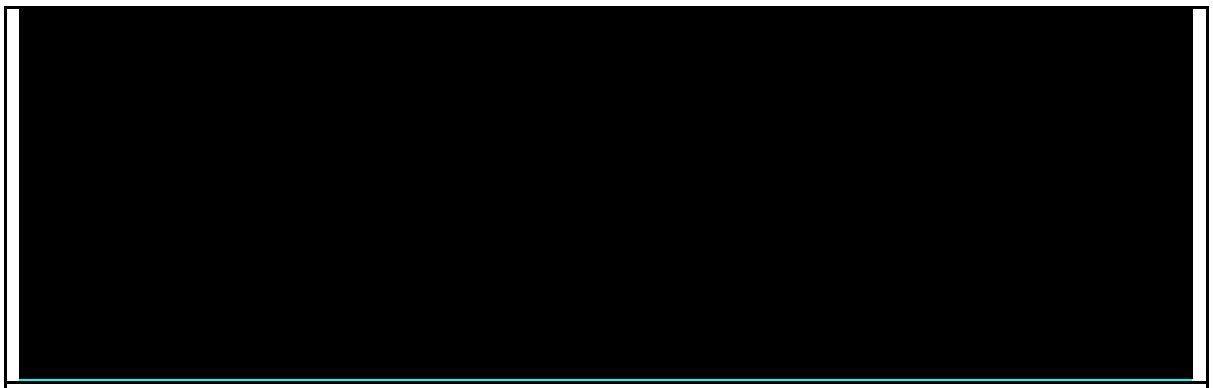


SZC – S–K ≥5.5–<6.0

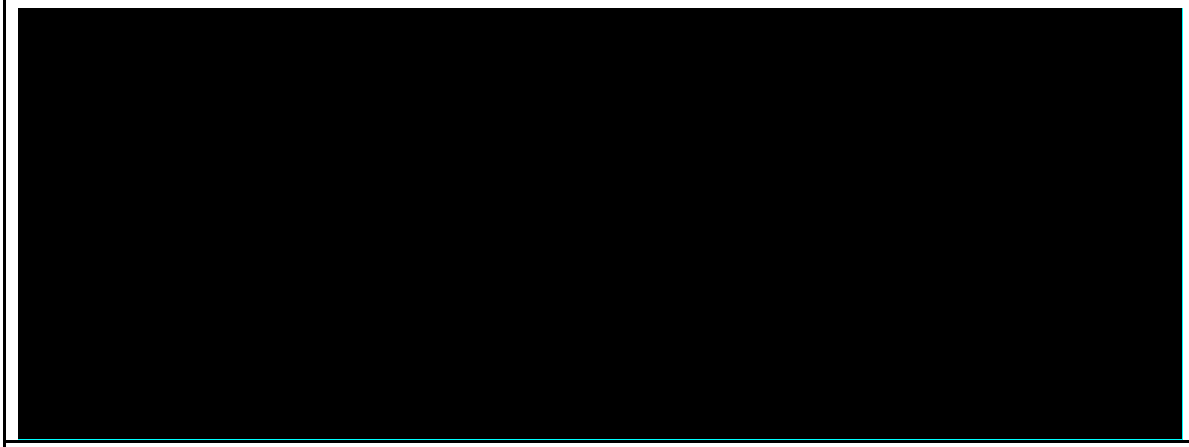
SZC – S–K ≥6.0



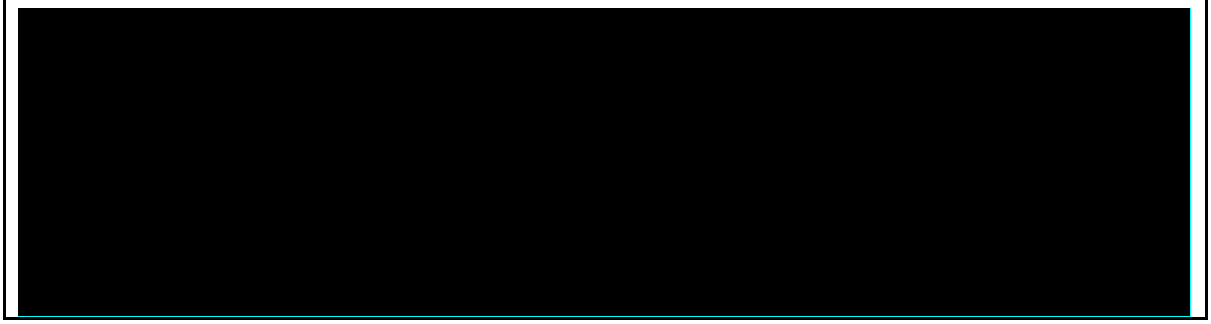
No K^+ binder – S–K ≥5.0–<5.5



No K^+ binder – S–K ≥5.5–<6.0



No K^+ binder – S–K ≥6.0



Abbreviations: HK: hyperkalaemia; S–K: serum potassium; SZC: sodium zirconium cyclosilicate.

A3. Please provide ZS-003 study placebo arm 5.5 ≤ S-K < 6.0mmol/L subgroup baseline characteristics as presented for the ITT population in ZS-003 study CSR, Table 11.4. If possible, please provide information on how many patients received suboptimal or optimal RAAS inhibitor dosages.

Please see requested baseline characteristics in Table 5. The proportion of patients receiving optimal or suboptimal RAASi dosage is not available and thus has not been included.

Table 5: Baseline characteristics for ITT Population, ZS-003 study placebo arm (SK >5.5 - <6.0 mmol/L)

Demographic Parameter Statistic	Placebo (N = [redacted])
Age at screening (Years)	
Mean (SD)	[redacted]
Median	[redacted]
Min, Max	[redacted]
Gender, n (%)	[redacted]
Male	[redacted]
Female	[redacted]
Race, * n (%)	[redacted]
White	[redacted]
Black or African American	[redacted]
Asian	[redacted]
American Indian or Alaska Native	[redacted]
Native Hawaiian or other Pacific Islander	[redacted]
Other	[redacted]
Multiple races	[redacted]
Weight at baseline ** (kg)	[redacted]
n	[redacted]
Mean (SD)	[redacted]
Median	[redacted]
Min, Max	[redacted]
Acute S-K baseline, n (%)	[redacted]
5.4-5.5 mmol/L	[redacted]
> 5.5 mmol/L	[redacted]
Acute eGFR at baseline, n (%)	[redacted]
< 15 mL/min	[redacted]
15-29+ mL/min	[redacted]
30-59+ mL/min	[redacted]
>= 60 mL/min	[redacted]
Etiology, n (%)	[redacted]
CKD	[redacted]
CHF	[redacted]
Diabetes Mellitus	[redacted]
RAAS Medication	[redacted]

Abbreviations: CHF: chronic heart failure; CKD: chronic kidney disease; ; eGFR: estimated glomerular filtration rate; RAAS: renin-angiotensin-aldosterone system; SD: standard deviation; S–K: serum potassium

SPARK study

A4. Priority question. Please clarify whether data from patients who received dialysis during the study follow-up period were excluded from the company analyses.

Patients who received dialysis during the follow-up period were not excluded from the study, with a total of [redacted] patients having end stage renal disease and/or undergoing dialysis during this time.

A5. Priority question. A generalised estimating equation (GEE) model was developed to evaluate the association between S-K level and clinical outcomes for the CKD and HF populations (study objective 2) (CS, p49). Please provide:

- **details of the working correlation structure(s) used in the model to account for within-cluster or repeated-measures dependencies**
- **the number of subjects who provided data used in the model**
- **the methods used to estimate the SEs of model parameters and, if the methods were not robust, please explain why non-robust methods were used**

The study used an exchangeable working correlation structure in the GEE models. This structure assumes a constant correlation between all repeated measures within a given individual. It was chosen for the following reasons:

- The data consist of repeated observations per individual (e.g., multiple potassium readings and associated person-time intervals), making it important to account for intra-individual correlation.
- It is particularly suitable for population-averaged inference and performs well in moderate-to-large samples, which is the case in our analysis.

The number of patients contributing to the models was as follows:

- Patients with prior HF and no CKD: [redacted]
- Patients with prior CKD and no HF: [redacted]
- Patients with prior HF or CKD: [redacted]

The study used robust (sandwich) standard errors. This method ensures valid inference even in potential misspecification of the working correlation structure. The sandwich estimator is robust to heteroscedasticity and within-cluster correlation, making it well-suited for analysis of repeated measures.

A6. Priority question. Please explain why the S-K 4.5 to 5.0mmol/L group, rather than the S-K 5.0 to 6mmol/L group or the S-K ≥6mmol/L group, was chosen as the reference group. Please provide IRRs for the following comparisons:

- **S-K 5.5 to 6.0mmol/L versus S-K 5.0 to 5.5mmol/L**
- **S-K 5.5 to 6.0mmol/L versus S-K >6mmol/L**

The threshold for HK is defined as an S–K of ≥5.0 mmol/L or ≥5.5 mmol/L by UK and international guidelines respectively.[4, 6, 14-17] These same guidelines define an S–K of ≥3.5–<5.0 mmol/L as the normokalaemic range, with levels below 3.5 mmol/L representing hypokalaemia.[4, 6, 14-19] Whilst the definition of HK varies, in the UK treatment for HK is not initiated until an S–K threshold of ≥5.5 mmol/L is reached.[14]

Untreated persistent HK is associated with an increased risk of all-cause mortality, hospitalisations and MACE.[20-30] Multiple studies have shown a 'U-shaped' association between S–K levels and the risk of death for CKD or HF patients.[21, 26-30] Further evidence has shown that those with an S–K level of ≥5.5–<6.0 mmol/L are at greater risk of a range of other adverse clinical outcomes, including hospitalisation and MACE than those with normokalaemia.[7, 26, 27, 29, 31, 32] As such, international guidelines now recognise the importance of this association, and guidance has transitioned to become more proactive in the management of persistent HK using K^+ binders, even amongst those with milder disease.[4-6]

In the SPARK analysis, use of the S–K ≥4.5–<5.0 mmol/L group as the reference group facilitates quantification of the increased risk experienced by patients with HK compared with patients with normokalaemia. Multiple studies have compared outcomes in hyperkalaemic patients to reference groups of patients within the normokalaemic range.[31, 33-35] A comparison with patients in the ≥5.0–<5.5 mmol/L or ≥6.0 groups would not provide the comparison required for decision making in the

population of interest, as we are specifically examining additional risk from a baseline of normokalaemia.

A7. Please provide the number of patients in the SPARK study S-K ≥6.0 mmol/L subgroup who were treated with a potassium binder.

The study included [redacted] patients treated with a K^+ binder at any time, of which only [redacted] were treated with SZC.

A8. Priority question. A published study, funded by AstraZeneca (James 2021 [2]), provides information on the relationship between time spent in different S-K level groups and MACE, hospitalisations and death. Results were generated using CPRD data, the same source of data used to generate SPARK study results. Please explain why:

- **Please explain why James 2021 study results were not considered relevant to this STA**
- **The James 2021 study generated results based on time spent in S-K level groups whilst the SPARK study generated results based on index S-K level. Please explain why different approaches were taken for the James 2021 and SPARK studies**
- **James 2021 study patients with CKD and HF who spend time having S-K levels ≥5.5mmol/L have a lower risk of mortality than patients with CKD and HF who have S-K levels ≤5.5mmol/L. Please explain why these results are not in line with SPARK study results.**

James et al. (2021) was captured in the 2024 RAASi SLR update but was excluded on the basis that the population taking RAASi was not solely HF, CKD, or diabetic nephropathy (DN) as outlined in the protocol.[2] Out of the 931,460 patients included in the analysis, only 32% (n=297,702) had CKD, 9% (n=84,210) had HF and 31% (n=288,871) had diabetes.[2]

The James et al. (2021) study provides valuable observational data on S–K variability and clinical outcomes in patients with CKD and HF.[2] However, its methodology and objectives differ significantly from the SPARK study.[2, 7] While

James et al. focused on assessing long-term S–K variability and time spent in specific S–K cut-offs (≥5.0 mmol/L, ≥5.5 mmol/L and ≥6.0 mmol/L), the SPARK study aimed to analyse the relationship between individual S–K measurements and the risk of significant clinical outcomes.[2, 7] The SPARK approach directly addresses concerns raised by NICE in TA599 regarding limitations such as unmeasured confounding, which were identified in the Linde et al. (2019) study (used in a previous submission).[3, 7] The SPARK study was also designed to generate robust results that align with the NICE Framework for RWE.[7, 36]

In 2021 there had been a number of publications investigating the relationship between HK episodes and risk of all-cause mortality and MACE events. However, there were limited data at the time that investigated S–K variability and time spent with elevated S–K levels and risk of adverse outcomes. The data used (CPRD) had previously been used to assess risk of adverse outcomes and index S–K levels in CKD and HF patients (Furuland et al. [2018] and Linde et al. [2019], respectively).[33, 34] The James 2021 study was an extension of these studies.[2] To accommodate potential fluctuations in S–K levels over time, the SPARK study performed additional time-updated and time-dependent sensitivity analyses to evaluate how changes in S–K levels impacted outcomes during the follow-up period.[7]

The James 2021 study did re-confirm the adverse relationship between index S–K levels >5.0 mmol/L and all-cause mortality in CKD and HF cohorts and further demonstrated that S–K variability did not provide any additional contribution to all-cause mortality risk.[2]

Regarding the query around the mortality risk for patients with S–K ≥5.5 mmol/L versus those with S–K ≤5.5 mmol/L, the James 2021 study does not provide evidence that patients with CKD and HF who spend time with S–K levels ≥5.5 mmol/L have a lower risk of mortality compared to those with S–K ≤5.5 mmol/L.[2] At an HK threshold of S–K ≥5.0 mmol/L, time spent in an HK state was associated with a reduced risk of all-cause mortality across all cohorts, including patients with CKD and HF, compared with patients who spent no time in an HK state during their follow-up period.[2] This trend of reduced mortality risk with HK started to reverse at a threshold of S–K ≥5.5 mmol/L; for the overall cohort and patients with diabetes or resistant hypertension, longer time spent in an HK state was associated with

increased risk of mortality compared with patients who spent no time in an HK state.[2] For patients with HF or CKD, the association between time spent in an HK state and reduced risk of mortality remained but became weaker as the threshold increased to 5.5 or 6.0 mmol/L.[2] While the James 2021 study provides some evidence of reduced mortality risk for patients with CKD and HF at S–K levels ≥5.0 mmol/L, this trend does not hold consistently at higher S–K thresholds (≥5.5 mmol/L and ≥6.0 mmol/L).[2] Importantly, the relative risk of mortality for patients with S–K ≥5.5 mmol/L compared with those with S–K ≤5.5 mmol/L is not presented.[2] The observation that mortality risk was lower in those spending more time with S–K levels ≥5.0 mmol/L may have been attributable to these patients benefitting from more proactive management.[2] As noted in the publication, both CKD and HF cohorts had the highest frequency of potassium testing (expressed as rate per patient years) and therefore may have been subject to additional treatment or intervention.[2] This limitation was discussed in the paper, but further analysis was not undertaken to confirm this.

In addition, the difference between SPARK findings and those of James et al. likely arises from substantial disparities in the dataset (CPRD GOLD vs AURUM), exposure definitions, confounding structures, and statistical modelling.[2, 7] For example, James et al. compared the risk of all-cause mortality in those with time spent in different HK states to patients who spent no time in an HK state.[2] The assessment of S–K variability over time in these groups, which is beneficial for understanding patient trajectories, may introduce complexities around time-at-risk and survivor bias, since patients who live longer naturally have more S–K measurements. The observed protective effect for S–K ≥5.5 mmol/L could also be due to confounding by clinical attention and reverse causation rather than a genuine protective biological effect of elevated potassium, since patients in this group are more likely to be frequently monitored, treated, or stabilised over time. Other key differences in the study design are also summarised below in Table 66 below.[2, 7]

Table 66: Key differences in study design and methods: James et al. (2021) vs. SPARK study

Aspect	James 2021[2]	SPARK[7]
Design	Retrospective cohort study (CPRD GOLD + HES)	Retrospective cohort study (CPRD Aurum + HES)
Population	Adults (≥18) with CKD stage 3+, HF, diabetes, RHTN, RAASi	Adults (≥18) with SK between 2016–2019. Model then looks at prior CKD and/or HF

Aspect	James 2021[2]	SPARK[7]
Follow-up period	2003–2018 (5-year look-back to 2003)	2016–2021 for outcomes
Exclusions	Dialysis patients included as a separate group	Excluded: dialysis in 14 days prior, organ transplant, pregnancy in prior 12 months
Exposure	% time spent in HK (SK ≥5.0/5.5/6.0 compared to patients who spent no time in an HK state); S–K variability (SD-based)	Time-updated S–K categories (e.g., <3.5, 3.5–4.0, 4.0–4.5, 4.5–5.0, 5.0–5.5, 5.5–6.0, ≥6.0)
Time-dependence	Yes – exposures modelled over time (repeated measures)	Yes – S–K and eGFR updated dynamically in outcome models
Outcome Modelling	Relative risk (log-scale) using time-in-HK intervals	GEE Poisson regression with time-updated S–K/eGFR; IRRs computed
Adjustment Factors	Disease-specific cohorts with published risk equations	Adjusted for age, sex, comorbidities, medications, and patient-years
Outcome Types	All-cause mortality, MACE	All-cause mortality, MACE, hospitalisation, healthcare resource use & cost

Abbreviations: CPRD: Clinical Practice Research Datalink; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; GEE: generalised estimating equations; HES: Hospital Episode Statistics; HF: heart failure; HK: hyperkalaemia; IRR: incidence rate ratio; MACE: major adverse cardiovascular events; RAASi: renin-angiotensin-aldosterone system inhibitor; RHTN: resistant hypertension; SD: standard deviation; S–K: serum potassium.

ZORA study

A9. Please explain why chi-squared tests were used to compare differences in outcome proportions between groups (and derive p-values) in the post-hoc re-analysis of ZORA, as opposed to logistic regression analysis used by Rastogi et al.

Logistic regression analysis was also used in the post-hoc re-analysis of ZORA. These results are provided in full in “AstraZeneca Data on File. ZORA Reanalysis Meta-Analysis” included in the reference pack.

A10. The company has carried out many subgroup comparisons. Please explain how multiplicity was considered or, if it was not considered, why it was not considered.

Correction for multiple testing is important in the case of exploratory analyses when looking broadly for patterns or associations, especially when examining multiple outcomes. However, in this case, correction for multiple testing was not considered because the associations of interest were identified *a priori*. This decision was based on the fact that all subgroup analyses were pre-specified, with clearly defined hypotheses established prior to data analysis and therefore we did not feel the need to perform corrections for multiplicity.

Section B: Clarification on cost effectiveness data

Summary of economic evidence previously evaluated by NICE

The CEM used in this current appraisal is aligned with the model informing the final draft guidance for TA599, incorporating the NICE committee and EAG preferences, where applicable.[3] As a partial review, the methods and data sources used to establish the clinical and cost-effectiveness of SZC for patients with an S–K of ≥5.5–<6.0 mmol/L align with those accepted in the original appraisal, except where newly available real-world evidence can be used to reduce the uncertainties raised by NICE and the EAG. Clinical expert opinion also confirmed that, in general, the assumptions used for committee decision-making for TA599 were still valid.[37] Inputs and assumptions are therefore aligned with those from TA599, other than those outlined below.

Key differences from TA599 final draft guidance model

The key development in the treatment landscape for HK since TA599 was published has been the introduction of K^+ binders (SZC and patiromer) into UK clinical practice. Following the regulatory approval and reimbursement of SZC for the treatment of HK in the UK and internationally, it has been possible to collect real-world data on SZC usage to better inform modelling inputs. Real-world data were incorporated into the model as follows:[3]

- Data from the observational SPARK study were used to inform the relationship between S–K and long-term outcomes in preference of the literature previously used to inform TA599[7]
- Data from the subgroup analysis of the observational ZORA study were used to inform the relationship between SZC and RAASi modification independent of S–K levels[9]

The model submitted for TA599 originally used a treatment duration of 52 weeks in the chronic setting and a lifetime duration in the revised base case. However, recently conducted Market Research and clinical expert opinion indicate that a 12 week treatment duration in the chronic setting is more aligned with clinical practice and therefore a 12 week duration is used in the base case.[37, 38]

To ensure relevance to the current decision problem population all costs were inflated to the current cost year and clinical trial evidence was sourced specifically from those with an S–K of ≥5.5–<6.0 mmol/L, aligned to the approach taken during TA599.[3]

Standard care

B1. Priority question. In the company model, patients who receive standard care do not appear to be treated with SZC (or another potassium binder) if their S-K level increases to ≥6mmol/L. If this is the case, please provide an updated company model in which patients receiving standard care are treated with a potassium binder if their S-K level increases to ≥6mmol/L.

The model was developed in alignment with a partial review of TA599 to expand access specifically to patients with an S–K of ≥5.5–<6.0 mmol/L. The S–K trajectories used in the analysis have therefore been updated to be reflective of this specific population who have a lower average S–K level when compared against the ≥5.5 mmol/L population presented as part of the previous appraisal.

Patient S–K levels do have the potential to increase over time and cause a repeat HK event, but the maximum S–K measurements for repeat episodes are generally comparable to the initial episode, meaning that the modelled patient population are highly unlikely to experience HK events with an S–K level ≥6.0 mmol/L. In the REVOLUTIONIZE I study, which enrolled 2,048 patients with stage 3 to 4 CKD, of whom 57.6% had comorbid HF, dietary counselling alone was used as the initial intervention for managing hyperkalaemia.[39] During the 6-month follow-up period, 56.0% of patients experienced at least one recurrent HK episode, with 37.4% recurring within the first month.[39] Patients experienced an average of 2.6 episodes over the study duration.[39] Notably, 25.7% of patients had three or more HK episodes, and within this subgroup, over 70% experienced an additional recurrence within the subsequent month, indicating a trend toward increasing episode frequency.[39] Importantly, S–K levels at recurrence did not fluctuate from the initial event.[39] The mean S–K at the time of each recurrent episode was within ±0.1 mmol/L of the initial HK value, suggesting that subsequent episodes returned to a similar level of severity rather than showing spontaneous resolution.[39] The study further noted that elevated S–K was particularly common among patients with comorbid HF, diabetes, or those

receiving RAASi therapy.[39] This is also demonstrated through the GALVANIZE-HF analysis, which showed comparable S–K thresholds for repeat HK events for patients not on SZC across up to four HK recurrences.[40]

The model structure allows patients within the treatment and standard care arms to experience HK events where the S–K level increased to ≥6.0 mmol/L, however these patients make up a very small part of the analysis. The average S–K in the maintenance phase of the standard care arm is 5.197 mmol/L, with a patient and observation standard deviation of 0.345 and 0.400 respectively. In addition to this, 12.7% of patients will down-titrate, and 38.7% will discontinue their RAASi therapy once above the 5.5 mmol/L S–K threshold, resulting in a further S–K reduction of 0.115 mmol/L and 0.230 mmol/L respectively, lowering the average S–K further. As an S–K measurement of ≥6.0 mmol/L is highly unlikely in the model, which is consistent with clinical practice, the impact caused by this is minimal and should be considered inconsequential for driving outcomes of the analysis.

B2. Priority question. In the company model, the mean S-K value for patients receiving standard care is assumed to remain constant from day 4 onwards, and independent of underlying disease (CKD or HF). Please provide clinical evidence to support these assumptions.

ZS-004 was a multicentre, multi-phase, multi-dose, prospective, randomised, double-blind, placebo-controlled maintenance Phase III study investigating the efficacy of SZC versus placebo in adult patients with HK.[41] ZS-005 was a prospective, international, open-label, single-arm Phase III study investigating the efficacy and safety of SZC in adult outpatients with HK.[42] In the original company submission for SZC (TA599), pooled data from the ZS-004[41] and ZS-005[42] were used to inform the pre-defined S–K profile in the SZC arm.[3] As ZS-005 was not placebo-controlled, the control arm of ZS-004[41] was used to inform the pre-defined S–K profile in the standard care arm.[3]

During technical engagement of TA599, data from the placebo arm of ZS-003, a multicentre, two-stage, double-blind, placebo-controlled, Phase III study,[43] were considered as an alternative source of evidence informing S–K profiles for the standard care arm. This was explored in order to overcome the potential residual SZC effect in the ZS-004 placebo arm, due to patients in the placebo arm of ZS-004

being treated with SZC in the acute phase of the trial.[3] Initially, the adjusted 48 hour absolute reduction in S–K was applied as the absolute reduction at the end of the correction phase of the model (Day 3).[3] As such, the time (days) slope coefficient was calculated by dividing the adjusted 48 hour absolute reduction by 3.[3] As the S–K levels in the placebo arm of ZS-003 were generally stable during the maintenance treatment, the S–K trajectory during the maintenance phase was modelled to be constant.[3]

Alternative standard care S–K trajectories were generated by the company for use in scenario analyses.[3] For these alternative trajectories, the 48 hour placebo effect observed in ZS-003 was applied to Day 2 of the S–K trajectory, and then extrapolated linearly to Day 3, resulting in a further reduction in S–K.[3] For the maintenance phase trajectory, the S–K value at Day 3 was assumed to remain constant.[3] This alternative S–K profile was preferred by the EAG, and was deemed conservative with respect to SZC as the rate of S–K reductions in the standard care arm is likely to be lower on Day 3 compared to Day 1 and Day 2.[3] The company accepted the EAG's preferred assumption in the model informing the final draft guidance for TA599.[3]

In this current partial review of TA599, the S–K trajectories for the standard care arm used in the economic analysis align with the EAG's preferred approach in TA599, and this is known to have a conservative effect on the ICER.[3]

The assumptions used in the model therefore align with the current evidence base and past NICE appraisals and so should be deemed suitable for this submission.

B3. Please explain why the patient and observation components of the mixed-effect model used to estimate S-K values for patients receiving standard care have non-zero (positive) means, whereas, for patients treated with SZC, these components have zero means.

Variation in the treatment arm acute phase was not included as a fixed effect model was used. This approach was taken because both acute and maintenance phase data were available for this arm, whereas this was not the case in the standard care arm, where only acute phase data was available. This approach aligns with the final TA599 model, which was used for decision making.

RAAS inhibitors

B4. Priority question. In the company model, it appears that the probabilities of discontinuing or down-titrating RAAS inhibitors are applied to all patients in the cohort treated with SZC, independent of whether the patient has discontinued SZC. If this is the case, please update the company model so that, for the standard care cohort, the probabilities of discontinuing or down-titrating RAAS inhibitors are applied to patients who have discontinued SZC.

In the original company submission (TA599), it was assumed that all patients in the chronic treatment phase receiving SZC remained on RAASi treatment.[3] This assumption was based on clinical expert opinion suggesting that SZC would enable physicians to manage HK whilst maintaining or optimising RAASi therapy.[3] As such, patients with an S–K of ≥5.5–<6.0 mmol/L had their probability of RAASi withdrawal or down-titration set to 0% in the SZC arm.[3] In the standard care arm, discontinuation was 20% and down-titration was 80%, due to the lack of protective effect imparted by SZC treatment.[3]

However, in TA599, the EAG preferred an alternative approach in which RAASi discontinuation rate is based on S–K level rather than SZC treatment status. The EAG preferred assumption was accepted by the company, and in the model informing the final draft guidance for TA599, the proportion of patients who down-titrate and discontinue RAASi in the SZC and standard care arms are equal for patients within the same S–K subgroup.[3] This approach was accepted as it addressed the uncertainty in the proportion of SZC patients who would down-titrate RAASi.[3] In clinical practice, clinicians with experience of SZC are more likely to allow patients to maintain RAASi therapy whilst being treated with SZC, and the assumption of equal RAASi down-titration and discontinuation across both treatment arms should be considered conservative with respect to SZC.[3]

In TA599 the EAG's preferred approach to the proportion of patients discontinuing and down-titrating RAASi depended on two factors: RAASi dose (i.e., optimal, suboptimal) and S–K level.[3] Firstly, the proportion of patients discontinuing and down-titrating depends on whether the patient begins the cycle on optimal or

suboptimal RAASi. Patients receiving sub-optimal dose can only discontinue RAASi therapy, as they already receive a down-titrated dose versus optimal RAASi dose. Secondly, the proportion of patients on optimal RAASi that discontinue or down-titrate depends on their S–K levels (≥5.5-<6.0 mmol/L; ≥6.0 mmol/L) and whether they are treated with SZC. The current appraisal develops further on this approach, in that the proportion of patients discontinuing and down-titrating RAASi depends on the aforementioned factors (RAASi dose, S-K levels), plus SZC treatment status (see Table 38 of the company submission for the current appraisal). This addition is a result of the real-world evidence now available from the multi-national observational ZORA study, which provides different RAASi discontinuation rates for the same S–K levels, for people receiving SZC versus standard care in the real-world.[8]

Treatment arm data derived from the ZORA analysis included patients who initiated SZC but subsequently discontinued before the end of the study follow-up period, meaning that these data implicitly capture the impact of SZC discontinuation on RAASi discontinuation rates for a given S–K level. Clinicians will be less conservative with RAASi dose alteration if they know that SZC is an available treatment option for patient they foresee having potential S–K stability issues.[37] The main impact that this assumption has on the model is for discontinued patients in the SZC arm with S–K >5.5 mmol/L. However, these patients will also be eligible for retreatment and can reinitiate SZC, so regardless, applying treatment-related discontinuation and down-titration rates to the whole SZC cohort is anticipated to have a limited impact on the cost-effectiveness results.

B5. Priority question. At baseline, all company model patients are assumed to be receiving the optimal RAAS inhibitor dose. However, the current NICE recommendation (TA559) restricts the use of SZC in the NHS to patients who are not taking an optimised RAAS inhibitor dosage due to hyperkalaemia. Please update the company model to include a scenario where, at baseline, all patients receive a suboptimal RAAS inhibitor dosage, and this proportion can be varied by the user.

In the cost-effectiveness model for the current appraisal, all patients will initiate the model on optimal RAASi and are subsequently stratified as being either on optimal,

sub-optimal, or no RAASi therapy in the first cycle (day 1). This stratification is made in alignment with data from the ZORA analysis and is reflective of real-world clinical practice.[8, 9] This approach allows for patients who would otherwise be required to down-titrate or discontinue RAASi if SZC was not a treatment option to be captured in the analysis, as there is evidence that without SZC treatment, patients may already be on a suboptimal RAASi dose due to the elevated risk of triggering an HK event. Therefore, the assumption that all patients at baseline receive an optimal RAASi dose can be considered conservative with respect to SZC, as it is likely that a greater proportion of patients in the standard care arm would already have their RAASi dosage proactively down-titrated to avoid a potential HK event compared with the SZC arm.[3] As a partial review, the current appraisal adopted this approach as it was previously accepted by the EAG in TA599.[3] The SPARK dataset also demonstrates a relationship between increasing S–K levels and mortality, MACE, and hospitalisation, showing that the benefit of SZC goes beyond the ability for clinicians to effectively optimise RAASi therapy.[7] Therefore, this treatment benefit should be included in the analysis as it is reflective of the current evidence base, and previous NICE appraisals.

B6. Priority question. In the CS (Figure 14), after discontinuing a RAAS inhibitor, patients may return to their optimal RAAS inhibitor dosage but not a suboptimal RAAS inhibitor dosage. Clinical advice to the EAG is that patients re-initiating a RAAS inhibitor will start at a suboptimal dosage and up-titrate over time. Please update the company model so that patients re-initiate RAAS inhibitors at a suboptimal dosage and up-titrate over time.

There is a lack of data on patients reinitiating RAASi and the dosage they would receive on reinitiation. However, it could be reasonably assumed that a patient reinitiating RAASi whom is not in receipt of SZC would be reinitiated more cautiously than those reinitiating alongside/with SZC due to the increased risk of triggering an HK event. As such, all patients reinitiating on an optimal RAASi dose should be considered a conservative assumption with respect to SZC. The model used for decision making in TA599 assumed that patients may return to their optimal RAASi dosage but not a suboptimal dosage.[3] In the current partial review, the modelling of RAASi reinitiation in terms of the time to return to optimal RAASi dose and the

proportion of patients reinitiating in each cycle is reflective of the approach taken in TA599,[3] and the approach remains conservative.

B7. Priority question. In the company model, the probability of returning to the optimal RAAS inhibitor dosage in the maintenance setting is 49.7% in each cycle; this probability is assumed to be equivalent for all treatments and S-K groups. The proportion of patients who up-titrate or maintain a RAAS inhibitor dosage was estimated in the ZORA study by treatment and S-K group (CS, Table 24).

i. **Please justify why the probability of patients up-titrating (or maintaining) their RAAS inhibitor dosage was not estimated using ZORA study subgroup data (the approach used to estimate probabilities of down-titrating or discontinuing).**

ii. **Please update the company model to include a scenario where the probabilities of discontinuing/down-titrating/maintaining and up-titrating RAAS inhibitor dosages are all informed by ZORA study subgroup analysis results.**

The ZORA analysis examined the proportion of patients who will up-titrate, maintain, down-titrate and discontinue RAASi therapy, stratified by S–K level.[9] The proportions of patients down-titrating or discontinuing RAASi are directly included in the model, with the proportion maintaining therapy indirectly included as the remaining patients who have not altered RAASi dose. Patients up-titrating RAASi are therefore included in the model within the same group of patients who maintain RAASi therapy due to limitations with the modelling approach. At each S–K stratification, the ZORA analysis reports a higher proportion of patients up-titrating RAASi in the SZC arm compared to standard care, so including these patients in the proportion who will maintain the same RAASi dose should be considered conservative.

For the proportion of patients identified as up-titrating RAASi therapy in the ZORA analysis, it is not known if up-titration resulted in the patient achieving optimised treatment.[9] It is also unknown from this analysis what proportion of patients reinitiate RAASi therapy following discontinuation. Therefore, these inputs have been kept consistent with the committee preferred assumptions in TA599 and should be

considered conservative, as the ZORA analysis suggests that the proportion of patients up-titrating whilst on SZC should be higher when compared to standard care.[3, 9]

B8. Please clarify how the probability of maintaining/stabilising either an optimal or suboptimal RAAS inhibitor dosage is calculated in the company model.

In the model, patients are stratified by S–K level (<5.0 mmol/L, ≥5.0–<5.5 mmol/L, ≥5.5–<6.0 mmol/L, and ≥6.0 mmol/L) and optimised or sub-optimised RAASi dose. Patients are then modelled as either discontinuing or down-titrating RAASi therapy (down-titration is only an option for patients on optimised RAASi dose), in alignment with probabilities derived from the ZORA analysis.[9] Patients who do not down-titrate or discontinue therapy are implicitly modelled as maintaining their current RAASi dose. Coding for this can be found in the evaluateRAASiChange sub in the mod_simulation VBA module.

SZC

B9. Priority question. Please justify why re-treatment with SZC in the company model is not restricted to patients who are receiving a suboptimal RAAS inhibitor dosage.

Optimised RAASi dosing is essential for the effective management of patients with CKD and/or HF.[4-6, 44-46] However, it is well recognised that many patients with CKD and/or HF often do not receive optimal RAASi doses, primarily due to physician concerns about the risk of HK.[47-50] As a result, a considerable proportion of patients remain on suboptimal RAASi therapy.[47, 48, 51] SZC enables patients to maintain optimal RAASi dosing by effectively controlling HK,[41, 43, 52-57] and therefore should be available to patients receiving or eligible for optimal RAASi therapy. Without adequate management of HK with SZC, patients on optimal RAASi doses are likely to require dose modifications during their treatment,[47-50] which could unnecessarily compromise their health and overall outcomes.[49, 51, 58-64]

In the model for the current partial review, patients that have discontinued SZC can be retreated should S–K levels return to ≥5.5 mmol/L, upon which the patient S–K profile will follow the same trajectory as the initial treatment at day 0. Discontinuation and re-treatments can occur until the patient reaches an absorbing state such as

end-stage renal failure (commencing renal replacement therapy) and death. The independence of SZC retreatment from RAASi dosage is reflective of the approach taken in TA599.[3]

B10. Priority question. Please explain why, in the company model, when a patient discontinues SZC treatment, the patient's S-K level does not return to the level prior to starting SZC treatment.

In the company model, patients discontinuing treatment with SZC revert to the S–K profile of the standard care arm, meaning that they incur the same risk of increased S–K and HK events as a patient on standard care. There is no evidence to suggest that discontinuation of SZC would result in a return to the S–K level prior to initiating treatment. As such, reverting to the standard care S–K profile should be considered an appropriate manner to model the loss of protective effect associated with SZC discontinuation. Additionally, this is in line with feedback from clinical experts which suggests that once the cause of HK has been managed, a patient's S–K usually returns to the norm for that individual,[37] therefore suggesting that a return to the S–K level prior to initiating treatment would not be clinically expected.

In the original company submission (TA599), the model used for decision making assumed that the S–K profile for patients in the SZC arm reverts to the standard care profile should SZC be discontinued for any reason.[3] In the current partial review, the modelling of patient S–K levels following SZC treatment discontinuation is reflective of the approach taken in TA599.[3]

B11. In the company model, S-K values over time are estimated using mixed-effects regression models fit to ZS-004, ZS-005 and ZS-003 trial data. However, the maintenance phase of these trials only included patients who had achieved normokalaemia (3.5 ≤ S-K ≤ 5.0 mmol/L) by the end of the acute treatment phase. Please comment on how the absence of data from patients with hyperkalaemia affects the validity of the S-K estimates used in the maintenance phase of the company model.

In the original company submission for SZC (TA599), data from ZS-004 and ZS-005 were used to inform the model and the effectiveness of standard care in the correction phase was assumed equivalent to that of SZC; this potentially unfavourable assumption was made because open-label SZC was provided to all

patients in the correction phase in ZS-004 and ZS-005.[3] Following feedback from the EAG, data from the Phase III, multicentre, prospective double-blind, placebo-controlled ZS-003 study were used to model the standard care arm.[3]

In the economic model for the current appraisal, S–K trajectories for the standard care arm are modelled using only data from the acute phase of ZS-003, as patients receiving placebo in the acute phase were switched to SZC in the maintenance phase of the trial.[43] Therefore, no patients are excluded from the analysis based on the achievement of normokalaemia for the standard care arm. S–K trajectories for the SZC arm are modelled using data from both the acute and maintenance phases from ZS-004 and ZS-005, with patients not achieving normokalaemia excluded from the analysis.[41, 65] Across these two trials, only 1% of patients (12/1,009) did not progress to the maintenance phase of the study because of both hypokalaemia and HK.[41, 65] The impact that this has on the analysis is therefore very limited, and should not impact decision making.

Overall, the approaches for both the standard care and SZC arms are in line with the committee preferred assumptions from TA599,[3] and the impact on the ICER of the exclusion of patients not achieving normokalaemia in the SZC arm is anticipated to be minimal.

B12. The company model includes an annual probability of SZC discontinuation (37.5%), as observed in the ZS-005 trial. Please clarify whether this probability accounts for patients who discontinue SZC because RAAS inhibitors are no longer suitable (as per the NICE TA599 recommendation).

The annual probability of SZC discontinuation was taken from the proportion of patients discontinuing treatment in ZS-005 for any reason.[42] Details of the reasons for treatment discontinuation are provided in Table 7.[42]

Table 7: ZS-005 Extended Dosing Phase: Subject Disposition – All Subjects

Disposition	n (%)
SZC Treated	[redacted]
Completed Extended Dosing Phase	[redacted]
Discontinued Extended Dosing Phase	[redacted]
Adverse event	[redacted]
Consent withdrawn	[redacted]

Disposition	n (%)
Subject compliance	[redacted]
Investigator's decision	[redacted]
Sponsor's decision	[redacted]
Lost to follow-up	[redacted]
Protocol violation	[redacted]
Hypokalaemia	[redacted]
HK	[redacted]
Expected progression of chronic kidney disease requiring dialysis, transplant, or other treatment	[redacted]
Death	[redacted]
Met electrocardiogram withdrawal criteria	[redacted]
Other[a]	[redacted]

Footnotes: [a] Did not return for study visit (4 patients), subject incarcerated (3 patients), subject relocation (3 patients), did not take study drug (2 patients), site error (1 patient), initiated potassium chloride (1 patient), time constraints (1 patient), and follow-up activities associated with post total knee replacement (1 patient).
Source: ZS-005 clinical study report.[42]
Abbreviations: HK: hyperkalaemia; SZC: sodium zirconium cyclosilicate.

A number of reasons for discontinuation of SZC in the ZS-005 trial overlap with factors that would make a patient ineligible to receive RAAS inhibitors, for example progression of CKD and physician's clinical decision.[6, 66, 67] As such, the annual probability of SZC discontinuation used in the economic model (37.5%) should be considered to account for patients who discontinue SZC because RAASi therapy is no longer deemed suitable.

The SPARK dataset also demonstrates a relationship between increasing S–K levels and mortality, MACE, and hospitalisation, showing that the benefit of SZC goes beyond the ability for clinicians to effectively optimise RAASi therapy.[7] Therefore, patients may remain on SZC even if RAASi therapy is no longer suitable.

Costs

B13. Please explain why the mean annual cost of an emergency HK event is higher for patients receiving standard care than for patients receiving SZC (CS, Table 53).

The annual cost of an emergency HK event in both arms is calculated using a micro-costing approach, as detailed in Table 8. Based on clinical expert input, patients receiving standard care on average require an additional inpatient day and an additional round of insulin/dextrose that are not required for patients receiving SZC,[37]

therefore increasing the mean annual cost of an emergency HK event for patients receiving standard care compared with those receiving SZC.

Table 8: Annual cost of an emergency HK event micro-costing approach

Resource	Unit Cost	Source	Number Required	Cost		
			SZC	Standard Care	SZC	Standard Care
Inpatient day	£857.00	PSSRU 2023	2	3	£1,714.00	£2,571.00
Insulin	£7.48	BNF	1	2	£7.48	£14.96
Glucose	£0.99	BNF	2	2	£1.98	£1.98
Calcium gluconate	£1.04	eMIT 2023	2	2	£2.08	£2.08
Salbutamol	£0.96	eMIT 2023	2	2	£1.92	£1.92
Total cost					**£1,727.46**	**£2,591.94**

Abbreviations: BNF: British National Formulary; eMIT: electronic market information tool; HK: hyperkalaemia; PSSRU: personal social services research unit; SZC: sodium zirconium cyclosilicate.

B14 The annual costs associated with each CKD stage (CS, Table 58) are substantially different than those used in TA599. Please justify why a different source has been used for this appraisal.

In the original company submission for SZC (TA599), CKD time-in-state costs were derived from NICE CG182, published in July 2014.[68] The current partial review derived these costs from Kent et al. (2015).[69] A comparison of the costs from the two sources is provided in Table 9.

Costs from Kent et al. (2015) are more recent than those from NICE CG182 and were accepted in recent NICE appraisals in CKD, such as TA775 and TA937 which both incorporated annual costs associated with each CKD stage into their cost-effectiveness model based on Kent et al. (2015).[70, 71] As such, the costs associated with each CKD stage in the current appraisal were updated to align with recent precedent.

Table 9: CKD time-in-state costs from CG182 and Kent et al. (2015)

State	NICE CG182[68]		Kent et al. (2015)[69]	
	Annual cost (mean)	Annual cost (SE)	Annual cost (mean)	Annual cost (SE)
CKD stage 3a	£3,510.96	£351.10	£1,354.02	£59.04
CKD stage 3b	£3,510.96	£351.10	£1,354.02	£59.04
CKD stage 4	£3,510.96	£351.10	£4,741.00	£107.81
CKD stage 5 (pre-RRT)	£5,477.78	£547.78	£16,623.00	£237.43

Abbreviations: CG: clinical guideline; CKD: chronic kidney disease; NICE: National Institute for Health and Care Excellence; RRT: renal replacement therapy; SE: standard error.

Section C: Textual clarification and additional points

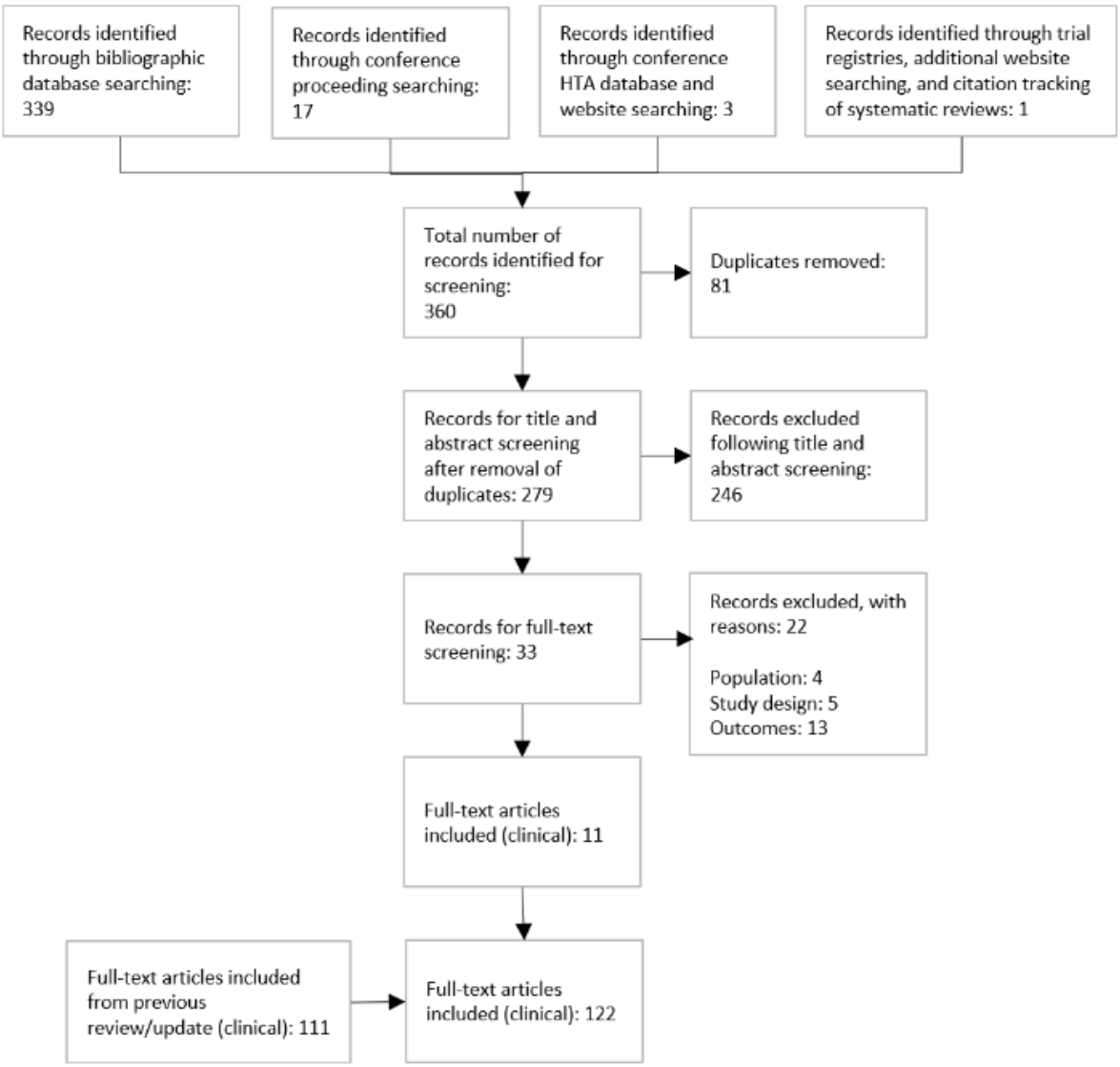
C1. Priority question. Please provide the document: AstraZeneca Data on File. RAASi Systematic Literature Review Report.

The requested file has been provided to the EAG.

C2. Please update the cost effectiveness and RAAS inhibitor literatures searches and highlight any new relevant studies that have been identified.

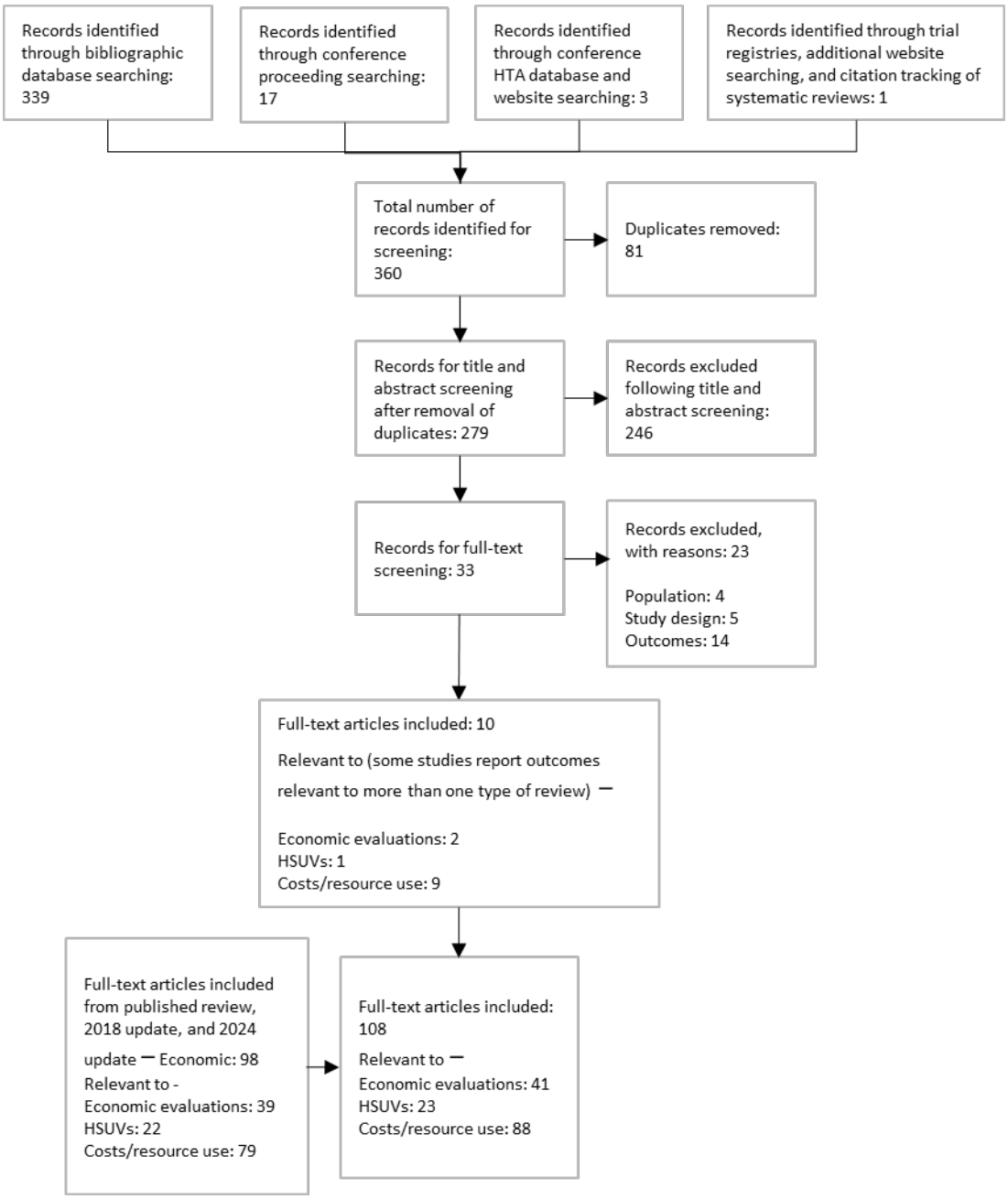
AstraZeneca have conducted an update to both the HTA and RAASi SLR. Searches for the RAASi and HTA SLR were carried out on 4th April 2025 and 8th April 2025, respectively. In the updated HTA SLR, 11 new clinical publications were included (Figure 8) and 10 new economic publications were included (Figure 9) relative to the 2024 SLR. In the updated RAASi SLR, 36 new publications were included relative to the 2024 SLR (Figure 10). The lists of included studies have been provided in "AstraZeneca DoF_Updated HTA SLR" and "AstraZeneca DoF_Updated RAASi SLR" for the updated HTA and RAASi SLR, respectively.

Figure 8: PRISMA diagram for the 2025 clinical SLR update



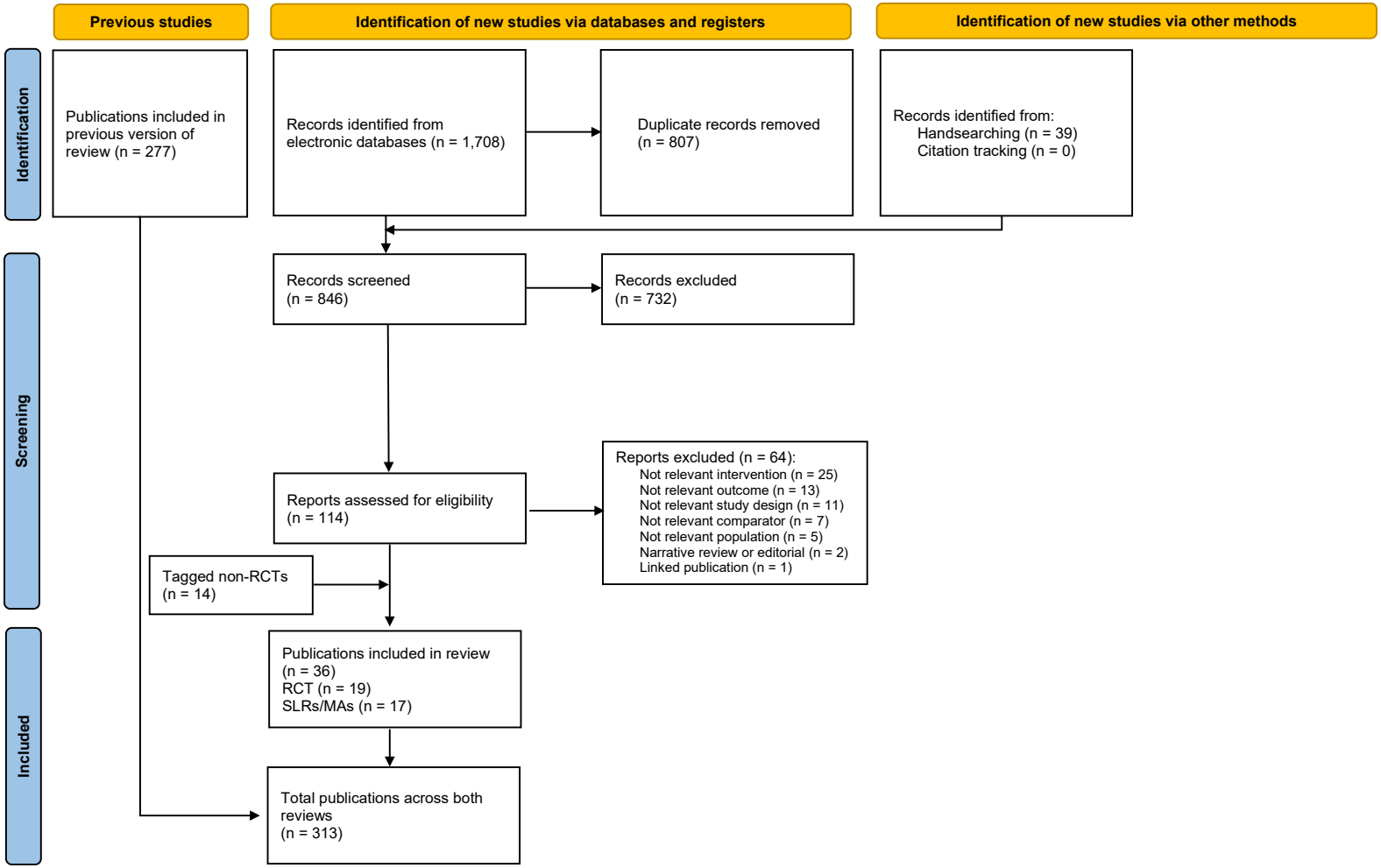
Abbreviations: HTA: health technology assessment; SLR: systematic literature review.

Figure 9: PRISMA diagram for the 2025 economic SLR update



Abbreviations: HTA: health technology assessment; HSUV: health state utility value; SLR: systematic literature review.

Figure 10: PRISMA diagram for the 2025 RAASi SLR update



Abbreviations: MA: meta-analysis; RAASi: renin-angiotensin-aldosterone system inhibitor; RCT: randomised controlled trial; SLR: systematic literature review.

C3. Please justify why a systematic literature review of the evidence relating to the association between S-K levels and clinical outcomes was not conducted.

An SLR of the primary evidence on the association between S–K levels and clinical outcomes was not conducted because the objective of evidence compilation was to identify high-quality, comprehensive summaries of the existing evidence base, rather than attempting to synthesise all available primary studies *de novo*. Pragmatic searches focused on identifying existing SLRs, as these reviews are designed to identify, appraise, and synthesise findings from relevant RCTs and observational studies, thereby providing a robust and efficient means of capturing the totality of available evidence. This approach was considered proportionate given the established nature of the relationship between S–K levels and adverse clinical outcomes, and the expectation that recent SLRs would adequately summarise and appraise the relevant data. Additionally, relevant RWE studies exploring the association between S–K levels and clinical outcomes were identified indirectly through the non-RCT RAASi SLR, which captured observational studies reporting on these associations in clinical practice.

C4. The CS reference pack appears to be incomplete. Please provide the complete reference pack.

The complete reference pack has been provided to the EAG.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Sodium zirconium cyclosilicate for treating hyperkalaemia (partial review of TA599) ID6439

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	UKKA
3. Job title or position	Consultant Nephrologist
4. Are you (please select Yes or No):	An employee or **representative** of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? **Yes** or No A specialist in the clinical evidence base for this condition or technology? **Yes** or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The UKKA was created through merger of the Renal Association, British Renal Society and its affiliates, to support the multi-professional team with delivery of kidney care, education and research – enabling people to live well with kidney disease. UKKA is funded by its members, grants, events, project work and capitation.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	£141,000 from AZ in 12 months- this is for sponsorship, grants and membership
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	N/A.

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To treat a potentially life-threatening electrolyte disorder – hyperkalaemia.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in serum potassium (K^+) level to ≤ 5.0 mmol/l.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Prior to the availability of sodium zirconium cyclosilicate (SZC) , the only oral option to treat hyperkalaemia was calcium resonium. Calcium resonium is poorly tolerated and efficacy unreliable. In reality, clinicians reduced or discontinued essential medications due to hyperkalaemia prior to availability of SZC.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Hyperkalaemia can occur in the context of acute illness or it can complicate management of chronic conditions (e.g. chronic kidney disease (CKD), diabetes or heart failure). **Acute hyperkalaemia** A multi-modal approach is used to treat acute hyperkalaemia. This includes treatment to protect the heart from

	arrhythmias (calcium gluconate) and drugs to lower the serum potassium (insulin-glucose infusion, nebulised salbutamol and an oral potassium binder). Dialysis is the most definitive strategy and may be required if unresponsive to medical management. Sodium zirconium cyclosilicate is now the potassium binder of choice in the setting of acute hyperkalaemia given its rate of onset of action (within 1 hour) and efficacy (1.1 mmol/l reduction at 48hrs in patients with a pre-treatment K^+ level of > 5.5 mmol/l). The UK Kidney Association (UKKA) Hyperkalaemia Guideline (2023) recommends sodium zirconium cyclosilicate for patients with moderate (K^+ 6.0-6.4 mmol/l) or severe (K^+ ≥6.5 mmol/l) hyperkalaemia in the acute setting. A threshold of K^+ ≥6.0 mmol/l for initiation is aimed to avoid further deterioration in acutely ill patients. Reference: 1. Alfonzo et al. UK Kidney Association Guideline: Management of Hyperkalaemia in Adults. Oct 2023. http://www.ukkidney.org **Chronic hyperkalaemia** Hyperkalaemia is a common occurrence in patients with CKD. It also complicates treatment with drugs that can raise the serum K^+ level (e.g. RAASi including ACE-inhibitors and angiotensin II antagonists; MRA drugs including spironolactone). RAASi drugs are critical for the management of patients with CKD, diabetes and heart disease. Prior to availability of sodium zirconium cyclosilicate, standard practice was to down-titrate or discontinue RAASi drugs due to hyperkalaemia risking in adverse outcomes. Several studies have demonstrated the benefits of utilising potassium binders to optimise RAASi therapy. Svensson et al (NDT 2024) recently conducted a study including > 27, 000 participants and demonstrated that patients who RAASi therapy were reduced after a hyperkalaemic episode had more hospitalization and fewer days alive out of hospital compared with those who were able to maintain RAASi therapy. Patients with CKD 3b-5 who are not receiving RAASi drugs are also at risk of hyperkalaemia, but have not been included in the NICE Guideline - TA599. Dietary modification, correcting acidosis and considering diuretics are the mainstay of managing mild to moderate hyperkalaemia in this group, but may not be sufficient. The REVOLUTIONIZE I Real-World Study demonstrated the risk of recurrent hyperkalaemia in over 2000 patients with CKD 3-4 after 'medical nutrition therapy' (Rowan et al, Adv Ther 2024). This study demonstrated 56% of patients had at ≥ 1 hyperkalaemia recurrence within one month. Hyperkalaemia-related hospitalisation occurred in 13.7% of patients and emergency department visits in 1.5% of patients. The authors concluded that dietary modifications may be insufficient in some patients and there may be a role for novel potassium binders to avoid recurrence. SZC has also been shown to have additional benefits in CKD patients as it helps to correct

	metabolic acidosis (Ortiz et al, Nefrologia 2023). Patients receiving haemodialysis are most at risk of hyperkalaemia. Adherence of dietary restrictions and dialysis regimen is the mainstay of management. Potassium binders can be helpful in selected patients at high risk of hyperkalaemia and bridge gaps in treatment (e.g.dialysis access problems, travel). Dialysis patients are currently excluded from NICE Guideline - TA599. References: 1. Svensson et L. Hyperkalaemia-related reduction of RAASi treatment associates with more subsequent inpatient care. Nephrol Dial Transplant 2024; 39: 1258-1267. 2. Rowan et al. Hyperkalaemia recurrence following medical nutrition therapy in patients with Stage 3-4 chronic kidney disease: The REVOLUTIONIZE I Real-World Study. Adv Ther 2024: 41: 2381-2398. 3. Ortiz et al. Consensus document on the management of hyperkalaemia. Nefrologia 2023. DOI: 10.1016/j.nefro.2023.05.004
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	**Acute hyperkalaemia** *UK Kidney Association Hyperkalaemia Guideline* (2023): recommends sodium zirconium cyclosilicate for patients with moderate (K^+ 6.0-6.4 mmol/l) or severe (K^+ ≥6.5mmol/l) hyperkalaemia in the acute setting in adults. *Regulation and Quality Improvement Authority* Guideline (2021): recommends sodium zirconium cyclosilicate for severe (K^+ ≥6.5mmol/l) hyperkalaemia or moderate (K^+ 6.0-6.4 mmol/l) with symptoms or ECG changes in hospitalised adults. *European Resuscitation Council guideline* (2021) – special circumstances (hyperkalaemia): recommends sodium zirconium cyclosilicate for patients with moderate (K^+ 6.0-6.4 mmol/l) or severe (K^+ ≥6.5mmol/l) HK in the acute setting in adults. **Chronic hyperkalaemia** *UK Kidney Association Hyperkalaemia Guideline* (2023) recommends sodium zirconium cyclosilicate for patients receiving RAASi drugs with persistent moderate (K^+ 6.0-6.4 mmol/l) who have CKD stage 3b-5 (not on dialysis) or heart failure. This is in keeping with current NICE guideline TA599.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your	Opinion based from Scotland experience. There is some variation in practice across the UK, but most Trusts have an agreed pathway modelled around the UKKA recommendations. Variations in clinical practice for use of sodium zirconium cyclosilicate include: Indications – Moderate HK (K^+ 6.0-6.4 mmol/l) in CKD patients not receiving RAASi drug, dialysis patients and

experience is from outside England.)	transplant patients. Threshold – Cardiologists tend to have lower threshold (K^+ 5.5-5.9 mmol/l) than nephrologists (K^+ ≥6.0 mmol/l). Community monitoring – Inconsistent acceptance of Primary Care for monitoring.
9c. What impact would the technology have on the current pathway of care?	The most significant impact of Sodium zirconium cyclosilicate is the optimisation of essential drugs to treat chronic conditions, e.g. CKD, heart failure, hypertension. SZC has not yet been fully optimised in clinical practice.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Mostly used in the same way, but a clear pathway for use of sodium zirconium cyclosilicate in a wider range of patient groups (e.g. CKD, dialysis, transplant, heart failure) would reduce variability in clinical practice.
10a. How does healthcare resource use differ between the technology and current care?	Current care already includes the use of sodium zirconium cyclosilicate in acute hyperkalaemia and for selected patients with chronic hyperkalaemia. Patients requiring longterm use of this therapy will require blood monitoring in Primary Care, but ultimately, this is a lower resource burden than hospital admission or attendances to the emergency department.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Acute Hyperkalaemia - Sodium zirconium cyclosilicate is already established for moderate and severe hyperkalaemia in the acute hospital setting. Management in community hospitals and Hospital@Home services are gray areas. These are often GP led services, but initiation in this setting could avoid transfer to acute hospital for management. Clear protocols should be developed to facilitate initiation of SZC in these settings. Chronic Hyperkalaemia - Sodium zirconium cyclosilicate should continue to be initiated in secondary care or specialist clinics and monitored in the community.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Experience of this technology is growing in secondary care, but is still lacking in Primary Care. Online education and training resources for this technology would be beneficial, easily accessible and improve collaborative working.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Definitely. Several studies have demonstrated the adverse outcomes to reduction or cessation of critical drugs for managing renal and heart disease as a consequence of hyperkalaemia. Optimising RAASi therapy can slow decline in renal function, improve heart failure symptoms and reduce hospitalisation. Extension of use of SZC in selected patients with CKD 3b-5 (not on RAASi drugs) and dialysis patients could

	reduce hospital admissions and increase patient safety.
11a. Do you expect the technology to increase length of life more than current care?	Potentially yes. SZC itself can control hyperkalaemia and reduce risk of cardiac arrhythmias, particularly in the acute setting. SZC also has an indirect benefit on life-expectancy by facilitating optimisation of essential drugs (e.g. RAASi drugs) to manage renal and heart disease.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Potentially yes. Reducing symptom burden from underlying chronic disease and hospitalisation would impact on quality of life significantly as SZC can allow optimisation of therapy.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with renal impairment would have the greatest benefit – CKD 3b-5 and potentially those on dialysis. In dialysis patients, SZC can control hyperkalaemia during periods when dialysis cannot be achieved (e.g. lack of vascular access). Renal impairment, diabetes and heart disease often co-exist. Patients with heart failure would also greatly benefit from SZC and the impact of SZC in optimising therapy can be measured with rate of hospital admission and survival. The benefit in patients with diabetes could be measured by rate of progression of diabetic nephropathy and BP control.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use	Acute setting – SZC will be easier and better tolerated for patients than previous standard of care (calcium resonium). There is no increase in workload for healthcare professionals. Clear communication with Primary Care is required if patient is discharged from hospital on this therapy to ensure regular blood monitoring and guidance on cessation of therapy. Chronic setting – SZC is well tolerated by patients and the need for blood monitoring is explained at the outset. There is no need for concomintant treatements (including laxatives). The main factor for patient acceptability is the risk of oedema.

or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes. This is outlined in the UKKA Hyperkalaemia Guideline (2023) as below, but practice may be variable across the UK. Serum potassium should be maintained ideally between 4.0 – 5.0 mmol/l. Threshold for initiation of SZC is 6.0 mmol/l in both the acute and chronic settings. In the acute setting, bloods are performed daily and SZC is usually only required short-term until hyperkalaemia is controlled. In the chronic setting, the UKKA guideline suggests bloods are performed weekly for the first 4 weeks, then monthly thereafter. The dose of SZC can be up or down titrated to achieve the target level.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The QALY calculation may not reflect the long-term benefits of sodium zirconium cyclosilicate for patients who are able to achieve optimisation of RAASi therapy. Elsisi et al (J Med Econ 2024) recently reported a cost-effectiveness analysis of SZC for hyperkalaemia in patients with CKD and heart failure. This study found that the cost saved from reduction in hyperkalaemic episodes, RAASi down-titration, major cardiovascular events and hospitalisation offset the cost of the drug. The incremental QALY of SZC ranged from 0.007 to 0.202. This technology is still fairly new, therefore the impact in the emergency setting may also not be reflected in the QALY calculation. The best surrogate marker would be a reduction in need for acute dialysis. There is already anecdotal evidence that this is the case (see below). Reference: 1. Elsisi et al. Cost-effectiveness analysis of sodium zirconium cyclosilicate for hyperkalaemia among patients with chronic kidney disease or heart failure in Kuwait. J med Econ 2024; 27: 253-265.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Sodium zirconium cyclosilicate has greatly enhanced the treatment of hyperkalaemia. Sodium zirconium cyclosilicate is proving to have a significant and substantive impact on clinical management – reducing need for urgent dialysis, more rapid and sustained control of hyperkalaemia, safe bridging in dialysis patients during periods without dialysis access. This technology was also crucial during the COVID pandemic in allowing dialysis schedules to be safely reduced to twice weekly. References: 1. Marshall et al. *Sodium zirconium cyclosilicate treatment and rates of emergency interventions for hyperkalaemia: a propensity-score weight case-control study*. Clin Kid J 2024; https://doi.org/10.1093/ckj/sfae313 2. Fujioka et al. *Sodium zirconium cyclosilicate hydrate reduces medical expenses compared with haemodialysis in patients*

	with acute hyperkalaemia. Renal Replacement Therapy 2023; https://doi.org/10.1186/s41100-023-00512-0
16a. Is the technology a 'step-change' in the management of the condition?	This technology is essentially a 'step-change' in the treatment of hyperkalaemia. Early use in the acute setting can enhance conventional treatments (insulin-glucose and salbutamol). Early use in the chronic setting can avoid disruption to RAASi therapy.
16b. Does the use of the technology address any particular unmet need of the patient population?	TA599 does not include use of this technology in patients with CKD 3b-5 who are not receiving RAASi drug or in dialysis patients. Ideally, the updated technology appraisal should provide guidance on use of sodium zirconium cyclosilicate in these groups of patients who are also at high risk for hyperkalaemia.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Sodium zirconium cyclosilicate is generally well tolerated and does not adversely impact significantly on quality of life. The main adverse effects are oedema (5.7%) and hypokalaemia (4.1%) as stated in the product information. Hypokalaemia requires a down-titration or cessation of the technology. Oedema may require drug cessation and consideration of an alternative therapy.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. The UKKA Guideline (2023) has reviewed the literature comprehensively and is a resource for guiding UK clinical practice. Unfortunately, there is still a paucity of evidence for use of Sodium zirconium cyclosilicate in the acute 'life-threatening' setting. A recent publication has compared SZC with Patiromer in the acute setting (Rydell et al, Ann Pharmather 2024) and reported equal efficacy. Reference: 1. Rydell et al. Effectiveness of Patiromer vs Sodium Zirconium Cyclosilicate for management of acute hyperkalaemia. Ann Pharmather 2024; 58: 790-795.
18a. If not, how could the results be extrapolated to the UK setting?	This technology is still relatively new, therefore the evidence-base is still evolving. Recent studies (Marshall et al and Fujioka et al) provide some evidence of impact of this technology in the acute setting – reduced need for emergency dialysis and more cost effective than dialysis.

	References: see above in Section 16
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes of clinical trials are: **Rate of onset of action** – studies were designed with an induction phase (first 48 hours) and demonstrated onset of action within 1 hour (ZS-002, ZS-003). **Efficacy** – There is evidence from double blind RCTs over a period ranging from 48hrs – 28 days (ZS-002, ZS-003 (Packman et al 2015), ZS-004, HARMONIZE-GLOBAL) and up to 52 weeks (ZS-004E, ZS-005). Sodium zirconium cyclosilicate lowers serum K by 1.1 mmol/; within 48 hours (ZS-004; Kosiborod 2014). There is also evidence that there is a greater K-lowering effect with increasing severity of HK (ZS-003 and ZS-004). **Ability of this technology to optimise RAASi therapy** – The OPTIMIZE study (2023) evaluated 589 patients and demonstrated that 77.4% achieved an optimal dose of RAASi. This included 7.8% of patients who were able to up-titrate RAASi therapy. At 1 year, 73.9% of patients who optimised RAASi were still on therapy. **Ability of this technology to optimise MRA therapy** – The REALIZE-K study (2024) evaluated 202 patients treated with spironolactone. This is the first trial to evaluate if SZC can enable safe optimisation of MRA therapy. **Tolerability** – generally well tolerated compared with calcium resonium. The main adverse effects are oedema (5.7%) and hypokalaemia (4.1%). References: 1. Astra Zeneca. Lokelma (sodium zirconium cyclosilicate) for oral suspension: Summary of Product Characteristics. 2018. www.ema.europa.eu/ema/ 2. Ash et al. 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 Int, 2015. 88: 404-11. 3. Packham et al. Sodium zirconium cyclosilicate in hyperkalemia. N Engl J Med, 2015. 372(3): p. 222-31. 4. Kosiborod et al. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. JAMA, 2014. 312: 2223-33. 5. Spinowitz et al. Sodium Zirconium Cyclosilicate among Individuals with Hyperkalemia: A 12- Month Phase 3 Study. Clin J Am Soc Nephrol, 2019. 14: 798-809. 6. Zannad et al. Efficacy and safety of sodium zirconium cyclosilicate for hyperkalaemia: the randomized, placebo-controlled HARMONIZE-Global study. ESC Heart Fail, 2020. 7: 54-64.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	RCTs were designed to predominantly demonstrate efficacy. The Cochrane review (Natale, 2020) included 15 studies (1849 participants) and noted that these studies were not designed to measure treatment effects on cardiac arrhythmias or major GI symptoms. There was no difference between SZC and placebo for cardiovascular death in CKD. There was also no evidence of a difference between

	potassium binders and placebo for HRQoL. Reference: 1. Natale et al. Potassium binders for chronic hyperkalaemia in people with chronic kidney disease. Cochrane Database Syst Rev 2020. doi: 10.1002/14651858.CD013165.pub2.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	SZC is generally well tolerated with GI upset, oedema and hypokalaemia identified as the main adverse effects in the RCTs. In a study by Kashihara et al (Clin Exp Nephrol 2021) investigating the long-term safety of SZC in Japanese population, constipation (6.7%), oedema (4%) and hypertension (2.7%) were the most common adverse effect. Hypertension was not noted as an adverse effect in the SPC drug information. Reference: 1. Kashihara et al. Correction of serum potassium with sodium zirconium cyclosilicate in Japanese patients with hyperkalaemia: a randomised, dose-response, phase 2/3 study. Clin Exp Nephrol 2020; 24: 1144-1153.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	In clinical practice, SZC is proving to be efficacious in the acute and chronic setting. XiaoJie et al (Cureus 2023) conducted a multi-centre audit of real-world experience of hyperkalaemia management using SZC in 293 haemodialysis patients. Indications included management of hyperkalaemia, prevention during disruption to dialysis or during travel. Significant reduction in K+ level and reduced mortality were reported. Agiro et al (Adv Ther 2023) conducted the OPTIMIZE I Study which investigated the real-world experience of optimisation of RAASi drugs using SZC in patients with hyperkalaemia. This included 589 patients and demonstrated that 73.9% of patients who optimized RAASi therapy were still on therapy at 1 year. This is consistent with clinical trials. This study also noted that predictors of RAASi optimisation included fewer prior hospitalizations and fewer prior emergency department attendances. References: 1. XiaoJie et al. A real-world experience of hyperkalaemia management using sodium zirconium cyclosilicate in chronic haemodialysis: a multicentre clinical audit. Cureus 2023; doi: 10.7759/cureus.45058. eCollection 2023 Sep. 2. Agiro et al. Real-world modifications of rennin-angiotensin-aldosterone system inhibitors in patients with hyperkalaemia initiating sodium zirconium cyclosilicate therapy: the OPTIMIZE I Study. Adv Ther 2023; 40: 2886-2901.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Studies have been conducted across wide geographic regions and included multiple ethnicities. I do not feel that there is any equality concerns.
21b. Consider whether these issues are different from issues with current care and why.	NA

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Sodium zirconium cyclosilicate (Lokelma) is proving to be invaluable in the acute setting, but a specific threshold for initiation should be stated in the updated NICE guideline. Moderate to severe hyperkalaemia in the acute setting should be considered to be potentially life-threatening, therefore a threshold of $K^+ \geq 6.0$ mmol/l is recommended. • A further sub-group of patients should be considered for the management of acute hyperkalaemia of moderate severity (K+ 6.0 – 6.4 mmol/l) in the setting of community hospitals and Hospital@Home. Protocols to administer sodium zirconium cyclosilicate could avoid need for transfer to the acute hospital. This will reduce hospital admissions and is a patient-centred approach. • The indications for use of Sodium zirconium cyclosilicate (Lokelma) in the chronic setting is currently narrow and does not include CKD 3b-5 not receiving RAASi drugs or dialysis patients. There are studies in these populations and in reality, some clinicians are using for selected patients. Formal guidance in these sub-groups would be welcomed. • Formal protocols for blood monitoring after initiation of Sodium zirconium cyclosilicate particularly in the chronic setting would be valuable. Clear and consistent guidance would support colleagues in Primary Care. • Educational tools (online) for Primary and Secondary care would be invaluable.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Sodium zirconium cyclosilicate for treating hyperkalaemia (partial review of TA599) [ID6439]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

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Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating hyperkalaemia and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Professor James Burton
2. Name of organisation	University of Leicester and Leicester Hospitals NHS Trust
3. Job title or position	Professor of Renal Medicine
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with hyperkalaemia? ☒ A specialist in the clinical evidence base for hyperkalaemia or technology? ☐ Other (please specify):
5. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
6. What is the main aim of treatment for hyperkalaemia? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	There are 2 main treatment aims, the management of hyperkalaemia in the acute setting (that is life threatening) where the goal is very simply to reduce potassium to a safe level and then the treatment in a more chronic setting (persistent and recurrent hyperkalaemia) where the aim would be to stabilise potassium levels and reduce variation in order to maintain guideline directed medical therapies for long term conditions such as chronic kidney disease (CKD) and heart failure.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A clinically significant response would be normokalemia. In this we need to consider what the definition of normokalemia would mean to the entire medical community not just to a renal specialist. Whilst there are differences in the definition of hyperkalemia within the literature, consensus workshops and statements have shown that the most widely accepted definition of hyperkalaemia is a potassium **above 5 mmol/L**. This is true for cardiological societies like the ESC (https://doi.org/10.1093/ehjcvp/pvy015) and the international renal guideline group KDIGO which also defines it as above 5mmol/L or the upper limit of normal.

	This does not mean that a potassium of 5.0-5.5 mmol/L needs immediate action but it speaks to the clinical importance of this condition to the medical and prescribing community as a whole, that hyperkalaemia is important and that the consequences can be severe. This is critically important as the consequence of this is that most clinicians do not optimise medical therapies in the face of hyperkalaemia. The newly updated heart failure guidance from NICE (NG106) still flags a potassium >5.5mmol/L as requiring a management change through local pathways. The BNF says of spironolactone for the management of heart failure and other conditions that it should be discontinued 'if hyperkalemia occurs' (https://bnf.nice.org.uk/drugs/spironolactone/), which for most clinicians will be a potassium above 5.5mmol/L and for specialist nursing colleagues and prescribing pharmacists, this could be a hard cut off. That means that medications that are core pillars for the management of heart failure and chronic kidney disease will almost certainly be discontinued before the potassium reaches 6 mmol/L and therefore the goal for treatment should be normokalaemia as defined by local laboratories and certainly a potassium level of <5.5mmol/L.
8. In your view, is there an unmet need for patients and healthcare professionals in hyperkalaemia?	Yes. The unmet need here is for patients. Patients who do not have their medical therapy optimised. For patients on optimised therapy who have their core, disease modifying medications discontinued or down-titrated (and then not re-instated or re-optimised) because of an episode of hyperkalaemia. Because the patients most at risk of clinical events and hospitalisations are those most at risk of hyperkalaemia. A study of over 4000 patients in Italy (doi:10.1007/s40620-021-01070-6) showed that appearance of hyperkalaemia results in discontinuation (21.8%) or sub-optimal (33.6%) management and an increased rate of CV events (45%) and death (126%) in RAASi adherent versus non-adherent patients. The unmet need for clinicians is broader access to medications (novel potassium binders including SZC) that will give confidence in the management of hyperkalaemia and therefore facilitate guideline directed medical therapy for more people with heart failure, CKD and diabetes. Waiting for the serum potassium to reach a laboratory value of 6.0 mmol/L is prohibitive in that clinical goal.
9. How is hyperkalaemia currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are	There are clinical guidelines for acute management. No the pathways are not clearly defined for chronic management: The UK Kidney Association has published guidance for the management of acute hyperkalaemia in adults, both in the community and hospital settings. Even this guidance acknowledges that the exact definition of hyperkalaemia can vary and also, this document is for the management of acute hyperkalaemia and not chronic management, which would be more appropriate in this case.

there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	However, there are algorithms for the management of hyperkalaemia in the community and hospital settings that are available to guide management. Note that in the case of mild hyperkalaemia, medicines review is advocated and in all cases, measures to prevent recurrent hyperkalaemia should be undertaken that includes the consideration of potassium binders (recommendations 11.1-11.3) *'particularly in the context of maintaining or optimising RAASi thera*py' (p55). We also need to consider in that the fact that a number of factors that cause hyperkalaemia are predictable but non-modifiable (heart failure, CKD and the need for certain medications like RAASi) and so this final recommendation is important. This review of TA599 would add clarity to pathways where there are contradictory guidance and information. It would enable clinicians across disciplines to optimise medical therapy for those with heart failure and CKD (especially those living with diabetes) without having to wait for a potassium to enter what would always be considered moderate to severe hyperkalaemia (>=6 mmol/L), which many would consider unsafe, and to do so without going against the cautions from publications such as the BNF.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Used in the same way but with a different threshold for clinical initiation. This technology should be available in primary and secondary care, although this should be through integrated working. That may be through specialist heart failure teams, integrated CKD / cardio-renal-metabolic clinics but should involve primary care clinicians within that. This fits exactly with the recommendations from the Lord Darzi report and the NHS 10-year plan of prevention and shifting that care from secondary into primary care. The investment would be education for clinicians around the change.
11. Do you expect the technology to provide clinically	Yes, there will be improvements compared to current care.

meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	OpenPrescribing data show, for example, that we have been the fastest ICB in England to implement guidance for the use of non-steroidal MRAs (finerenone) for people living with both diabetes and CKD at risk of progression (TA877). https://openprescribing.net/analyse/#org=stp&orgIds=QK1&numIds=0202030Y0&denom=total_list_size&selectedTab=chart Concurrently (and although only an association and with confounders of open source data) this maps to an increase in the prescription of SZC. Through integrated working between primary and secondary care (doi:10.1093/ckj/sfaf049) this technology will likely lead to improvement in the numbers of people treated with guideline directed medical therapy, with the associated improvements in clinical outcomes that will come alongside that. This includes improvements in quality of life that would be associated with optimal treatment of heart failure (less symptoms and hospitalisations) and CKD (less likely to progress to end stage disease requiring dialysis and with less symptom burden that comes with more advanced CKD).
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not to my knowledge.
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Not to my knowledge.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology?	In the event that hyperkalaemia is acute in nature and related to a cause that is reversible (e.g. an intercurrent illness like gastroenteritis), then there may be a reason to stop the SZC therapy after that short period. Otherwise it will likely be that the therapy will continue (see below). When initiating therapy, no additionally rules would apply once on a stable dose (this is the same as now).

Do these include any additional testing?	
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	I cannot think of additional benefits beyond those from the original appraisal.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition?	Given that this is a partial review of the previous published technology appraisal, I don't think that there is anything additional to be considered here, beyond the step change that will come from reducing the threshold at which it is recommended, mentioned above.

• Does the use of the technology address any particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	None that I am aware of.
18. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes and no. I think the UK experience is reflective of the trial data but the implementation is still lacking as the evidence is that people are not being treated to guideline directed therapies, that discontinuation and down titration is still common. The most important outcome is the initiation and maintenance of RAASi therapies (and other foundational therapies that can increase serum potassium in those at risk of hyperkalaemia). I accept that GDMT is a surrogate for hard clinical outcomes but there are data that support this strategy and these outcomes.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	None to my knowledge.

20. How do data on real-world experience compare with the trial data?	There is no evidence (to my knowledge) that the real world experience contradict the efficacy data from the clinical trials. If anything, they confirm the narrative that SZC enables and maintains guideline directed medical therapy for heart failure and CKD (See other boxes)
21. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on	None to my knowledge

people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	
22. The population described in the final scope is people with persistent hyperkalaemia and a serum potassium (S-K) level ≥5.5 to 6.0mmol/L and people with persistent hyperkalaemia who need dialysis. However, the company did not consider people with persistent hyperkalaemia who need haemodialysis in its submission. Clinical advice to the External Assessment Group (EAG) is that people with persistent hyperkalaemia (S-K level ≥5.5 to <6.0mmol/L) who have dialysis	I would not agree with this statement and know that the use of Lokelma is the haemodialysis population is common (although not routine) in patients with persistent hyperkalaemia. Higher pre-dialysis potassium and potassium variability are both associated with increased rates of mortality, the use of SZC has been shown to reduce both of these clinical issues by lowering pre-dialysis levels and stabilising the variability with less potassium spikes (DIALYZE study, DOI:10.1681/ASN.2019050450). The question becomes about the potassium threshold at which to prescribe. A cohort study of >1000 HD patients from the Netherlands showed that the risk of an increase in all cause mortality is only evident if the potassium level is >6.0mmol/L but, the variability can be important, even if the potassium is in the normal range (doi.org/10.1038/s41598-024-80709-3). For this reason, otherwise stable HD patients would usually be administered SZC with persistant hyperkalaemia with potassium >6.0mmol/L but for individuals in whom there are significant fluctuations in potassium (due to missed or foreshortened treatments, issues with dietary intake etc), this might be appropriate in people with potassium levels in the region of 5.5-6.0 mmol/L.

are unlikely to require treatment with a potassium binder. In clinical practice, is it appropriate to prescribe potassium binders to patients with persistent hyperkalaemia who require haemodialysis?	
23. The ZORA analyses used data from Japanese and US patients. Clinical advice to the EAG suggests that differences in baseline characteristics and healthcare systems between the UK, Japan, and the US may affect the generalisability of ZORA study re-analysis results to NHS patients. Therefore, the EAG considers the ZORA study does not generate robust evidence to demonstrates that treatment with SZC will increase the likelihood of optimal renin–Angiotensin–Aldosterone System inhibitor (RAASi) usage in the NHS population with persistent hyperkalaemia (S-K level ≥5.5 to 6mmol/L). **How applicable are the ZORA study findings to NHS practice in your view, given the differences in baseline**	I understand this point of view, external validity / generalisability of finding is crucial to applying data to different cohorts and settings. However, these 2 healthcare systems are themselves diverse with differences in the baseline demography and clinical characteristics between countries. That makes the findings more generalisable to other countries, not less so as despite these differences between populations and the data sources, significantly greater odds of maintaining RAASi therapy with SZC versus no binder treatment were consistently observed across the countries. In addition, the guidelines that are being applied here are the same, that is to say that there will not be variations in practice that might impact the likelihood of optimisation as goals of guideline directed medical therapy are the same. There may be some differences in system level barriers (these are not addressed by the authors of ZORA) but evidence from the published literature would suggest these barriers are similar: physician hesitation, lack of access to new therapies like potassium binders, co-ordinated care between clinical teams. I believe that the ZORA study findings would be applicable to NHS practice.

characteristics and healthcare systems?	
24. Are you aware of any evidence or study that assesses the relationship between treatment with sodium zirconium cyclosilicate (SZC) and the likelihood of optimal RAASi usage in people with persistent hyperkalaemia and a S-K level ≥5.5 to <6mmol/L?	Yes, there are real-world studies showing SZC is associated with better ability to keep patients on guideline-directed RAASi after a hyperkalaemia episode, but not that display data for persistent and with a potassium of 5.5-6.0 mmol/L potassium of ≥5.5 to <6.0 mmol/L. ZORA (see above for further reflections) looked into CKD/HF patients on RAASi who had a hyperkalaemia episode: those treated with SZC for ≥120 days were ~2.6× more likely to have maintained RAASi at 6 months than propensity-matched patients with no potassium binder (meta-analysed OR 2.56, 95% CI 1.92–3.41). This is the most direct evidence that SZC treatment is associated with optimal RAASi use after a hyperkalemia episode. OPTIMIZE I (DOI:10.1007/s12325-023-02518-w) – among 589 adults who initiated SZC while on RAASi, 77% had RAASi optimization (maintained dose or up-titrated) after starting SZC; at 1 year, 74% of those who optimized were still on RAASi vs 18% of those who didn't. Serum potassium thresholds weren't restricted to 5.5–<6.0 mmol/L but the findings support the hypothesis that SZC enables optimised RAASi. OPTIMIZE II (doi:10.1007/s12325-023-02631-w) continues the enablement narrative from OPTIMIZE I by demonstrating that in patients who had a hyperkalaemia episode while receiving RAASi, adding SZC (vs RAASi reduction without SZC) was associated with maintaining RAASi and lower short-term medical costs. Finally, REALIZE-K looked at the number of people with HFrEF who were maintained on guideline directed spironolactone therapy - continuing SZC substantially improved the ability to maintain normokalaemia and keep patients on ≥25 mg/day spironolactone (71% with SZC vs 36% with placebo, OR 4.45; 95% CI 2.89–6.86; p<0.001), reducing recurrent hyperkalaemia and down-titration/discontinuation of spironolactone.
25. The company assumed that patients treated with SZC are more likely to remain on an optimal RAASi dose regardless of S-K levels. Does this reflect what would be observed in clinical practice? Is the change in S-K level over time likely to have an impact on the	I am uncertain of this and I am not aware of any data to support either side of that argument. My personal reflection on this is that the likelihood of remaining on optimal dose remains related to the serum potassium level and not simply the presence or absence of a prescription for SZC. The causes and treatments of hyperkalaemia are multi-facted and although many of the causes are not easily modifiable, an optimal treatment strategy would still include other measures beyond the prescription of SZC alone. It is fair to say that the risk of hyperkalaemia will evolve over time, for example as CKD progresses, the risk would go up but this would trigger a dose titration of SZC, a dietary or other intervention rather than just assuming the individual would remain on optimal RAASi without another intervention (the DELPHI consensus piece recommends a thorough history to elicit other causes in this situation).

relationship between SZC and RAASi dose?	
26. If recommended, what would be the likely SZC treatment duration for patients with persistent hyperkalaemia (S-K ≥5.5 to <6.0mmol/L) in clinical practice? Is the use likely to be lifelong or for a period of time, if the latter, for how long?	In truth, most of the underlying causes of chronic / recurrent hyperkalaemia are not reversible (CKD, HF, Diabetes, the need for RAASi therapy) and as such, treatment is almost certainly going to be lifelong. Open label extensions and subsequent real world data have shown that when the SZC is discontinued, hyperkalaemia events re-occur and the risk of hospitalisation returns. Although these data only reach out as far as 12-months or so, the implication is that treatment will be lifelong.
27. In the company model patients having standard care do not have SZC if their S-K ≥6.0 mmol/L. The EAG notes only a small proportion of patients in the company base case would be eligible to receive SZC as average S-K values are assumed to remain constant over a patient's lifetime (from Day 4 onwards).The EAG notes that if average S-K values are expected to increase over time, it is plausible that a substantial proportion of patients would be eligible to receive SZC. **What is the expected lifetime S-K trajectory for patients having standard care in clinical practice? Would S-K values remain constant for most people with hyperkalaemia?**	I am not sure I understand this question. If S-K values increased and were impacting on patient safety and optimised therapy for CKD / heart failure then they would be eligible to receive SZC at per the NICE TA?

28. Are you aware of any evidence or studies that assess the relationship between changes in S-K level and outcomes including major adverse cardiovascular events, hospitalisation, and mortality in people with persistent HK (S-K ≥5.5 to <6.0mmol/L)?	RCTs show that novel potassium binders like Lokelma enable RAASi use rather than reducing mortality / MACE / hospitalisation outcomes directly. However, there are observational data to support the hypothesis that a serum potassium level in the 5.5-6.0mmol/L range is associated with worsening of these outcomes. UK data from almost 1m people collected from UK CPRD and HES data over 15 years (DOI:10.1093/ckj/sfab225) with one relevant condition (CKD including those on dialysis, resistant hypertension, diabetes or heart failure) and/or on RAASi therapy explored the impact of serum potassium levels and potassium variability, on clinical outcomes. They looked at thresholds above 5.0mmol/L, 5.5mmol/L and 6.0mmol/L (so conclusions can be drawn for the group in the range of 5.5-6.0mmol/L). This confirmed that people with diabetes, CKD and heart failure have higher rates of hyperkalaemia (predictable). Whilst the impact on risk of mortality in this range was uncertain, at all potassium thresholds, the risk of major adverse CV events for the overall cohort and patients with CKD, diabetes or resistant hypertension or prescribed RAASi increased rapidly with time spent in a hyperkalaemic state, at least initially. In the CKD Prognosis Consortium that included data from >1m people including UK cohorts (doi:10.1093/eurheartj/ehy100), the risk relationship between potassium and all-cause mortality demonstrated lowest risk with serum potassium levels between 4 mmol/L and 4.5 mmol/L and higher risk outside of the 3.5–5.0 mmol/L range. Compared with a reference of 4.2 mmol/L, the overall adjusted hazard ratio for all-cause mortality was 1.22 at serum potassium 5.5 mmol/L, i.e. a 22% increased risk for mortality. Risk relationships were similar for CV mortality and progression to end-stage kidney disease. Note these data are observational with no evidence that a reduction in serum potassium would reduce the risk of mortality and other events but do suggest a relationship. A recently published secondary analysis of data from the TOPCAT trial (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) looking at 'time in target range' defined as a serum potassium of 4.3-4.9mmol/L (August 2025; doi:10.1136/openhrt-2025-003439) showed that maintaining serum potassium levels within the therapeutic range of 4.3–4.9 mmol/L (i.e <5mmol/L) in patients with heart failure preserved ejection fraction was associated with a lower risk of CV events (MACE) or all-cause mortality. Again, this is a post-hoc analysis of historical data and not quite in the range of interest but relevant. Finally in the SPARK study (presented at UK Kidney Week 2025, manuscript under review), UK CPRD data from a base population of >4.5m people were interrogated to estimate the incidence and prevalence of hypekalaemia and to understand the relationship between serum potassium and clinical outcomes. >55k people had a serum potassium in the range of 5.5-6.0 mmol/L and for patients with either CKD or heart failure, the incident rate ratios for all-cause mortality for those with a serum potassium of 5.5-5.9 mmol/l was 1.51 (95% CI 1.46-1.55). The pattern was broadly similar for MACE, although at a lower magnitude with corresponding incident rate ratios of 1.10 (95% CI 1.06–1.14). For all-cause hospitalisation the ratio for the range 5.5-5.9mmol/L was 1.18 (95% CI 1.15–1.21). This was on a backdrop of increasing incidence and prevalence

	rates of hyperkalaemia in the UK, likely due to increasing evidence for guideline directed therapies in the heart failure and CKD landscape that can impact on potassium concentrations.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Incident and prevalent hyperkalaemia are becoming more common in the UK

Despite being predictable and treatable, hyperkalaemia is a major barrier to goal directed medical therapy in people with CKD and heart failure.

Current definitions of hyperkalaemia (supported by observational data) require management decisions when serum potassium is in the range of 5.5-6.0mmol/L

The current TA for SZC means that this is currently not a treatment option until the potassium exceeds 6.0mmol/L

This inevitably means that the current practice of stopping or down-titrating guideline directed therapy will continue, with negative outcomes for patients and the NHS.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Sodium zirconium cyclosilicate for treating hyperkalaemia (partial review of TA599) [ID6439]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Friday 12 September 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating hyperkalaemia and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Aaron Wong
2. Name of organisation	Princess of Wales Hospital, CTM University Health Board
3. Job title or position	Consultant Cardiologist and General Physician
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with hyperkalaemia? ☒ A specialist in the clinical evidence base for hyperkalaemia or technology? ☐ Other (please specify):
5. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No past or current, direct or indirect link with tobacco industry.
6. What is the main aim of treatment for hyperkalaemia? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Hyperkalemia can present either acutely or recurrently. It is commonly observed in patients with a history of heart failure, chronic kidney disease, diabetes, or those receiving renin-angiotensin-aldosterone system inhibitors (RAASi). The primary objective in the acute management of hyperkalemia is to mitigate the risk of potentially fatal arrhythmias. In contrast, for patients with recurrent hyperkalemia, the focus is on maintaining normal potassium levels while allowing continued use of RAASi therapies. These therapies, as recommended by international cardiac and renal guidelines, provide significant benefits in terms of reducing both mortality and morbidity.

7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A key goal in the treatment of hyperkalaemia is to maintain serum potassium within the normal range. While the strict physiological target is 3.5–5.0 mmol/L, in clinical practice it is often pragmatic to use the conventional laboratory reference range of 3.5–5.3 mmol/L as a guide for potassium management.
8. In your view, is there an unmet need for patients and healthcare professionals in hyperkalaemia?	Definitely. Healthcare professionals are generally familiar with the management of acute hyperkalaemia (HK), but the need to assess and manage the risk of recurrent HK is often underappreciated. HK frequently represents a barrier to initiating or optimising guideline-directed RAASi therapy, particularly in high-risk populations such as patients with heart failure, chronic kidney disease, or diabetes. Paradoxically, these high-risk patients—who are most susceptible to HK—also stand to gain the greatest benefit from RAASi therapy in terms of reducing cardiovascular and renal morbidity and mortality. This therapeutic dilemma highlights the importance of strategies to prevent recurrent HK, rather than solely treating acute episodes. There is a clear need to explore safe and effective options for the management of recurrent HK, including the use of oral potassium binders, to enable patients to achieve and maintain optimal RAASi therapy. By mitigating the risk of recurrent HK, such interventions can improve both patient outcomes and adherence to guideline-directed therapy, addressing a critical gap in the management of high-risk cardiovascular and renal patients.
9. How is hyperkalaemia currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	In the acute management of hyperkalemia, treatment protocols often vary locally, with common interventions including the use of insulin-dextrose infusions or nebulized β-agonists to drive potassium into cells, calcium gluconate to stabilize the cardiac membrane and reduce the risk of arrhythmias, bicarbonate to correct acidosis, and diuretics to eliminate potassium and manage fluid overload. In recent years, some hospitals have incorporated newer oral potassium binders such as SZC as part of the treatment regimen for acute hyperkalemia.

• What impact would the technology have on the current pathway of care?	However, the management pathway for recurrent hyperkalemia remains less well-defined across the NHS. In Wales, for instance, a clearly defined protocol for the management of recurrent hyperkalemia is lacking. Although newer potassium binders are recommended by international cardiology and renal guidelines for the treatment of recurrent hyperkalemia, particularly to facilitate the optimization of RAASi therapies, there is considerable inconsistency in approach across various health boards and hospitals. Consequently, many high-risk patients who present with hyperkalemia often experience reductions or discontinuations of their RAASi therapy, which may lead to adverse outcomes. This technology aims to streamline the management pathway by providing healthcare professionals with clearer treatment guidance and improved monitoring, ultimately ensuring more consistent and effective care for patients with recurrent hyperkalemia.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	This technology has potential applications across both primary and secondary care, given that hyperkalaemia (HK) is encountered in patients managed in the community as well as in hospital settings. Improved access to oral potassium binders may reduce the need for hospitalisation by enabling earlier intervention in the community. In addition, effective outpatient potassium control can facilitate the continuation and optimisation of guideline-directed RAASi therapy, which is often compromised when HK develops. For successful implementation, healthcare professionals (HCPs) will require additional training. This should include guidance on appropriate initiation of oral potassium binders, adjustment of dosing regimens, and the recommended frequency of serum potassium monitoring. Education across different specialties—cardiology, nephrology, endocrinology, and primary care—will be essential to ensure consistent practice and maximise the clinical benefits of this therapy.

	In this way, oral potassium binders can support both patient safety and system efficiency by preventing avoidable admissions, preserving the use of life-prolonging RAASi therapies, and providing a practical tool for managing a common and high-risk electrolyte disorder across the continuum of care.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	RAASi therapies have long been a cornerstone of treatment for patients with heart failure and chronic kidney disease (CKD). Previous clinical trials have consistently demonstrated the significant impact of these therapies on both mortality and morbidity, including symptom improvement, reduced hospitalization rates, and enhanced cardiac function. Furthermore, higher doses of RAASi have been associated with better patient outcomes, with guidelines recommending up-titration to the highest tolerable dose to maximize benefit. However, hyperkalemia (HK) is a common barrier to the optimization of RAASi therapy, as elevated potassium levels often necessitate dose reductions or discontinuations of these medications. In this context, the use of well-tolerated oral potassium binders can serve as an important enabler. By effectively managing hyperkalemia, these binders allow patients to maintain or even increase their RAASi doses, ensuring that they receive the full benefit of guideline-directed therapies without the risk of exacerbating potassium imbalances.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients who need RAASi treatment (those with heart failure, CKD, hypertension).
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient	This technology provides healthcare professionals (HCPs) with clear guidance on indications for hyperkalaemia (HK) treatment, while allowing clinical judgment regarding the optimal timing of therapy based on each patient's medical history, current clinical status, and willingness to engage with ongoing treatment and monitoring. By standardising treatment criteria,

acceptability or ease of use or additional tests or monitoring needed)	the technology can help streamline the management of this common and potentially high-risk electrolyte disorder. Once patients are established on a stable dose of an oral potassium binder alongside RAASi therapy, additional monitoring may not be routinely required, unless there is a significant change in clinical status or medication dosing. This approach supports efficient, safe, and patient-centred care, reducing unnecessary interventions while maintaining potassium within a safe range to allow continued optimisation of guideline-directed RAASi therapy. .
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The primary indication for initiating treatment of hyperkalaemia (HK) is the presence of elevated serum potassium. Assessment of the risk for recurrent HK should be conducted to inform a plan for ongoing management of both HK and RAASi therapy. Beyond the standard monitoring required for HK and RAASi optimisation, additional potassium testing is generally not necessary unless there are changes in the patient's clinical status or treatment regimen.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The use of potassium binders as RAASi enablers allows patients to derive the full benefits of RAASi therapy, as demonstrated in clinical trials. Patients maintained on optimal RAASi doses experience improved quality of life, reduced hospitalisations, and lower mortality. By controlling serum potassium, potassium binders are also expected to reduce both the frequency and severity of hospital admissions due to hyperkalaemia. Traditionally, patients with recurrent hyperkalemia have been advised to follow a low-potassium diet, which often conflicts with recommended healthy dietary practices. The use of potassium binders allows patients greater flexibility and reduces the need for strict dietary restrictions. Optimising RAASi therapy may further contribute to recovery of cardiac function, potentially reducing the need for costly device-based interventions such as cardiac resynchronisation therapy (CRT) and implantable defibrillators, as well as advanced heart failure management strategies, including left ventricular assist devices and heart transplantation. By enabling effective RAASi therapy and preventing hyperkalaemia-related

	complications, potassium binders have the potential to improve patient outcomes while also reducing overall healthcare costs.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	This technology offers patients with hyperkalaemia (HK) who require RAASi therapy the opportunity to optimise their guideline-directed treatment in line with international heart failure and CKD recommendations, potentially translating into the health-related benefits previously described. Serum potassium levels are strongly correlated with adverse outcomes, and risk begins to rise progressively once potassium exceeds 5.5 mmol/L. In clinical practice, RAASi therapy is often down titrated or discontinued when potassium levels exceed this threshold. Patients with potassium levels between 5.5–5.9 mmol/L have very little "safety buffer." Minor changes in fluid status, dehydration, or other factors that impair renal function can quickly push potassium into a dangerous range, increasing the risk of severe HK and associated complications. This technology represents a step-change in the management of HK. It enables timely access to treatment, mitigates the risk of severe hyperkalaemia, and facilitates ongoing optimisation of RAASi therapy in patients with heart failure and HK. By maintaining safe potassium levels, it supports both patient safety and the long-term benefits of life-saving guideline-directed therapies.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	New oral potassium binders are generally well tolerated, as demonstrated in both clinical trials and real-world studies. These agents act locally in the gastrointestinal tract by binding potassium in exchange for hydrogen and sodium, with minimal systemic absorption. Heart failure therapies, particularly RAASi and MRAs, have a profound impact on patients' quality of life, which has been assessed using functional measures such as the six-minute walk test and validated patient-reported tools like the Kansas City Cardiomyopathy Questionnaire (KCCQ). By enabling patients to remain on optimised heart failure therapies through

	effective potassium control, potassium binders have the potential to improve both functional capacity and overall quality of life. REALIZE-K trial reported that SZC use was associated with a higher likelihood of maintaining patients on spironolactone (at least 25 mg daily) without requiring rescue therapy for hyperkalaemia. Exploratory endpoints indicated a numerical increase in oedema and heart failure events in the SZC arm. However, the trial was relatively small (approximately 100 patients per arm) and baseline imbalances were noted: patients in the SZC group were older, had higher NT-proBNP levels, poorer renal function, and greater use of loop diuretics. These baseline differences were hypothesised to account for the higher incidence of oedema and heart failure in the SZC group. From my own real-world clinical experience, I have not observed concerning safety signals with SZC use in patients with advanced heart failure and chronic kidney disease who are receiving RAASi therapy.
18. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Clinical trials with sodium zirconium cyclosilicate (SZC) have demonstrated its efficacy in controlling serum potassium levels for up to one year, while allowing patients to continue renin–angiotensin–aldosterone system inhibitor (RAASi) therapy. Trial protocols generally initiated SZC when potassium levels exceeded 5.0 mmol/L. In contrast, UK clinical practice typically does not initiate treatment for hyperkalaemia until potassium levels rise above 5.5 mmol/L, particularly in patients receiving RAASi. The usual approach in such cases is to down-titrate or discontinue guideline-directed medical therapy (GDMT) with RAASi agents. The most clinically relevant outcome from SZC trials is its ability to maintain potassium control without significant disturbances in other electrolytes or renal function, alongside good overall tolerability. REALIZE-K trial reported that SZC use was associated with a higher likelihood of maintaining patients on spironolactone (at least 25 mg daily)

	without requiring rescue therapy for hyperkalaemia. Exploratory endpoints indicated a numerical increase in oedema and heart failure events in the SZC arm. However, the trial was relatively small (approximately 100 patients per arm) and baseline imbalances were noted: patients in the SZC group were older, had higher NT-proBNP levels, poorer renal function, and greater use of loop diuretics. These differences were hypothesised to account for the higher incidence of oedema and heart failure in the SZC group. From my own real-world clinical experience, I have not observed concerning safety signals with SZC use in patients with advanced heart failure and chronic kidney disease who are receiving RAASi therapy.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	I am not aware.
20. How do data on real-world experience compare with the trial data?	The real-world experience/ evidence has shown that SZC is effective in controlling K level to enable patients to be optimised on RAASi. Patients of SZC are more likely to maintain RAASi and have their dosing optimised. Tolerability is good. Our real-world data also showed lower than average hospitalisation for HF and mortality for those who were optimised. As per my response on Q18, I am not aware of any safety signals from real world experience and evidence to date.
21. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.	I do not foresee any potential equality issues.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	
22. The population described in the final scope is people with persistent hyperkalaemia and a serum potassium (S-K) level ≥5.5 to 6.0mmol/L and people with persistent hyperkalaemia who need dialysis. However, the company did not consider people with persistent hyperkalaemia who need haemodialysis in its submission. Clinical advice to the External Assessment Group (EAG) is that people with persistent hyperkalaemia (S-K level ≥5.5 to <6.0mmol/L) who have dialysis are unlikely to require treatment with a potassium binder. In clinical practice,	I am not a nephrologist, but I would like to share my perspective. The term "patients who need dialysis" can be interpreted in two ways: (1) those with advanced chronic kidney disease (CKD) who are approaching dialysis initiation and often experience hyperkalaemia (HK), and (2) those who are already receiving dialysis. For the first group, many patients remain on RAASi therapy for its renal and cardiovascular protective effects. The UK-based STOP-ACEi trial demonstrated that patients with advanced CKD who continued ACEi therapy had a reduced risk of cardiovascular events, with no significant difference in progression to dialysis compared with those who discontinued ACEi once GFR declined to a certain threshold. This group is at particularly high risk of

is it appropriate to prescribe potassium binders to patients with persistent hyperkalaemia who require haemodialysis?	hyperkalaemia, often with serum potassium levels in the range of 5.5–6.0 mmol/L. However, they continue to derive cardiovascular benefit from RAASi therapy. In such cases, potassium binders may be useful by lowering potassium into the 5.0–5.5 mmol/L range, thereby creating a "buffer." This buffer reduces the likelihood of potassium exceeding 6.0 mmol/L during fluctuations in clinical or fluid status, which could otherwise precipitate hospitalisation and need for emergency/urgent dialysis. For patients who are already established on dialysis, our nephrology colleagues reported using SZC during the COVID-19 pandemic to help control potassium levels and, in some cases, to reduce the frequency of dialysis sessions.
23. The ZORA analyses used data from Japanese and US patients. Clinical advice to the EAG suggests that differences in baseline characteristics and healthcare systems between the UK, Japan, and the US may affect the generalisability of ZORA study re-analysis results to NHS patients. Therefore, the EAG considers the ZORA study does not generate robust evidence to demonstrates that treatment with SZC will increase the likelihood of optimal renin–Angiotensin–Aldosterone System inhibitor (RAASi) usage in the NHS population with persistent hyperkalaemia (S-K level ≥5.5 to 6mmol/L). **How applicable are the ZORA study findings to NHS practice in your view, given the differences in baseline characteristics and healthcare systems?**	The ZORA study is a global real-world evidence programme that identified patients with chronic kidney disease (CKD), diabetes, and heart failure (HF) from the USA, Spain, and Japan who were receiving RAASi therapy and experienced an episode of hyperkalaemia. I do not consider this patient cohort to be substantially different from those commonly encountered within the NHS in the UK. There are several reasons for this view. Firstly, patients enrolled in large-scale heart failure trials frequently originate from these same regions, and the resulting evidence has informed the development of international guidelines, which are then adopted and implemented across healthcare systems, including the NHS. Secondly, the baseline characteristics reported in ZORA—namely age, prevalence of CKD, diabetes, heart failure, use of RAASi therapy, and the degree of hyperkalaemia observed—appear broadly consistent with the clinical profiles of patients managed in UK practice. From a pragmatic standpoint, the external validity of ZORA is therefore highly relevant to the NHS context. The similarities in patient demographics and comorbidities support the extrapolation of its findings to our own healthcare setting. Moreover, given that guideline-directed therapies and thresholds for intervention are comparable across these countries, it is reasonable to view the ZORA data as both applicable and informative for UK

	clinicians when considering strategies to optimise RAASi use in patients at risk of hyperkalaemia.
24. Are you aware of any evidence or study that assesses the relationship between treatment with sodium zirconium cyclosilicate (SZC) and the likelihood of optimal RAASi usage in people with persistent hyperkalaemia and a S-K level ≥5.5 to <6mmol/L?	The REALIZE-K trial (Study to Assess Efficacy and Safety of SZC for the Management of High Potassium in Patients With Symptomatic HFrEF Receiving Spironolactone) was a prospective, double-blind, randomised withdrawal study evaluating the role of sodium zirconium cyclosilicate (SZC) in patients with symptomatic HFrEF (NYHA class II–IV, left ventricular ejection fraction ≤40%). All participants were on optimal guideline-directed therapy with the exception of mineralocorticoid receptor antagonists (MRAs), and had either prevalent or incident MRA-induced hyperkalaemia (HK). Normal potassium was defined as 3.5–5.0 mmol/L. The trial included two cohorts: Cohort 1 (patients with established HK): SZC was initiated to normalise serum potassium. Once normokalaemia was achieved, spironolactone was introduced and titrated up to 50 mg daily (as recommended by cardiology guidelines), with SZC adjusted as needed to maintain potassium in the normal range. Cohort 2 (patients at risk of HK): During the run-in period, spironolactone was initiated. Patients who developed HK were treated with SZC (similar to Cohort 1), and spironolactone was titrated with SZC onboard to maintain normokalaemia. Patients who did not develop HK during the run-in were excluded prior to randomisation. The study demonstrated that patients with HFrEF and HK treated with SZC were four times more likely to remain on at least 25 mg of spironolactone without the need for rescue therapy for hyperkalaemia, compared with placebo. This trial provides important clinical evidence that SZC not only corrects hyperkalaemia but also enables the safe initiation and maintenance of MRA therapy—an agent known to provide substantial morbidity and mortality

	benefits in HFrEF, but frequently underutilised due to potassium-related concerns. Serum potassium should be viewed as a continuous variable rather than interpreted only through strict cut-off thresholds. This perspective is clinically important, as even modest elevations can provide meaningful information for guiding treatment decisions, particularly when optimizing guideline-directed RAASi therapy. Patients with serum potassium levels in the range of 5.5–6.0 mmol/L often represent a high-risk group—typically those with progressive heart failure or chronic kidney disease—who may otherwise face RAASi dose reduction or discontinuation. In such cases, careful management of potassium is essential to balance the risks of hyperkalemia against the proven benefits of maintaining RAASi therapy.
25. The company assumed that patients treated with SZC are more likely to remain on an optimal RAASi dose regardless of S-K levels. Does this reflect what would be observed in clinical practice? Is the change in S-K level over time likely to have an impact on the relationship between SZC and RAASi dose?	Hyperkalaemia (HK) remains one of the key barriers to the optimisation of RAASi therapy. This is consistently observed in routine clinical practice and has been confirmed in international surveys. For example, a recent survey conducted by the Heart Failure Association of the ESC and the ESC Council for Cardiology Practice highlighted that the occurrence of HK frequently leads to physicians down-titrating or discontinuing RAASi therapy, despite the recognised prognostic benefits of these agents (Eur J Heart Fail. 2024;26(6):1408–1418). Evidence from both clinical trials and real-world studies supports the role of sodium zirconium cyclosilicate (SZC) in addressing this challenge. Randomised controlled trials such as HARMONIZE and REALIZE-K, together with large-scale real-world evidence from studies like ZORA and registry data, have consistently demonstrated that SZC effectively maintains potassium within target ranges. This, in turn, enables the initiation, continuation, and optimisation of RAASi therapy in patients with heart failure and/or CKD who would otherwise be at risk of treatment reduction or discontinuation due to HK. Importantly, patients receiving SZC alongside RAASi are significantly less likely to have their guideline-directed medical therapy (GDMT) down-titrated or withdrawn. By providing a reliable strategy to manage potassium, SZC

	therefore addresses one of the most important barriers to achieving optimal RAASi dosing, ultimately supporting improved cardiovascular and renal outcomes.
26. If recommended, what would be the likely SZC treatment duration for patients with persistent hyperkalaemia (S-K ≥5.5 to <6.0mmol/L) in clinical practice? Is the use likely to be lifelong or for a period of time, if the latter, for how long?	The duration of potassium binder therapy should be guided by several key clinical considerations. First, it is important to assess whether the risk of hyperkalaemia (HK) is modifiable—for example, through optimisation of concomitant medications, dietary adjustments, or stabilisation of underlying comorbidities. Second, the ongoing need for RAASi therapy must be evaluated, as these agents remain cornerstone treatments in both heart failure (HF) and chronic kidney disease (CKD), yet are also a major contributor to HK risk. Third, the patient's overall clinical status, including renal and cardiac function, must be taken into account, alongside any changes in disease trajectory or underlying pathophysiology. Given these variables, the duration of sodium zirconium cyclosilicate (SZC) therapy should be individualised. For some patients, short-term treatment may suffice—for example, to correct an acute episode of HK or to provide a temporary safety buffer during clinical instability. For others, particularly those with progressive CKD or advanced HF who require long-term RAASi therapy, ongoing treatment with SZC may be necessary to sustain potassium control and ensure optimisation of guideline-directed medical therapy. Ultimately, the decision should balance the dynamic risk of recurrent HK against the benefits of uninterrupted RAASi therapy, recognising that prolonged or indefinite use of SZC may be appropriate in selected high-risk patients to maintain both safety and therapeutic efficacy.
27. In the company model patients having standard care do not have SZC if their S-K ≥6.0 mmol/L. The EAG notes only a small proportion of patients in the company base case would be eligible to receive SZC as average S-K values are assumed to remain constant over a patient's lifetime (from Day 4	The presentation of hyperkalaemia (HK) is often a direct reflection of a patient's underlying comorbidities—such as heart failure, chronic kidney disease (CKD), and diabetes—as well as the intensity of RAASi therapy, since higher doses are associated with an increased risk of HK. In this

onwards).The EAG notes that if average S-K values are expected to increase over time, it is plausible that a substantial proportion of patients would be eligible to receive SZC. **What is the expected lifetime S-K trajectory for patients having standard care in clinical practice? Would S-K values remain constant for most people with hyperkalaemia?**	sense, an episode of HK frequently serves as a clinical marker, signalling that the patient is at particularly high risk. Unless the underlying disease processes can be reversed or stabilised, the likelihood of recurrent or worsening HK typically increases over time, particularly in patients with progressive CKD. This creates a therapeutic paradox: those at the greatest risk of HK—namely patients with heart failure and CKD—are also the very patients who derive the greatest benefit from continuing RAASi therapy. By reducing cardiovascular and renal disease progression, RAASi agents not only improve outcomes but may also attenuate the very trajectory that contributes to recurrent HK. In other words, the patients most vulnerable to HK are simultaneously those who stand to gain the most from maintaining or even optimising RAASi therapy. This highlighted the importance of effective potassium management strategies, as they provide a pathway to preserve the life-prolonging and disease-modifying benefits of RAASi in the populations that need them most.
28. Are you aware of any evidence or studies that assess the relationship between changes in S-K level and outcomes including major adverse cardiovascular events, hospitalisation, and mortality in people with persistent HK (S-K ≥5.5 to <6.0mmol/L)?	Serum potassium demonstrates a U-shaped association with clinical outcomes, where both hypokalaemia and hyperkalaemia are linked to increased morbidity and mortality. The risk of adverse events begins to rise significantly once potassium exceeds 5.5 mmol/L. Importantly, potassium should be considered a continuous variable rather than a categorical threshold, as even modest increases above the normal range carry prognostic significance. Patients with serum potassium between 5.5–6.0 mmol/L often represent a particularly high-risk group. This range is frequently seen in individuals with progressive heart failure (HF) or chronic kidney disease (CKD), or in those at risk of having their life-saving RAASi therapy reduced or discontinued due to concerns over recurrent hyperkalaemia. This creates a therapeutic dilemma: the very patients who are most prone to HK are also those who benefit most from continued RAASi therapy. Several studies have shown the prognostic implications of hyperkalaemia and the consequences of RAASi withdrawal. Xu et al. (Am Heart J.

	2022;243:83–93) demonstrated that while discontinuation of RAASi after an episode of hyperkalaemia was associated with a lower risk of HK recurrence, it was also linked to a higher risk of death and cardiovascular events. Similarly, Rossignol et al. (Eur J Heart Fail. 2020;22:1378–1389) highlighted the strong association between hyperkalaemia, mortality risk, and the critical importance of maintaining RAASi therapy to improve outcomes. Together, these findings emphasise the dual role of hyperkalaemia as both a marker of disease progression and a modifiable barrier to optimal therapy. Effective potassium management strategies are therefore essential, not only to reduce the immediate risks associated with elevated potassium but also to safeguard the long-term benefits of RAASi in patients with HF and CKD.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Hyperkalaemia is a frequent barrier to RAASi optimisation in patients with heart failure (HF) and chronic kidney disease (CKD). It is associated with increased hospitalisations and with RAASi down-titration or discontinuation.
- Sodium zirconium cyclosilicate (SZC) can effectively control potassium, enabling patients with HF and CKD to maintain optimal RAASi dosing without the need for rescue therapy. Optimising RAASi in this population improves clinical outcomes.
- Lowering the treatment threshold for SZC to 5.5–6.0 mmol/L would provide high-risk patients with greater protection against hyperkalaemia, facilitating sustained RAASi use and leading to better symptom control and long-term outcomes.

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EAG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Sodium zirconium cyclosilicate for treating hyperkalaemia (partial review of TA599) [ID6439]

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LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

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Sunil Bhandari	Clinical advice and critical appraisal of the clinical evidence

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LIST OF ABBREVIATIONS

AE	Adverse event
CHF	Congestive heart failure
CI	Confidence interval
CKD	Chronic kidney disease
CSR	Clinical study report
eGFR	Estimated glomerular filtration rate
GEE	Generalised estimating equations
HES	Hospital episode statistics
HF	Heart failure
HK	Hyperkalaemia
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
IRR	Incidence rate ratio
ITT	Intent-to-treat
KDIGO	Kidney Disease: Improving Global Outcomes
LS	Least-squares
MedDRA	Medical Dictionary of Regulatory Activities
NHS	National Health Service
ONS	Office for National Statistics
PS	Propensity score
PSS	Personal Social Services
QALY	Quality adjusted life year
QoL	Quality of life
RAASi	Renin-angiotensin-aldosterone system inhibitor
RR	Relative risk
RWE	Real-world evidence
SD	Standard deviation
SE	Standard error
SGLT-2	Sodium-glucose cotransporter 2
S-K	Serum potassium
SMD	Standardised mean difference
SZC	Sodium zirconium cyclosilicate
TRAE	Treatment-related adverse event
UKKA	UK Kidney Association

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making.

Section 1.1 provides an overview of the key issues identified by the EAG. Section 1.2 provides an overview of key modelling assumptions that have the greatest effect on the incremental cost effectiveness ratio (ICER) per quality adjusted life year (QALY) gained. Sections 1.3 to 1.5 explain the key issues identified by the EAG in more detail. Key cost effectiveness results are presented in Section 1.2.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of EAG's key issues

Table A Summary of EAG's key issues

Issue	Summary of issue	Report sections
Issue 1	Consideration of patients with persistent HK who require haemodialysis	2.5.8
Issue 2	SPARK study results do not provide robust evidence to confirm the association between persistent HK and adverse outcomes	3.4
Issue 3	ZORA study results may not be generalisable to NHS patients	3.5
Issue 4	Impact of SZC on RAASi use	6.2
Issue 5	SZC treatment duration	6.3
Issue 6	Standard care: SZC treatment if S-K ≥6.0mmol/L	6.4
Issue 7	Relationship between S-K and adverse outcomes	6.5
Issue 8	Generalisability of RAASi model algorithm to NHS	6.7
Issue 9	CKD health state costs	6.8

CKD=chronic kidney disease; HK=hyperkalaemia; RAASi=renin-angiotensin-aldosterone system inhibitor; S-K=serum potassium; SZC=sodium zirconium cyclosilicate

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a QALY. An ICER per QALY gained is the ratio of the extra cost for every QALY gained.

The company model generates cost effectiveness results for the comparison of SZC versus standard care. The EAG revisions that have the biggest effect on company costs and QALYs are:

- setting the probabilities of RAASi down-titration or discontinuation for each S-K group equivalent by treatment using either SZC values or standard care values
- using a lifetime SZC treatment duration

- applying CKD health state costs used in TA599 (NICE CG182)

The EAG also explored the impact on costs and QALYs of the following change:

- assuming S-K level has no effect on the risk of MACE, hospitalisation or mortality

1.3 The decision problem: summary of the EAG's key issues

Issue 1 Consideration of patients with persistent HK who require haemodialysis

Report section	2.5.8
Description of issue and why the EAG has identified it as important	In the final scope issued by NICE, the description of the population includes people with persistent HK who require dialysis. The company has not provided clinical effectiveness evidence to support treating this group of patients with SZC. However, the company considers that restricting access to SZC based on insufficient data to demonstrate cost effectiveness, after having previously allowed access via emergency COVID-19 Rapid Guideline: Dialysis Service Delivery (NG160), would result in inequitable access across the full group of people for whom SZC has a UK marketing authorisation. Clinical advice to the EAG is that in NHS clinical practice patients with persistent HK who require haemodialysis are not generally prescribed potassium binders as dialysis effectively removes excess potassium from the blood.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	NA
What additional evidence or analyses might help to resolve this key issue?	Seek clinical advice on whether it is appropriate to prescribe potassium binders to patients with persistent H-K who require haemodialysis.

EAG=External Assessment Group; HK=hyperkalaemia; NG=NICE Guidelines; NICE=National Institute for Health and Care Excellence; SZC=sodium zirconium cyclosilicate

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 2 SPARK study results do not provide robust evidence to confirm the association between persistent HK and adverse outcomes

Report section	3.4
Description of issue and why the EAG has identified it as important	The SPARK study does not provide robust evidence to confirm the association between persistent HK (S-K level ≥5.5 to 6.0mmol/L) and MACE and mortality outcomes; evidence from James 2021 shows that the relationship is complicated and persistent HK (S-K level ≥5.0 or ≥5.5mmol/L) may be protective against mortality
What alternative approach has the EAG suggested?	See cost effectiveness **Error! Not a valid result for table.**
What is the expected effect on the cost effectiveness estimates?	
What additional evidence or analyses might help to resolve this key issue?	Using SPARK study data, carry out an analysis that uses time spent with persistent HK (for different S-K groups) as an independent variable

EAG=External Assessment Group; HK=hyperkalaemia; MACE=major adverse cardiovascular events; S-K=serum potassium; SZC=sodium zirconium cyclosilicate

Issue 3 ZORA study results may not be generalisable to NHS patients

Report section	3.5
Description of issue and why the EAG has identified it as important	The ZORA analyses used data from Japanese and US patients. Clinical advice to the EAG is that differences in the baseline characteristics of UK, Japan and US patients may affect the generalisability of ZORA study re-analysis results to NHS patients. The differences between healthcare systems in the three countries may also affect generalisability. The EAG therefore considers that the ZORA study does not generate robust evidence to demonstrates that treatment with SZC will increase the likelihood of optimal RAASi usage in the NHS population with persistent HK (S-K level ≥5.5 to 6mmol/L).
What alternative approach has the EAG suggested?	See cost effectiveness Issue 4
What is the expected effect on the cost effectiveness estimates?	
What additional evidence or analyses might help to resolve this key issue?	The EAG is unaware of any analyses that could be carried out in the short-term to resolve this uncertainty.

EAG=External Assessment Group; HK=hyperkalaemia; RAASi=renin-angiotensin-aldosterone system inhibitor; S-K=serum potassium; SZC=sodium zirconium cyclosilicate

1.5 The cost effectiveness evidence: summary of the EAG's key issues

Issue 4 Impact of SZC on RAASi use

Report section	6.2
Description of issue and why the EAG has identified it as important	1. The company has assumed that patients treated with SZC are more likely to remain on an optimal RAASi dose independent of S-K levels. This is not supported by the ZORA study re-analysis as S-K groups were defined using S-K at baseline; no adjustment was made to account for S-K changes over the follow-up period. 2. Patients in the ZORA study re-analysis remained on SZC treatment for longer in relative terms than patients in the company base case analysis. Applying SZC-specific probabilities to patients who have discontinued SZC is likely to overestimate the benefit of SZC on RAASi use.
What alternative approach has the EAG suggested?	The probabilities of RAASi down-titration or discontinuation for each S-K group are set equivalent by treatment using either a) SZC values or b) standard care values
What is the expected effect on the cost effectiveness estimates?	When using SZC values, the deterministic ICER per QALY gained increases to: i) £25,972 (an increase of £9,139) for the CKD population ii) £12,059 (an increase of £3,006) for the HF population When using standard care values, the deterministic ICER per QALY gained increases to: i) £34,551 (an increase of £17,718) for the CKD population ii) £15,569 (an increase of £6,516) for the HF population
What additional evidence or analyses might help to resolve this key issue?	An analysis of the ZORA study that accounts for changes in S-K over the follow-up period and clinical expert input as to whether SZC would be expected to impact RAASi use after accounting for changes in S-K.

CKD=chronic kidney disease; HF=heart failure; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; QALY=quality-adjusted life year; RAASi=renin-angiotensin-aldosterone system inhibitor; S-K=serum-potassium; SZC=sodium zirconium cyclosilicate

Issue 5 SZC treatment duration

Report section	6.3
Description of issue and why the EAG has identified it as important	The company have assumed that all patients still receiving SZC at 12 weeks discontinue treatment; SZC is only reinitiated (for 12 weeks) if a patient's S-K ≥5.5mmol/L. Clinical advice to the EAG is that most patients with persistent HK would not discontinue treatment with SZC as on discontinuation S-K would likely increase to the level prior to SZC treatment initiation for these patients.
What alternative approach has the EAG suggested?	Assumed a lifetime SZC treatment duration.
What is the expected effect on the cost effectiveness estimates?	The deterministic ICER per QALY gained increases to: i) £28,333 (an increase of £11,500) for the CKD population ii) £13,892 (an increase of £4,839) for the HF population
What additional evidence or analyses might help to resolve this key issue?	Seek clinical opinion on the likely SZC treatment duration for patients with persistent HK (S-K ≥5.5 to <6.0mmol/L).

EAG=External Assessment Group; HK=hyperkalaemia; ICER=incremental cost effectiveness ratio; QALY=quality-adjusted life year; S-K=serum-potassium; SZC=sodium zirconium cyclosilicate

Issue 6 Standard care: SZC treatment if S-K ≥6.0 mmol/L

Report section	6.4
Description of issue and why the EAG has identified it as important	In the company model patients receiving standard care do not receive SZC if their S-K ≥6.0 mmol/L. Only a small proportion of patients in the company base case would be eligible to receive SZC as average S-K values are assumed to remain constant over a patient's lifetime (from Day 4 onwards). If average S-K values are expected to increase over time, it is plausible that a substantial proportion of patients would be eligible to receive SZC.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost effectiveness estimates?	The impact on cost effectiveness results is uncertain as it is not known how many patients may be eligible to receive SZC over the model time horizon.
What additional evidence or analyses might help to resolve this key issue?	Clinical expert input as to the expected lifetime S-K trajectory for patients receiving standard care and model scenarios that include the possibility of SZC treatment for patients receiving standard care.

EAG=External Assessment Group; S-K=serum-potassium; SZC=sodium zirconium cyclosilicate

Issue 7 Relationship between S-K and adverse outcomes

Report section	6.5
Description of issue and why the EAG has identified it as important	If the SPARK study does not provide reliable information on how reducing S-K in patients with persistent HK (S-K ≥5.5 to <6.0mmol/L) impacts on MACE, hospitalisation and mortality, the SPARK data should not be used in the company model
What alternative approach has the EAG suggested?	In an explanatory scenario, S-K level is assumed to have no effect on the risk of MACE, hospitalisations and mortality (S-K group IRRs set equal to one).
What is the expected effect on the cost effectiveness estimates?	The company base case deterministic ICER per QALY gained: i) decreases to £16,832 for the CKD population ii) increases to £9,712 for the HF population
What additional evidence or analyses might help to resolve this key issue?	None.

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; IRRs=incidence rate ratios; MACE=major adverse cardiac event; QALY=quality-adjusted life year; RAASi=renin-angiotensin-aldosterone system inhibitor; S-K=serum-potassium

Issue 8 Generalisability of RAASi model algorithm to NHS

Report section	6.7
Description of issue and why the EAG has identified it as important	The EAG considers that two aspects of the company's approach to modelling RAASi use do not reflect what would happen in current clinical practice: i) Baseline RAASi use: at the start of the model all patients are assumed to be receiving maximum RAASi dosages. However, some patients eligible for SZC in the NHS will be receiving suboptimal RAASi dosages. ii) Up-titration: after RAASi discontinuation, patients can only return to the maximum RAASi dosage. Clinical advice to the EAG is that patients reinitiate RAASi at suboptimal dosages and up-titrate over time. The company model is likely to overestimate the proportion of patients and/or length of time patients spend receiving maximum RAASi dosages.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	Uncertain
What additional evidence or analyses might help to resolve this key issue?	Model scenarios that incorporate the features described above.

EAG=External Assessment Group; RAASi=renin-angiotensin-aldosterone system inhibitor; SZC=sodium zirconium cyclosilicate

Issue 9 CKD health state costs

Report section	6.8
Description of issue and why the EAG has identified it as important	The company applied annual CKD health state costs from the Kent (2015) study in the cost effectiveness model. In the Kent (2015) study, 28% of patients with CKD stage 4 and 79% of patients with CKD stage 5 (not receiving dialysis) at baseline went on to receive RRT by the end of the study period. Since patients exit the model on initiation of RRT, using estimates from the Kent (2015) study will overestimate the cost associated with CKD progression (up to but not including RRT)
What alternative approach has the EAG suggested?	Apply the health state costs used in TA599 (sourced from NICE CG182)
What is the expected effect on the cost effectiveness estimates?	The deterministic ICER per QALY gained for the CKD population increases to £20,089 (an increase of £3,256)
What additional evidence or analyses might help to resolve this key issue?	None.

CG=clinical guidelines; CKD=chronic kidney disease; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; QALY=quality-adjusted life year; RRT=renal replacement therapy

1.6 Summary of EAG's exploratory ICERs per QALY gained

Summary deterministic cost effectiveness results for the comparison of SZC versus standard care are presented in Table B (CKD population), Table C (HF population) and Table D (mixed CKD and HF population). For further details of the revisions carried out by the EAG, see Section 6.9.

Table B Deterministic cost effectiveness results for CKD population

Scenario/EAG revisions	Incremental		ICER (£/QALY)	Change from A1
	Cost	QALYs		
A1. Company base case	**£4,572**	**0.272**	**£16,833**	**-**
R1a) Probabilities of RAASi down-titration/discontinuation for each S-K group equivalent by treatment: SZC values	£3,335	0.128	£25,972	£9,139
R1b) Probabilities of RAASi down-titration/discontinuation for each S-K group equivalent by treatment: standard care values	£2,816	0.082	£34,551	£17,718
R2) Lifetime SZC treatment duration	£11,494	0.406	£28,333	£11,500
R3) Probability of up-titration informed by ZORA study subgroup analysis	£3,723	0.217	£17,131	£298
R4) Eligible to return to “max” RAASi state 4 weeks after discontinuation/down-titration	£4,668	0.280	£16,654	-£179
R5) CKD health state costs informed by NICE CG182	£5,456	0.272	£20,089	£3,256
S1) S-K has no effect on the risk of MACE, hospitalisation or mortality	£4,077	0.242	£16,832	-£1
B1. EAG exploratory base case (R1a, R2-R5)	**£9,984**	**0.236**	**£42,351**	**£25,518**
B2. EAG exploratory base case (R1b, R2-R5)	**£8,382**	**0.133**	**£63,010**	**£46,177**
C1. B1+S1	**£9,678**	**0.185**	**£52,254**	**£35,421**
C2. B2+S1	**£8,056**	**0.085**	**£94,676**	**£77,843**

CG=clinical guideline; CKD=chronic kidney disease; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; MACE=major adverse cardiovascular event; QALY=quality adjusted life year; RAASi=renin–angiotensin–aldosterone system inhibitors; S-K=serum potassium

Table C Deterministic cost effectiveness results for HF population

Scenario/EAG revisions	Incremental		ICER (£/QALY)	Change from A1
	Cost	QALYs		
A1. Company base case	**£6,506**	**0.719**	**£9,053**	**-**
R1a) Probabilities of RAASi down-titration/discontinuation for each S-K group equivalent by treatment: SZC values	£4,339	0.360	£12,059	£3,006
R1b) Probabilities of RAASi down-titration/discontinuation for each S-K group equivalent by treatment: standard care values	£3,360	0.216	£15,569	£6,516
R2) Lifetime SZC treatment duration	£15,260	1.099	£13,892	£4,839
R3) Probability of up-titration informed by ZORA study subgroup analysis	£5,133	0.524	£9,799	£746
R4) Eligible to return to “max” RAASi state 4 weeks after discontinuation/down-titration	£6,539	0.727	£8,993	-£60
S1) S-K has no effect on the risk of MACE, hospitalisation or mortality	£5,936	0.611	£9,712	£659
B1. EAG exploratory base case (R1a, R2-R4)	**£11,717**	**0.607**	**£19,290**	**£10,237**
B2. EAG exploratory base case (R1b, R2-R4)	**£9,463**	**0.331**	**£28,618**	**£19,565**
C1. B1+S1	**£11,283**	**0.460**	**£24,545**	**£15,492**
C2. B2+S1	**£9,140**	**0.211**	**£43,360**	**£34,307**

CG=clinical guideline; EAG=External Assessment Group; HF=heart failure; ICER=incremental cost effectiveness ratio; MACE=major adverse cardiovascular event; QALYs=quality adjusted life year; RAASi=renin–angiotensin–aldosterone system inhibitors; S-K=serum potassium; SZC=sodium zirconium cyclosilicate

Table D Deterministic cost effectiveness results for mixed CKD and HF population

Scenario/EAG revisions	Incremental		ICER (£/QALY)	Change from A1
	Cost	QALYs		
A1. Company base case	**£5,312**	**0.425**	**£12,495**	**-**
R1a) Probabilities of RAASi down-titration/discontinuation for each S-K group equivalent by treatment: SZC values	£3,824	0.208	£18,391	£5,895
R1b) Probabilities of RAASi down-titration/discontinuation for each S-K group equivalent by treatment: standard care values	£3,292	0.129	£25,529	£13,034
R2) Lifetime SZC treatment duration	£13,252	0.641	£20,689	£8,193
R3) Probability of up-titration informed by ZORA study subgroup analysis	£4,352	0.321	£13,546	£1,050
R4) Eligible to return to “max” RAASi state 4 weeks after discontinuation/down-titration	£5,316	0.430	£12,365	-£130
R5) CKD health state costs informed by NICE CG182	£6,142	0.425	£14,446	£1,951
S1) S-K has no effect on the risk of MACE, hospitalisation or mortality	£4,837	0.375	£12,884	£389
B1. EAG exploratory base case (R1a, R2-R5)	**£11,423**	**0.358**	**£31,898**	**£19,403**
B2. EAG exploratory base case (R1b, R2-R5)	**£9,637**	**0.198**	**£48,641**	**£36,146**
C1. B1+S1	**£11,123**	**0.285**	**£39,012**	**£26,517**
C2. B2+S1	**£9,300**	**0.127**	**£73,033**	**£60,538**

CG=clinical guideline; CKD=chronic kidney disease; EAG=External Assessment Group; HF=heart failure; ICER=incremental cost effectiveness ratio; MACE=major adverse cardiac event; QALY=quality adjusted life year; RAASi=renin–angiotensin–aldosterone system inhibitor; S-K=serum potassium; SZC=sodium zirconium cyclosilicate

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The focus of this appraisal is on sodium zirconium cyclosilicate (SZC, Lokelma®) for the first-line treatment of persistent hyperkalaemia (HK) and a serum potassium (S-K) level ≥5.5 to <6.0mmol/L; this appraisal is a partial review of National Institute for Health and Care Excellence (NICE) Technology Appraisal TA599.[1]

Within this External Assessment Group (EAG) report, references to the company submission (CS) are to the company's Document B, which is the company's full evidence submission. Additional information was provided by the company in response to the clarification letter.

2.2 Background

The clinical and cost effectiveness of SZC as a treatment for HK for people with chronic kidney disease (CKD) or heart failure (HF) was originally assessed by a NICE Appraisal Committee (AC) in 2019 (TA599[1]). During TA599,[1] the clinical effectiveness of SZC for this population was established based on clinical effectiveness results from the following sodium zirconium cyclosilicate (ZS) trials: ZS-002,[2] ZS-003,[3-5] ZS-004,[6-8] ZS-004E[9] (extension of ZS-004) and ZS-005.[10-12] A concise company overview of the ZS trials is provided in the CS (CS, Table 5 to Table 9).

The NICE TA599[1] guidance was issued in 2019 and updated in January 2022; the current NICE recommendation[13] is provided in Box 1.

Box 2 NICE recommendation for SZC as a treatment for patients with hyperkalaemia[1]

- Sodium zirconium cyclosilicate is recommended as an option for treating hyperkalaemia in adults only if used:
  - in emergency care for acute life-threatening hyperkalaemia alongside standard care or
  - for people with persistent hyperkalaemia and chronic kidney disease Stage 3b to 5 or heart failure, if they:
    - have a confirmed serum potassium level of at least 6.0mmol/L and
    - because of hyperkalaemia, are not taking an optimised dosage of renin-angiotensin-aldosterone system inhibitor and
    - are not on dialysis. [amended 2022]
- Stop sodium zirconium cyclosilicate if RAAS inhibitors are no longer suitable. [amended 2022]

Source: NICE TA599[1] recommendation

In 2019, the NICE AC, was unable to recommend SZC as a treatment option for patients with CKD or HF who had a confirmed S-K level ≥5.5 to <6mmol/L; the main areas of uncertainty identified by the NICE AC were (CS, p18):

1. there was a paucity of clinical data linking S-K levels and long-term clinical outcomes (major adverse cardiac event [MACE], mortality and hospitalisations)
2. clinical evidence did not adequately demonstrate that SZC usage allowed reinitiation, up-titration or maintenance of optimum renin–angiotensin–aldosterone system inhibitors (RAASi) dosage
3. clinical evidence did not adequately demonstrate the relationship between RAASi dosage and long-term clinical outcomes

To address uncertainties 1 and 2, the company carried out two real-world evidence (RWE) studies: the SPARK[14] study and a re-analysis of the ZORA[15] study (primary ZORA study results were published in 2024[16]). To address uncertainty 3, the company conducted a systematic literature review (SLR). Data from these studies are presented in the CS and have been used to update the company model and generate cost effectiveness results for the population with S-K level ≥5.5 to <6.0mmol/L.

2.3 Overview of current service provision

HK refers to an abnormally high level of potassium in the blood. The European Resuscitation Council[17] classifies HK as mild (serum potassium level of 5.5 to 5.9mmol/L), moderate (6.0 to 6.4mmol/L) or severe (≥6.5mmol/L); clinical advice to the EAG is that, typically, the normal range is 3.5 to 5.5mmol/L. In UK clinical practice, patients with HK may have either an emergency (acute) HK event or persistent HK.[18] The focus of this appraisal is the population with persistent HK. There is no generally agreed definition of persistent HK; however, the UK Kidney Association[18] guidelines advise that repetitive consecutive measures of serum potassium are needed to determine if HK is a sustained or a transient event.

People with underlying cardiorenal conditions, such as CKD and HF, as well as older adults, are at increased risk of developing HK; this is primarily due to declining renal function and reduced capacity to renally excrete potassium.[19-21] Due to their proven benefits in reducing disease progression and improving clinical outcomes, RAASi therapy is the cornerstone of CKD and HF[22-29] management. However, RAASi therapy can further increase S-K levels by reducing renal excretion of potassium and may lead to HK. Since 2019, international clinical guidelines[23,24,30] have increasingly emphasised the importance of maintaining an optimised RAASi dose to preserve therapeutic benefits. To minimise the need to down-titrate or discontinue RAASi therapy in the presence of persistent HK, clinical guidelines[23,24,30] recommend potassium-binding agents as the preferred management strategy. SZC and patiromer are two potassium binders currently recommended by NICE[1,31] Patiromer was

recommended by NICE[31] in 2020; the NICE patiromer recommendation reflects the NICE SZC recommendation for patients with hyperkalaemia (Box 1).

2.4 Sodium zirconium cyclosilicate

Information relevant to SZC is presented in the CS (CS, Table 2). Briefly, SZC has a UK marketing authorisation for the treatment of HK in adult patients.[32] The marketing authorisation was granted in 2018 and revised in 2020 to include treatment of patients receiving chronic haemodialysis. SZC is a non-absorbed, non-polymer inorganic powder with a uniform micropore structure that preferentially captures potassium ions in exchange for hydrogen and sodium cations (CS, Table 2). It is available in 5g and 10g sachets and is administered orally as a water-based suspension. There are two phases of treatment:

- **Correction phase**: The recommended starting dose of SZC is 10g, administered orally three times a day as a suspension in water. When normokalaemia is achieved, the maintenance regimen should be followed.
- **Maintenance phase**: When normokalaemia has been achieved, the minimal effective dose of SZC to prevent recurrence of HK should be established. A starting dose of 5g once daily is recommended, with possible titration up to 10g once daily, or down to 5g once every other day, as needed, to maintain a normal potassium level. No more than 10g once daily should be used for maintenance therapy for patients who are not on haemodialysis. For patients on dialysis, the dose could be adjusted at intervals of one week in increments of 5g up to 15g once daily on non-dialysis days.

It is recommended that treatment with SZC is started by a specialist and treatment continued in primary care.[18]

The Medicines and Healthcare Products Regulatory Agency[32] recommends that S-K levels should be monitored regularly during treatment. Based on the ZS-005[10-12] trial (conducted over 12 months), the UK Kidney Association suggests that blood monitoring should be performed weekly for the first month and then monthly thereafter; further, S-K level should also be assessed 1 week after drug cessation as a rebound in S-K level can occur.[18]

The current pathway of care and the company's anticipated positioning of SZC in the NHS as a treatment for patients with persistent HK with S-K level ≥5.5 to <6.0mmol/L is presented in Figure 1.

Clinical advice to the EAG is that Figure 1 is a largely accurate reflection of current NHS practice; however, the duration of treatment with SZC for patients with persistent HK is not established and will vary based on an individual's clinical factors.

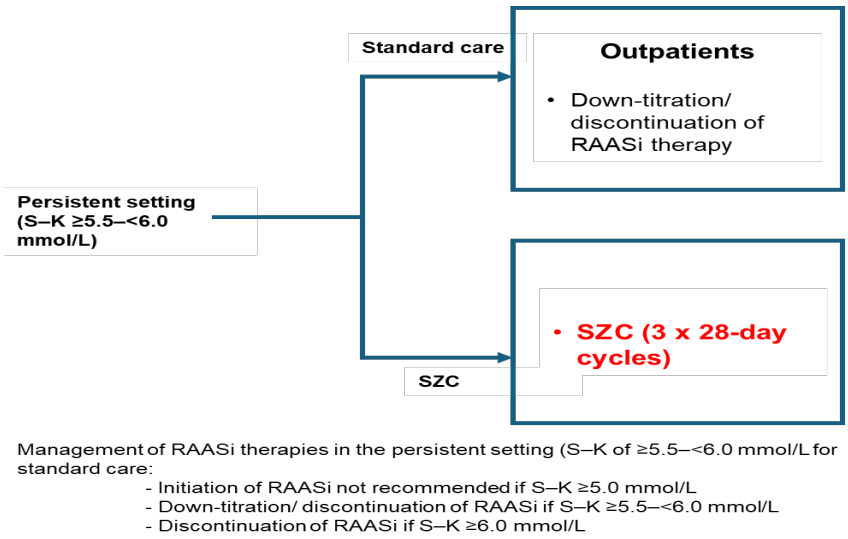

Figure 1 Current pathway of care and the company's anticipated positioning of SZC in the NHS for patients with persistent HK with S-K ≥5.5 to <6.0mmol/L

HK=hyperkalaemia; RAASi=renin-angiotensin-aldosterone system inhibitor; S-K=serum potassium
Source: CS, Figure 5

2.5 Critique of company's definition of decision problem

The key elements of the decision problem outlined in the final scope[33] issued by NICE and addressed by the company are summarised in Table 1. More information regarding the key issues relating to the decision problem is provided in Sections 2.5.1 to 2.5.8.

Table 1 Key elements of the decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission	EAG comment
Population	People with persistent HK and a S–K level between 5.5 to 6.0mmol/L People with persistent HK who need dialysis	Adults with persistent HK that have a serum potassium concentration (S–K) level between ≥5.5–<6.0mmol/L This submission focuses specifically on the comorbid patient population comprising patients with HK and CKD (stage 3b–5) or HF and who are not taking an optimised dosage of RAASi because of HK. People with persistent HK who need haemodialysis are not considered in this submission	The company explain (CS, Table 1) that the population is aligned to the NICE TA599 population, i.e., patients with persistent hyperkalaemia and CKD stage 3b to 5 or HF who are not taking an optimised RAASi dosage and that this partial update focuses specifically on expanding the existing NICE guidance to those with persistent HK and S–K level ≥5.5 to <6.0 mmol/L People with persistent HK who need haemodialysis are not considered in this submission. Clinical advice to the EAG is that people with persistent HK (S-K level ≥5.5 to <6.0mmol/L) who receive dialysis are unlikely to require treatment with a potassium binder
Intervention	SZC	As per scope	The company has not provided any new evidence from the ZS trials to demonstrate the clinical effectiveness or safety of SZC for a population with CKD or HF and an S-K level ≥5.5 to <6.0mmol/L).
Comparator(s)	Standard care	As per scope	As per scope
Outcomes	Outcome measures to be considered: • S–K level • Use of RAASi therapy • Mortality • Time to S–K normalisation • Use of sodium-glucose cotransporter 2 (SGLT-2) inhibitors	Outcomes included in the submission: • S–K level • Use of RAASi therapy • Mortality • Time to S–K normalisation • Adverse effects of treatment	The company has not presented any evidence for two of the outcomes listed in the final scope issued by NICE: • Use of SGLT-2 inhibitors • HRQoL As there is no robust evidence available for these outcomes, the EAG considers

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission	EAG comment
	• Adverse effects of treatment • Major adverse cardiac events (MACE) • Health-related quality of life (HRQoL)	• MACE • Hospitalisation	that this approach was appropriate
Economic analysis	The cost effectiveness of treatments should be expressed in terms of incremental cost per quality adjusted life year (QALY) The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs should be considered from an NHS and Personal Social Services perspective The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies should be taken into account The availability and cost of biosimilar and generic products should be taken into account	As per scope	As per scope
Subgroups	If the evidence allows, the following subgroups should be considered: • People with CKD • People with HF	As per scope	Clinical effectiveness evidence is presented separately for patients with CKD and patients with HF; cost effectiveness evidence has been provided for patients with CKD, patients with HF and the mixed population (i.e., patients with CKD [redacted%] and patients with HF [redacted%])

CKD=chronic kidney disease; HF=heart failure; HK=hyperkalaemia; NHS=National Health Service; SGLT-2=sodium-glucose co-transporter 2); S-K=serum potassium

2.5.1 Evidence sources

The company has not provided any new evidence from the ZS trials to demonstrate the clinical effectiveness or safety of SZC for a population with CKD or HF and an S-K level ≥5.5 to <6.0mmol/L (CS, Appendix E, p67). The ZS trial efficacy data were used to populate the company economic model, as per the approach taken in TA599.[1] However, a data-cut for the population of patients with S-K ≥5.5 to <6.0 mmol/L specifically was used to inform the economic model in the CS.

The company has presented real-world evidence to demonstrate that: i) that there is an association between persistent HK and adverse clinical outcomes (SPARK study) and ii) that the use of SZC allows maintenance/up-titration of optimum RAASi dosage (ZORA study).

The SPARK study is described in the CS (CS, Section B.2.3.1); summary study details and the EAG critique are provided in Section 3.4. The SPARK study was a UK-specific, retrospective, observational, longitudinal study conducted using secondary data extracted from the Clinical Practice Research Datalink (CPRD) and linked datasets. Data from [redacted] patients met the SPARK study inclusion criteria (CS, p45). One element of the SPARK study (Primary objective 2) was to investigate the association between S-K levels and clinical outcomes (CS, Table 12); results from these analyses have been used to populate the company economic model. The EAG considers that the SPARK study does not robustly evidence the association between persistent HK (S-K level of ≥5.5 to <6.0mmol/L) and MACE and mortality outcomes (Section 3.4.3).

The ZORA study re-analysis is described in the CS (CS, Section B.2.3.2); summary study details and the EAG critique are provided in Section 3.5. The ZORA study was an observational, cohort study programme that used secondary data extracted from Japanese (n=3405), Spanish (n=259) and US (n=2633), health registers and hospital medical records (CS, p62 and Appendix N.2, Table 94). Patients were grouped into two cohorts: those receiving SZC, and those not receiving any prescribed potassium binders. Primary analysis results have been published (Rastogi 2024[16]). The ZORA study data used to populate the company model are derived from ad-hoc re-analyses of the Japanese and US data; permission was not given to use the Spanish data in the re-analysis. The study periods were May 2020 to April 2024 for Japanese patients and July 2019 to March 2024 for US patients. The re-analyses were carried out to determine the proportions of patients discontinuing or down-titrating RAASi therapy stratified by recorded S-K levels (≥5.0 to <5.5mmol/L; ≥5.5 to <6; ≥6.0mmol/L). Clinical advice to the EAG is that differences in the baseline characteristics

of UK, Japan and US patients may affect the generalisability of ZORA study re-analysis results to NHS patients (Section 3.4.1).

2.5.2 Population

SZC (Lokelma) has a UK marketing authorisation for the treatment of hyperkalaemia in adult patients.[32] The population considered by the company (and NICE) is narrower than the licensed indication.

The population described in the final scope[33] issued by NICE is people with persistent HK and an S-K level ≥5.5 to 6.0mmol/L and people with persistent HK who need dialysis. The company explained (CS, Table 1) that the population addressed in the CS was narrower than the population specified in the final scope issued by NICE;[33] specifically, that it had been aligned to the TA599[1] population, i.e., patients with persistent HK and CKD (stage 3b to 5) or HF who, because of HK were not being treated with an optimised RAASi dose. This partial review focuses on expanding the existing NICE TA599[1] guidance for patients with S-K level ≥6.0mmol/L to include those with S-K level ≥5.5 to <6.0mmol/L. Clinical effectiveness evidence is presented separately for patients with CKD and patients with HF; cost effectiveness evidence has been provided for patients with CKD, patients with HF and the mixed population (i.e., patients with CKD [[redacted]%] and patients with HF [[redacted]%]).

The population described in the final scope[33] issued by NICE includes patients with persistent HK who need haemodialysis. The company has not provided cost effectiveness results for this population. However, the company has made an argument that a positive NICE recommendation should include this population (see Section 2.5.8). Clinical advice to the EAG is that people with persistent H-K (S-K level ≥5.5 to <6.0mmol/L) who are receiving haemodialysis are not generally prescribed potassium binders as dialysis effectively removes excess potassium from the blood.

Clinical advice to the EAG is that an S-K level of ≥5.5 to <6mmol/L is often tolerated in patients with CKD as these patients frequently have chronically elevated potassium levels, and their cardiac and neuromuscular systems adapt to the higher potassium.

2.5.3 Intervention

Information about SZC dosage is provided in Section 2.4. SZC is a powder that must be mixed with water. Clinical advice to the EAG is that some patients find the taste and/or the gritty texture of this mixture unpleasant and that there can be treatment compliance issues due to fluid retention.

In the company model, the cost effectiveness of SZC plus standard care is compared with standard care.

2.5.4 Comparators

Lifestyle interventions aimed at maintaining S-K levels within the normal range are an important part of HK management. Clinical advice to the EAG is that patients with HK are referred to specialist dieticians for dietary advice; however, it is difficult to follow a healthy low-potassium diet, and adherence to such a diet is typically low. Clinical advice to the EAG was also that, for patients with S-K levels between ≥5.5 to <6.0mmol/L, RAASi therapy doses may be adjusted or down-titrated. However, this approach often results in suboptimal RAASi therapy dosing, potentially compromising the clinical benefits associated with these agents.

2.5.5 Outcomes

The company has provided evidence for six of the eight outcomes listed in the final scope[33] issued by NICE; the company has also provided hospitalisation data. Outcome data provided by the company and data sources are presented in

Table 2.

Table 2 Outcome data provided by the company

Outcome	Outcome source
S-K level and long-term clinical outcomes	SPARK study
Use of RAAS inhibitor therapy	Re-analysis and company SLR
Mortality	SPARK study (company SLR considers RAASi use and mortality)
Time to S-K normalisation	ZS trials presented as part of TA599 and summarised in the CS (CS, Table 5 to 9)
Adverse effects of treatment	ZS trials presented as part of TA599 and summarised in the CS (CS, Table 5 to 9) Data from ZS-005 are used in the company model
MACE	SPARK study and company SLR
Hospitalisations	SPARK study and company SLR

CS=company submission; MACE=major adverse cardiac events; RAASi=renin-angiotensin-aldosterone system inhibitor; S-K=serum potassium; SLR=systematic literature review
Source: EAG

The company was unable to provide data for two outcomes listed in the final scope[33] issued by NICE, namely health-related quality of life (HRQoL) and use of SGLT-2 therapy.

Health-related quality of life

The company model is populated with the HRQoL data that were used to populate the TA599[1] economic model; no new HRQoL data have been presented. HRQoL data were not collected as part of the company SZC clinical trial programme, nor in any of the company follow-up

observational studies (ZS-004 and ZS-005). The NICE TA599[1] AC concluded that there was no direct evidence that SZC improves HRQoL compared to other treatments for people with chronic HK.

SGLT-2 treatment

Data relating to SGLT-2 inhibitors were not collected as part of the company ZS clinical trial programme or in any company SZC follow-up observational studies (ZS-004 and ZS-005). The company explains (CS, Table 1) that SGLT-2 inhibitors are treatments that can be prescribed to patients with CKD and HF (in addition to RAASi therapy). SGLT-2 inhibitors reduce S-K level, which may allow better use of RAASi therapy. In response to clarification question A1, the company reported that in the UK, SGLT-2 inhibitors are not indicated for HK and are not used by clinicians with the aim of lowering patient S-K levels. Furthermore, UK clinical guidelines state that patients should only initiate SGLT-2 inhibitors if they are in receipt of an optimised RAASi dosage. SZC facilitates maintenance of an optimised RAASi dosage, meaning that SZC has the potential to enable more patients to be eligible for SGLT-2 inhibitors than standard care. The company therefore considers that omission of use of SGLT-2 inhibitors from the company model is likely to result in conservative cost effectiveness estimates.

Safety data

The company model is populated with the same safety data that were used to populate the TA599[1] economic model; no new safety data have been presented. It is stated in the SZC Summary of Product Characteristics[32] that the most commonly reported adverse reactions arising from treatment with SZC are hypokalaemia (4.1%) and oedema-related events (5.7%).

During TA599,[1] the company presented data showing that treatment with SZC is associated with hypokalaemia and stated that hypokalaemia is associated with life-threatening arrhythmias. The company explained that treating HK at ≥6.0mmol/L was less likely to cause hypokalaemia than treating HK at lower S-K levels. The risk of hypokalaemia associated with treating NHS patients with S-K levels of ≥5.5 to <6.0mmol/L with SZC is not known, however, ZS-005 trial data (CS, Appendix E, Table 20) show that rates of hypokalaemia in patients with S-K levels of ≥5.5 to <6.0mmol/L treated with SZC during extended phase days 85 to 365 were low (0.0%; 95% confidence interval: 0.0%, 1.3%).

2.5.6 Economic analysis

As specified in the final scope[33] issued by NICE, the cost effectiveness of treatments was expressed in terms of incremental cost effectiveness ratios (ICERs) per quality adjusted life year (QALY) gained. Outcomes were assessed over an 80-year time horizon (which the

company considered was equivalent to a lifetime horizon) and costs were considered from an NHS and Personal Social Services (PSS) perspective. Confidential discounts are not available for any of the drugs used in the company model.

The EAG agrees with the company that a severity weighting is not applicable for this appraisal.

2.5.7 Subgroups

The subgroups listed in the final scope[33] issued by NICE are i) people with CKD and ii) people with HF. The company has presented cost effectiveness evidence for three populations, i) patients with CKD, ii) patients with HF and iii) the mixed population (i.e., patients with CKD [[redacted]%] and patients with HF [[redacted]%]). The company model inputs for these subgroups differ by baseline characteristics (age, eGFR, statin usage and other concomitant therapies, sodium, cholesterol, haemoglobin and lymphocytes, proportion females, systolic blood pressure, white blood cell count, comorbidities and smoking history), risk of adverse outcomes by S-K and RAASi use, utility values and healthcare resource use.

2.5.8 Other considerations

In the CS (CS, Section B.1.3.8), the company highlights that SZC is licensed as a treatment for patients[32] who are receiving chronic haemodialysis and considers that it would be reasonable to include these patients in any wider positive NICE recommendation. The company highlights that SZC was incorporated into the emergency COVID-19 Rapid Guideline: Dialysis Service Delivery (NG160[34]) as an important measure to allow a delay in dialysis until COVID-19 test results were known. The company considers that restricting access to SZC on the basis of insufficient data to demonstrate cost effectiveness, after having previously allowed access via NG160,[34] would result in inequitable access across the full group of people for whom SZC has a UK marketing authorisation. Clinical advice to the EAG is that people with persistent H-K (S-K level ≥5.5 to <6.0mmol/L) who are receiving haemodialysis are not generally prescribed potassium binders.

3 CLINICAL EFFECTIVENESS

The company carried out two clinical effectiveness SLRs:

1. To synthesise evidence on the efficacy and safety of SZC for patients with persistent HK (SLR1)
2. To identify and summarise evidence demonstrating the relationship between RAASi dosage and long-term clinical outcomes (SLR2)

3.1 Efficacy and safety of SZC for patients with persistent HK (SLR1)

The company conducted a SLR in 2018 to inform TA599;[1] this review was updated in June 2024 to inform this partial review of TA599.[1] Searches (run for 2018 to 2024) were designed to identify clinical and cost effectiveness evidence. The objective of the clinical effectiveness component of the SLR was to identify recent RCTs of treatments for adults with HK in adults (CS, Appendix D.2).

In total, 38 records met the eligibility criteria for the clinical effectiveness review (CS, Appendix D.6). Of these records, 22 reported data relating to SZC as the main intervention of interest (across 12 RCTs, 11 of which were sponsored by the company); the identified studies included ZS P2/3, ZS-002, ZS-003 and ZS-004. The remaining 16 records (across 10 RCTs) considered patiromer (n=13), calcium polystyrene sulfonate (CPS) (n=1), CPS doses (n=1), glucose-insulin infusion to salbutamol (n=1).

Two further RCTs (ZS-004E, ZS-005), both SZC studies sponsored by the company, were also considered relevant; however, these studies are not associated with any published papers (CS, Appendix D.6.2). The data used to populate the company economic analysis were sourced from, ZS-003, ZS-004, and ZS-005; the remaining SZC trial evidence was not considered relevant to the scope of this partial review of TA599[1] (CS, Appendix D.6.3, Table 11).

Subgroup analysis results are presented in CS, Appendix E for the SZC licensed doses (10g and 5g); the data presented in CS, Appendix E were presented in TA599[1] Appendix E. The company has not provided any new RCT evidence to support the clinical effectiveness of SZC in patients with persistent HK (S-K ≥5.5 to <6.0mmol/L).

An assessment of the extent to which SLR1 was conducted in accordance with the LR*i*G in-house systematic review checklist is presented in Table 3. In response to clarification question C2, the company carried out updated searches in April 2025 and did not highlight any trials that were relevant to this appraisal. The EAG's independent searches did not identify any trials additional to those found by the company.

Table 3 EAG appraisal of the company's systematic review methods

Review process	EAG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	CS, Appendix D.4, Table 6
Were appropriate sources searched?	Yes	CS, Appendix D.3
Was the timespan of the searches appropriate?	Yes	The company searches were conducted in June 2024 ahead of an expected appraisal date of January 2025. In response to clarification question C2, the company carried out updated searches in April 2025 and presented a list of additional included studies (n=36)
Were appropriate search terms used?	Yes	CS, Appendix D.3
Were the eligibility criteria appropriate to the decision problem?	Yes	CS, Appendix D.4, Table 6
Was study selection applied by two or more reviewers independently?	Yes	CS, Appendix D.5.1
Was data extracted by two or more reviewers independently?	Partially	CS, Appendix D.5.2 Data were extracted by one reviewer and checked for accuracy by a second reviewer. Discrepancies were resolved through discussion or by consulting a third reviewer when required. The EAG considers this strategy is acceptable
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	Assessment of all trials was carried out using the minimum criteria recommended by NICE[35]
Was the quality assessment conducted by two or more reviewers independently?	Yes	CS, Appendix D.5.3
Were attempts to synthesise evidence appropriate?	NA	The trials discussed in the CS were presented narratively

CS=company submission; EAG=External Assessment Group; NA=not applicable
Source: LR*i*G in-house checklist

3.2 Relationship between RAASi dosage and long-term clinical outcomes (SLR2)

The company conducted a SLR to address the uncertainty arising during TA599[1] that the clinical evidence did not adequately demonstrate the relationship between RAASi dosage and long-term clinical outcomes (SLR2). The purpose of SLR2 was to provide an overview of research relevant to the use of RAASi in patients with CKD or HF (CS, p36). The objectives of SLR2 were to address the following questions (CS, Appendix K, p242):

- What are the long-term outcomes in patients discontinuing/down-titrating RAASi?

- What are long-term clinical benefits (cardiovascular events, mortality, hospitalisation) of taking RAASi in patients with CKD or HF?
- What changes occur in S-K with RAASi down-titration and discontinuation?
- Is there evidence of disease progression in patients with CKD or HF treated with RAASi?

3.2.1 Quality assessment of the SLR2 methods

The EAG conducted a quality assessment of SLR2 using the AMSTAR 2[36] tool; this tool is designed for critically appraising SLRs. The EAG quality assessment was informed by information provided in the CS (Document B and Appendix K) and by the 2019 SLR report[37] (a confidential document provided as a reference by the company). Overall, the EAG considers that SLR2 was well-conducted and is of good methodological quality (see Section 8.1 for details).

3.2.2 Summary of company 2024 SLR2 results

The 2024 SLR2 included 100 publications (69 SLRs and 31 RCTs CS, p36) that had not been included in the 2019 SLR2. The company reported (CS, Appendix K, p244) that the 2024 SLR2 findings were similar to the 2019 SLR2 findings. Overviews of the 2024 SLR2 findings are presented in Section 8.2.

The company considers (CS, Appendix K, Section K.1.1.4) that, overall, the SLR2 results demonstrate that RAASi is an effective treatment for patients with HF or CKD, and that the beneficial effects are apparent across all the outcomes assessed. The company acknowledged that there was a lack of data evidencing the effects of down-titration or discontinuation of RAASi on S-K for patients with HF or CKD.

Updates to the company 2024 SLR2

As the company 2024 SLR2 was more than 6 months old, the EAG asked the company to update this SLR (clarification question C2). Updated searches were carried out on 4 April 2025 and, following application of inclusion/exclusion criteria, 36 additional included studies were identified; 12 of these studies were published in 2024, and the remaining 24 studies were published in 2025. The company categorised the included studies into the following types:

- clinical trial report/data: n=16; finerenone: n=12; eplerenone: n=2; spironolactone: n=1; angiotensin receptor blockers: n=1)
- literature review: n=3
- meta-analysis with/without review: n=4
- in press: n=5
- conference abstract: n=5
- NR: n=3

The company has not made any attempt to assess whether these additional studies provided any new, relevant data. It is, therefore, not clear whether this additional evidence confirms or refutes previously identified evidence.

3.3 Additional evidence: introduction

To address concerns raised by NICE during TA599,[1] the company provided results from two studies:

- **SPARK study** – designed to investigate the relationship between S-K and hospitalisation, MACE and mortality outcomes
- **ZORA study re-analysis** - undertaken to compare the odds of maintained RAASi therapy at 6 months in two cohorts: SZC versus no potassium binder (results stratified by S-K level)

Results from these studies were used to populate the company economic model.

3.4 The SPARK study

To address concerns raised by NICE during TA599,[1] the company provided results from the SPARK study. The SPARK study was designed to investigate the relationship between S-K and hospitalisation, MACE and mortality outcomes. Results from this study were used to populate the company economic model.

3.4.1 SPARK study: study characteristics

The SPARK study was a UK-specific, retrospective, observational, longitudinal study conducted using secondary data extracted from the CPRD and linked datasets. Specifically, data from CPRD datasets (Aurum and GOLD) were linked to the Office for National Statistics (ONS) death registration database,[38] and the Hospital Episodes Statistics (HES) database.[39]

The SPARK study had three primary objectives:

- **Objective 1**: to describe patient characteristics and treatment patterns stratified by demography, S-K levels, and comorbidities at baseline
- **Objective 2**: to describe the association between S–K levels and clinical outcomes (MACE, all-cause death, all-cause hospital admissions, eGFR decline)
- **Objective 3**: to demonstrate the ability to maintain optimal RAASi dose by S–K level through the use of SZC (i.e., quantify and compare SZC users and non-users who discontinue, down-titrate, and/or return to optimal RAASi dose, and time to return to optimal dose)

An overview of SPARK study eligibility criteria is presented in Table 4.

Table 4 Overview of SPARK study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria

All objectives:
• Patients aged ≥18 years old at index date
• At least 12 months of records before index date
  ○ For primary objective 3, at least 90 days of follow-up post-index
Primary objectives 1 and 2:
• Records of any of the following before 1st January 2019:
  ○ A reported S–K measurement
  ○ HK, including either a diagnosis of HK (SNOMED-CT, read code, ICD-10 E87.5) in any position recorded in inpatient hospital setting (including emergency department)
  ○ potassium binder use
• An S–K measurement between 1st January 2016–1st January 2019
Primary objective 3:
• Either of the following between 1st January 2004–31st December 2023:
  ○ HK, including either a diagnosis of HK (SNOMED-CT, read, ICD-10 E87.5) in any position recorded in inpatient hospital setting (including emergency department)
  ○ K^+ binder use
• A reported S–K measurement of ≥5.0mmol/L nearest to HK diagnosis or K^+ binder initiation
• A prior diagnosis of CKD and/or HF
• On RAASi treatment within 120 days prior to index date and up to 180 days after index date
	• Patients currently treated with dialysis (14 days prior to index date)
	• Organ transplant (prior ever)
	• Pregnancy in the 12 months prior to index date

CKD=chronic kidney disease; HF=heart failure; hHF=heart failure hospitalisation; HK=hyperkalaemia; ICD=International Classification of Diseases; K^+=potassium cation; RAASi=renin-angiotensin-aldosterone system inhibitors; S–K=serum potassium; SNOMED-CT=Systematized Nomenclature of Medicine - Clinical Terms
Source: CS, Table 13

Data from objectives 1 and 2 have been used to populate the company model.

3.4.2 SPARK study: quality assessment

The company assessment of SPARK study data is presented in Appendix M.5. The company conducted the SPARK study in line with the NICE Real World Evidence (RWE) framework and completed the NICE DataSAT[40] assessment template; the NICE DataSAT[40] is designed to help assess whether real-world data sources are suitable for use in NICE evaluations. The company also provided details of data quality for key study variables and justified data relevance. The EAG agrees with the company assessment.

3.4.3 SPARK study: EAG summary and critique of the statistical approach

The aim of the company SPARK study was to address NICE TA599[1] AC concerns about the association between increased S-K levels and adverse clinical outcomes. The EAG considers that the analyses carried out by the company do not provide evidence that addresses NICE AC concerns.

Data presented by the company in response to clarification question A2 (see Table 5) show that the SPARK study population may not reflect the population with persistent HK.

- in the S-K level ≥5.5 to <6.0mmol/L cohort, [redacted]% of patients in the prior CKD cohort and [redacted]% of patients in the prior HF cohort had only one S-K measure; clinical advice to the EAG is that, for patients with CKD, having only one S-K measurement in a period of a year may not be that concerning
- in the NICE TA599[1] guidance (Section 3.1), it is recognised that S-K tests may incorrectly identify HK and that potassium levels often need to be confirmed. The NICE AC concluded that '…any use of SZC would be limited to confirmed HK'. It is advised that clinicians should confirm hyperkalaemia if S-K level is ≥5.5mmol/L (≥5.5mEq/L) and check that this is not due to pseudo hyperkalaemia
- the proportion of patients with more than one S-K measure decreases as baseline S-K level increases
- in the S-K level ≥5.5 to ≤6.0mmol/L cohort, despite not receiving potassium binders, [redacted]% of patients in the prior CKD cohort and [redacted]% of patients in the prior HF cohort who had more than one S-K measures had an S-K level that, at least once during the study period, fell below their baseline S-K group
- no information has been provided by the company on how long patients spent in each S-K group; these data would be required to understand the relationship between persistent HK and adverse outcomes

Table 5 SPARK study patient-level S-K data: changes over the study period

Cohort	Baseline S-K group (mmol/L)	All patients	Patients with >1 S-K measures (%*)				
		N	N	Remained	Exceeded	Fell below	Exceeded and fell
Prior HF no CKD	5.0 to 5.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5.5 to 6.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≥6.0	[redacted]	[redacted]	[redacted]		[redacted]	
Prior CKD no HF	5.0 to 5.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5.5 to 6.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≥6.0	[redacted]	[redacted]	[redacted]		[redacted]	

* Percentage with respect to patients with ≥1 S-K measures
CKD=chronic kidney disease: HF=heart failure; S-K=serum potassium
Source: clarification response, Table 1

The James 2021 study

The EAG identified the James 2021 study;[41] this study provides information on the relationship between time spent in different S-K level groups (i.e., potentially focusing on persistent HK) and MACE, hospitalisations and death. James 2021 study results were generated using CPRD data (CPRD data were also used to generate SPARK study results). As the EAG considered that the James 2021 study provides more relevant evidence for the relationship between

persistent HK and adverse outcomes than the SPARK study, the EAG asked the company (clarification question A8) to explain why results from the James 2021 study had not been mentioned in the CS. The company explained that whilst the James 2021 study had been identified by the company 2024 SLR2 searches, the study had been excluded from SLR2 because the population treated with a RAASi did not only have HF, CKD or diabetic nephropathy. The company provided a full explanation of the relevance of the James 2021 study in response to clarification question A8.

The EAG highlights that the James 2021 study provides evidence from a large number of patients with CKD or HF (Table 6) and that patients who spend time with S-K levels ≥5.5mmol/L have a lower risk of mortality compared to patients who spend time with S-K level ≤5.5mmol/L. The company suggested that the observation that mortality risk was lower in those spending more time with S-K levels ≥5.5mmol/L may be because these patients are benefitting from more proactive management and highlighted that it is noted in the publication that the CKD and HF cohorts had the highest frequency of potassium testing (expressed as rate per patient years) and therefore may have been subject to additional treatment or intervention.

Table 6 Numbers of patients providing data for the SPARK study and the James 2021 study

	CKD	HF
SPARK study	[redacted]	[redacted]
James 2021 study	297,702	84,210

CS=company submission
Source: CS, Table 15 and company response to clarification question A7

The company suggested that any differences between SPARK study and James 2021 study results are likely to arise from disparities in the dataset, exposure definitions, confounding structures and statistical modelling (Table 7). The EAG considers that differences do not mean that James 2021 study results should not be used to inform decision making, rather that these results highlight the complexity of the relationship between S-K levels and patient outcomes.

Table 7 Key differences in study design and methods: James 2021 and SPARK study

Aspect	SPARK study[14]	James 2021[2]
Design	Retrospective cohort study (CPRD Aurum+HES)	Retrospective cohort study (CPRD GOLD+HES)
Population	Adults (≥18) with S-K between 2016 and 2019. Model then looks at prior CKD and/or HF	Adults (≥18) with CKD stage 3+, HF, diabetes, RHTN, RAASi
Follow-up period	2016 to 2021 for outcomes	2003 to 2018 (5-year look-back to 2003)

Aspect	SPARK study[14]	James 2021[2]
Exclusions	Excluded: dialysis in 14 days prior, organ transplant, pregnancy in prior 12 months	Dialysis patients included as a separate group
Exposure	Time-updated S-K categories (e.g., <3.5, 3.5 to 4.0, 4.0 to 4.5, 4.5 to 5.0, 5.0 to 5.5, 5.5 to 6.0, ≥6.0)	% time spent in HK (SK ≥5.0/5.5/6.0 compared to patients who spent no time in an HK state); S-K variability (SD-based)
Time-dependence	Yes. S-K and eGFR updated dynamically in outcome models	Yes – exposures modelled over time (repeated measures)
Outcome modelling	GEE Poisson regression with time-updated S-K/eGFR; IRRs computed	Relative risk (log-scale) using time-in-HK intervals
Adjustment factors	Adjusted for age, sex, comorbidities, medications, and patient-years	Disease-specific cohorts with published risk equations
Outcome types	All-cause mortality, MACE, hospitalisation, healthcare resource use and cost	All-cause mortality, MACE

CPRD=Clinical Practice Research Datalink; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; GEE=generalised estimating equations; HES=Hospital Episode Statistics; HF=heart failure; HK=hyperkalaemia; IRR=incidence rate ratio; MACE=major adverse cardiovascular events; RAASi=renin-angiotensin-aldosterone system inhibitor; RHTN=resistant hypertension; SD=standard deviation; S-K=serum potassium
Source: company clarification response, Table 6

3.4.4 SPARK study primary objective 1 – describe patient characteristics: statistical approach

Patient baseline characteristics were described using means (SD), medians (LQ-UQ), counts and proportions, as appropriate. Summary baseline patient characteristics are presented in the CS (CS, Table 15). The company has provided more detailed baseline characteristics in CS, Appendix M; in CS, Appendix M, data are presented for 18 different patient groups; the characteristics assessed are standard baseline characteristics (age, gender, body mass index (BMI) and smoking status), four laboratory parameters, 23 medical conditions and 12 different types of treatment. The company also provided patient counts data and crude proportions data for primary objective 3. Further exploratory analysis results were provided in a confidential Excel file. The analyses carried out by the company were extensive; however, much of the detail is not presented in a way that directly informs the decision problem.

3.4.5 SPARK study primary objective 2 – association of S-K levels and clinical outcomes: statistical approach

To describe the association between S-K levels and clinical outcomes, the company ran multivariable regression models; these were stratified by variables of interest to account for confounding variables and an analysis was conducted to account for unknown confounding factors using e-values. A generalised estimating equations (GEE) model was used to estimate adjusted incidence rate ratios(IRRs); this incorporated a working correlation structure to account for within-cluster or repeated-measures dependencies. The GEE model was run twice, once for patients with HK and CKD and once for patients with HK and HF.

The EAG considers that the company methods were largely appropriate, however:

- GEE models are only robust to data that are missing completely at random (MCAR); in the observational context, missing data are unlikely to be entirely MCAR. The company states, "…Missing data were quantified for all study variables, but no attempts were made to impute them" (CS, p49).
- the company attempted to assess the impact of unmeasured confounders using e-values (CS, p45); e-values are not commonly seen in technology appraisals and there is no consensus around their interpretation. The EAG considers that the company interpretation may be optimistic and does not agree with the company statement that, "… it is highly unlikely for any remaining unknown confounder to nullify the relationship" (CS, p54); however, the EAG acknowledges that the company did include many potential confounders in the GEE model.

The company has used the SPARK analysis directly in the economic model to estimate how decreasing S-K level decreases the risk of experiencing adverse outcomes. However, the SPARK study analysis provides evidence of the risk of adverse outcomes for a single S-K reading, not the risk reduction from patients with persistent S-K levels ≥5.5 to <6.0mmol/L reducing their S-K level through the use of potassium binders. Whilst the company states that S-K levels were updated dynamically in the GEE model, the methods used by the company were not explained in the CS or in the clarification response. The inputs and outputs provided for the SPARK study analysis suggest that time spent in an S-K group was not an independent variable in the GEE model. Clinical advice to the EAG is that, for patients with mild to moderate HK, the causal link between elevated S-K and adverse outcomes remains to be established.

3.4.6 SPARK study primary objective 3 - RAASi dose, S-K level and SZC: statistical approach

The company stated that following the application of the study inclusion criteria, the sample size of UK SZC users was too small to yield robust results, particularly when assessing subgroups based on S-K measurements: [redacted] treated with SZC had a RAASi prescription and only [redacted] had an optimised RAASi dose and S-K ≥5.5 to <6.0mmol/L (CS, p61). The EAG agrees with the company that the number of subjects in the active arm is too low for a meaningful analysis to be conducted; a sample of this size means that it is likely that there would be few events and therefore only a few covariates could be included in any statistical model.

3.4.7 SPARK study: key results

SPARK study primary objective 1 – patient characteristics: results

SPARK study patient characteristics are summarised in CS, Section B.2.3.1.6 and key baseline characteristics are presented in Table 8 for the ≥5.5 to <6.0mmol/L and ≥6.0mmol/L cohorts; full details, including baseline characteristics for other S-K and medical condition cohorts are available in CS, Table 15 and CS, Appendix M.1.

Table 8 SPARK study: patient baseline characteristics

Characteristics	SPARK: primary objectives 1 & 2	
	S-K ≥5.5 to <6.0mmol/L	S-K ≥6.0mmol/L
Total	[redacted]	[redacted]
Patient demographics, n (%)		
Age (years), Mean (SD)	[redacted]	[redacted]
Female	[redacted]	[redacted]
Current smoker	[redacted]	[redacted]
Baseline clinical measurements, mean (SD)		
BMI (kg/m^2)	[redacted]	[redacted]
SBP (mmHg)	[redacted]	[redacted]
DBP (mmHg)	[redacted]	[redacted]
S-K (mmol/L)	[redacted]	[redacted]
Clinical history at baseline		
HK	[redacted]	[redacted]
HF		
CKD	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
IHD	[redacted]	[redacted]
Congestive HF	[redacted]	[redacted]
CAD	[redacted]	[redacted]
Myocardial infraction	[redacted]	[redacted]
Treatment history at baseline, n (%)		
Any RAASi	[redacted]	[redacted]

BMI=body mass index; CAD=coronary artery disease; CKD=chronic kidney disease; DBP=diastolic blood pressure; HF=heart failure; HK=hyperkalaemia; IHD=ischaemic heart disease; RAASi=renin-angiotensin-aldosterone system inhibitors; SBP=systolic blood pressure; SD=standard deviation; S-K=serum-potassium
Source: CS, Table 15

SPARK study primary objective 2 – association between S-K levels and clinical outcomes: results

The company has presented results separately for i) CKD patients and ii) HF patients. IRRs for MACE, mortality and hospitalisations have been reproduced in this EAG report (Figure 2 and Figure 3). Adjusted IRRs and associated confidence intervals (CIs), e-values and CI e-values for hospitalisations as a function of S-K level and eGFR are provided in the CS (CS, Section B.2.3.1.7)

Results showed that, for patients with CKD, an S-K level of ≥5.5 to <6.0mmol/L was associated with [redacted] MACE, mortality, and hospitalisation incidence rates than having an S-K level of ≥4.5 to <5.0mmol/L; adjusted IRRs were [redacted], and [redacted], respectively. IRRs (standard error [SE]) are reported in Appendix M.3, Table 90. The EAG highlights that the point estimates reported in main body of the CS differ slightly from those reported in Appendix M.3; however, these differences do not affect the

interpretation of results. The company states that results are consistent with published results;[20,42-44] the EAG agrees that there is a consistent association in the same direction; however, the magnitude of effect differs considerably between studies and only one published study[20] reported hospitalisation incidence rate data. The company reported that e-value results demonstrated that an unmeasured confounder would need to be highly correlated with the clinical outcome and imbalanced between S-K groups to reverse or nullify results.

IRRs were adjusted using the S–K level of ≥4.5 to <5.0 as a reference
CKD=chronic kidney disease; IRR=incident rate ratio; MACE=major adverse cardiac event; S-K=serum potassium

Figure 2 Adjusted IRRs for MACE, death, and hospitalisations: CKD patients

Source: CS, Figure 8

The company stated that results showed that, for patients with HF, an S-K level of ≥5.5 to <6.0mmol/L was associated with [redacted] mortality and hospitalisation incidence rates than having an S-K level of ≥4.5 to <5.0mmol/L; adjusted IRRs were [redacted], and [redacted], respectively. The MACE adjusted IRR was [redacted] for patients with an S-K level of ≥5.5 to <6.0mmol/L than for patients with an S-K level of ≥4.5 to <5.0mmol/L [redacted]. IRRs (SE) are reported in Appendix M.4, Table 91. The EAG highlights that the point estimates reported in main body of the CS differ slightly from those reported in Appendix M.4; however, these differences do not affect interpretation of results. The company reported that e-value results demonstrated that an unmeasured confounder would need to be highly correlated with the clinical outcome and imbalanced between S-K groups to reverse or nullify these findings.

IRRs were adjusted using the S-K level of ≥4.5 to <5.0 as a reference
HF=heart failure; IRR=incident rate ratio; MACE=major adverse cardiac event; S-K=serum potassium

Figure 3 Adjusted IRRs for MACE, death, and hospitalisations: HF patients

Source: CS, Figure 10

SPARK study primary objective 3 – RAASi dose, S-K level and SZC: results

No primary objective 3 results were presented in the CS. The company carried out the ZORA study re-analysis to address this question.

3.5 The ZORA study re-analysis

To address concerns raised by NICE during TA599,1 the company provided results from the ZORA study re-analysis. The ZORA study re-analysis was undertaken to compare the odds of maintained RAASi therapy at 6 months in two cohorts: SZC versus no potassium binder (results stratified by S-K level). Results from this study were used to populate the company economic model.

The ZORA study re-analysis used data that informed the Rastogi 2024[16] study; however, the ZORA study re-analysis only considered data from Japan and the USA (not Spain). ZORA study re-analysis data were used to populate the company economic model.

3.5.1 ZORA study re-analysis: patient baseline characteristics

To undertake the ZORA study re-analysis, data were stratified by S-K groups (≥5.0 to <5.5mmol/L, ≥5.5 to <6, ≥6.0mmol/L). Propensity score (PS) matching was conducted based on stratified groups to achieve balance (<0.2 standardised mean difference [SMD]) between the SZC cohort and the no potassium binder cohort with respect to 33 potential confounders (listed in CS, Appendix N.3; identified a priori through subject matter knowledge).

The EAG considers that the use of logistic regression to develop a PS was a valid approach and that despite matching for 33 covariates, PS matching was successful and resulted in treatment arms that were very well matched. However, Rastogi 2024[16] data show that, for the

subgroups of Japanese and US patients who were not treated with a potassium binder, after PS matching the size of the groups decreased by 88.5% and 98.0% respectively (Table 9)

Table 9 Baseline size of unmatched and propensity score-matched SZC and no-binder cohorts (Rastogi 2024[16])

	Japan		US	
	SZC	PS-SZC matched	SZC	PS-SZC matched
SZC	888	776	582	565
No potassium binder	22,771	2,629	102,537	2,068

PS=propensity score
Source: CS, Appendix N.1, Table 93

ZORA study re-analysis (after PS matching; for the S-K ≥5.5 to <6.0mmol/L and S-K ≥6.0mmol/L groups) patient baseline characteristics are provided in Table 10. The EAG highlights that:

- **Age:** US and Japanese ZORA study re-analysis patients are a similar age to the CKD-only and HF-only cohorts of the SPARK study.
- **Treatment history**: there is considerable variation between the ZORA Japanese and ZORA US patients in terms of receipt of potassium binders; at baseline, between [redacted]% and [redacted]% of Japanese patients were receiving a potassium binder compared to between [redacted]% and [redacted]% of US patients.

Differences in UK, Japanese and US patient baseline characteristics may affect the generalisability of ZORA study re-analysis results to NHS patients. Further, research has shown that average potassium consumption in the Japanese population is lower than that in Western countries.[45,46] In addition, the potential impact of differences between countries in attitudes towards treatment adherence and health-seeking behaviour is not known. The EAG highlights that reimbursement protocols differ between the UK, Japan and the US.

Further, whilst only ZORA study re-analysis data (Japan and the US) were used to populate the company model, Rastogi 2024[16] meta-analysed proportions of patients who discontinued, down-titrated, stabilised, and up-titrated their RAASi therapy post-index versus pre-index data (Appendix N, Figure 26) showed that I^2, the most commonly used measure of study heterogeneity, was often quite high, suggesting that there is a heterogeneity of effect across Japan, the US and Spain. This casts further doubt on whether ZORA study re-analysis results are generalisable to NHS patients.

The EAG highlights that whilst the purpose of the ZORA study re-analysis was to identify the relationship between SZC and RAASi dose adjustment, clinical advice to the EAG is that whilst HK is one reason to down-titrate RAASi dose, other reasons include worsening renal function, symptomatic hypotension and drug-related adverse events (AEs).

Table 10 ZORA re-analysis (after propensity score matching) patient baseline characteristics|

Characteristics	ZORA re-analysis: JAPAN matched cases				ZORA re-analysis: US matched cases			
	SZC		Control (no potassium binder)		SZC		Control (no potassium binder)	
	S–K ≥5.5 to <6.0	S–K ≥6.0	S–K ≥5.5 to <6.0	S–K ≥6.0	S–K ≥5.5 to <6.0	S–K ≥6.0	S–K ≥5.5 to <6.0	S–K ≥6.0
Total	[redacted]							
Patient demographics, n (%)								
Age (years, Mean (SD)	[redacted]							
Female	[redacted]							
Clinical history at baseline								
HK*	[redacted]							
HF								
CKD	[redacted]							
Treatment history at baseline, n (%)								
Any RAASi	[redacted]							
Any potassium binder	[redacted]							

* ZORA study re-analysis: HK diagnosis in 12 months pre-index
† ZORA study re-analysis: RAASi use in 120d pre-index excluding index
CKD=chronic kidney disease; CS=company submission; HF=heart failure; HK=hyperkalaemia; RAASi=renin-angiotensin-aldosterone system inhibitors; SD=standard deviation; S-K=serum potassium
Source: CS, Appendix N, Table 97 and Table 98

3.5.2 ZORA study re-analysis: quality assessment

The company assessment of ZORA study data is presented in the CS, Appendix N.6. The company completed the NICE DataSAT[40]; this tool is designed to help assess whether real-world data sources are suitable for use in NICE evaluations. The company also provided details of data quality for key study variables and justified data relevance. The EAG agrees with the company assessment.

3.5.3 ZORA study re-analysis: EAG summary and assessment of company statistical approach

The company approach is described in CS, Section B.2.3.2.5. Proportions of patients in the SZC cohort and in the no potassium binder cohort who up-titrated, stabilised, down-titrated or discontinued RAASi therapy at 180 days post-index versus pre-index were calculated; p-values for differences between cohorts were calculated using chi-squared (χ^2) tests. A cross-country meta-analysis was conducted using a random effects model on logit transformed proportions. The EAG considers that the statistical approach adopted by the company was appropriate.

3.5.4 ZORA study re-analysis: key meta-analysis results

The company highlighted that ZORA re-analysis results (Table 11) consistently [redacted] for the proportion of patients who discontinued, down-titrated, stabilised, or up-titrated their RAASi therapy.

Table 11 Proportions of ZORA study re-analysis patients who discontinued, adjusted or maintained RAASi dose (meta-analysed across Japan and the US, stratified by S-K levels)

Subgroup	SZC	Control (no potassium binder)	Odds ratio	p value
≥5.0 to <5.5mmol/L– proportion (95% CI)	[redacted]	[redacted]		
Discontinued	[redacted]	[redacted]	[redacted]	[redacted]
Down titrated	[redacted]	[redacted]	[redacted]	[redacted]
Stabilised	[redacted]	[redacted]	[redacted]	[redacted]
Up titrated	[redacted]	[redacted]	[redacted]	[redacted]
≥5.5 to <6.0mmol/L– proportion (95% CI)	[redacted]	[redacted]		
Discontinued	[redacted]	[redacted]	[redacted]	[redacted]
Down titrated	[redacted]	[redacted]	[redacted]	[redacted]
Stabilised	[redacted]	[redacted]	[redacted]	[redacted]
Up titrated	[redacted]	[redacted]	[redacted]	[redacted]
≥6.0mmol/L– proportion (95% CI)	[redacted]	[redacted]		
Discontinued	[redacted]	[redacted]	[redacted]	[redacted]
Down titrated	[redacted]	[redacted]	[redacted]	[redacted]

Subgroup	SZC	Control (no potassium binder)	Odds ratio	p value
	[redacted]			
Stabilised	[redacted]	[redacted]	[redacted]	[redacted]
Up titrated	[redacted]	[redacted]	[redacted]	[redacted]
Any S-K–proportion (95% CI)	[redacted]	[redacted]		
Discontinued	[redacted]	[redacted]	[redacted]	[redacted]
Down titrated	[redacted]	[redacted]	[redacted]	[redacted]
Stabilised	[redacted]	[redacted]	[redacted]	[redacted]
Up titrated	[redacted]	[redacted]	[redacted]	[redacted]

CI=confidence interval; CS=company submission; RAASi=renin-angiotensin-aldosterone system inhibitors; S-K=serum potassium
Source: CS, Table 24

3.6 Health-related quality of life

The company model is populated with the same HRQoL data that were used to populate the TA599[1] economic model; no new HRQoL data have been presented. (see Section 2.5.5).

3.7 Safety and tolerability

The company model is populated with the same safety data that were used to populate the TA599[1] economic model; no new safety data have been presented. (see Section 2.5.5).

3.8 Conclusions of the clinical effectiveness section

This appraisal is a partial review of TA599;[1] the focus is on expanding the existing NICE TA599[1] guidance for patients with S-K level ≥6.0mmol/L to include those with S-K level ≥5.5 to <6.0mmol/L. Specifically, the population addressed in the CS is patients with persistent HK and CKD (stage 3b to 5) or HF who, due to HK, are not being treated with an optimised RAASi dose; this population is narrower than licensed population and narrower than the population specified in the final scope issued by NICE.[33]

The company has not provided any new evidence from the ZS trials to demonstrate the clinical effectiveness or safety of SZC for a population with CKD or HF and an S-K level ≥5.5 to <6.0mmol/L.

In the final scope[33] issued by NICE, the description of the population includes people with persistent HK who require dialysis. The company has not provided clinical effectiveness evidence to support treating this group of patients with SZC. Clinical advice to the EAG is that people with persistent H-K (S-K level ≥5.5 to <6.0mmol/L) who are receiving haemodialysis are not generally prescribed potassium binders as dialysis effectively removes excess potassium from the blood.

The EAG considers that the SPARK study does not provide robust evidence to confirm an association between persistent HK (S-K level ≥5.5 to <6.0mmol/L) and MACE and mortality outcomes; evidence from James 2021 shows that the relationship is complicated and persistent HK (S-K level ≥5.5 to 6.0mmol/L) may be protective against mortality.

The ZORA study re-analyses used data from Japanese and US patients. Clinical advice to the EAG is that differences in the baseline characteristics of UK, Japan and US patients may affect the generalisability of ZORA study re-analysis results to NHS patients. The differences between healthcare systems in the three countries may also affect generalisability. The EAG therefore considers that the ZORA study does not generate robust evidence to demonstrates that treatment with SZC will increase the likelihood of optimal RAASi usage in the NHS population with persistent HK (S-K level ≥5.5 to <6mmol/L).

4 COST EFFECTIVENESS EVIDENCE

This section provides a summary of the economic evidence submitted by the company in support of SZC for the first-line treatment of HK. The two key components of the economic evidence presented in the CS are (i) the 2024 SLR2 and (ii) a report of the company's economic evaluation. The company has provided an electronic copy of their economic model, which was developed in Microsoft® Excel.

4.1 Company review of published cost effectiveness evidence

To support the original appraisal (TA599[1]), the company undertook SLR1 in April 2018 to identify and appraise: i) published cost effectiveness evaluations, ii) HRQoL data, and iii) cost and resource use data relevant to the decision problem. To inform the current re-appraisal, the company carried out electronic database searches to identify cost effectiveness, HRQoL, cost and resource use studies on 18th June 2024. In response to clarification question C2, the company updated the cost effectiveness searches. Full details of the methods used to identify and select relevant cost effectiveness evidence are provided in the CS (CS, Appendix G, Appendix H and Appendix I).

The 2024 SLR2 identified a total of 35 cost effectiveness studies (CS, Table 26; Appendix G), including eight studies conducted from a UK or Irish perspective. Seventeen HRQoL studies were identified (CS, Appendix H), 12 of which reported utility values for relevant health states (CS, Table 48) and nine reported AE disutility values (CS, Table 49). In addition, the company identified 62 cost and/or resource use studies, including eight conducted from a UK or Irish perspective (CS, Appendix I).

The EAG reviewed the 10 studies identified by the company's updated cost effectiveness searches (for the 2024 SLR2) at clarification and considered none had information that were relevant to the cost effectiveness model.

Table 12 EAG appraisal of company economic systematic review methods

Review process	EAG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	Yes
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes
Was study selection applied by two or more reviewers independently?	Yes
Was data extracted by two or more reviewers independently?	No - data were extracted by a single reviewer and independently verified by a senior reviewer
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes
Was the quality assessment conducted by two or more reviewers independently?	Unclear
Were attempts to synthesise evidence appropriate?	Yes

EAG=External Assessment Group
Source: LR*i*G in-house checklist

The EAG considers the methods used to conduct the company's systematic reviews of cost effectiveness evidence, HRQoL, and cost and healthcare and resource use studies were of a good standard.

4.2 EAG summary and critique of the company's submitted economic evaluation

4.2.1 NICE Reference Case checklist and Drummond checklist

The EAG appraisals of the company's economic analyses using the NICE Reference Case[47] checklist and Drummond[48] checklist are presented in Table 13 and Table 14.

Table 13 NICE Reference Case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Defining the decision problem	The scope issued by NICE.	Yes
Comparators	As listed in the scope issued by NICE	Yes
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
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	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

EAG=External Assessment Group; EQ-5D=EuroQol-5 Dimensions; NHS=National Health Service; NICE=National Institute for Health and Care Excellence; PSS=Personal Social Services; QALY=quality adjusted life year
Source: EAG assessment of NICE Reference Case[47]

Table 14 Critical appraisal checklist for the economic analysis completed by the EAG

Question	Critical appraisal	EAG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partial	The assumption that SZC impacts RAASi use independent of a patient's S-K is not supported by the ZORA study re-analysis
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Yes	
Were costs and consequences adjusted for differential timing?	No	No half-cycle correction was applied due to the use of variable cycle lengths
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	No	In the company model, patients treated with standard care do not receive SZC if they have an S-K level ≥6.0mmol/L

EAG=External Assessment Group; S-K=serum-potassium; RAASi=renin-angiotensin-aldosterone system inhibitor;
Source: Drummond and Jefferson (1996)[48] and EAG comment

4.2.2 Model structure

The company used the model previously assessed and considered suitable for decision-making by NICE in TA599[1] to evaluate the cost effectiveness of SZC as a first-line treatment for HK. A patient-level, fixed-time increment stochastic simulation model was developed in Microsoft® Excel; core calculations were implemented using Visual Basic for Applications (VBA).

A flow diagram showing the company SZC model health states and events is provided in Figure 4. In the model, disease progression in patients with HF is represented by movement between New York Heart Association (NYHA) classes I to IV, which reflect increasing symptom severity. For patients with CKD, progression is represented by a continuous decline in eGFR; transitions through CKD stages are tracked until the onset of end-stage renal disease (ESRD) and the initiation of renal replacement therapy (RRT).

Relevant clinical events, including emergency HK events, MACE, hospitalisations, changes in RAASi therapy, and treatment-related adverse events (TRAEs) are incorporated into the model as patients progress through the simulation. Patients exit the model either due to death or on initiation of RRT.

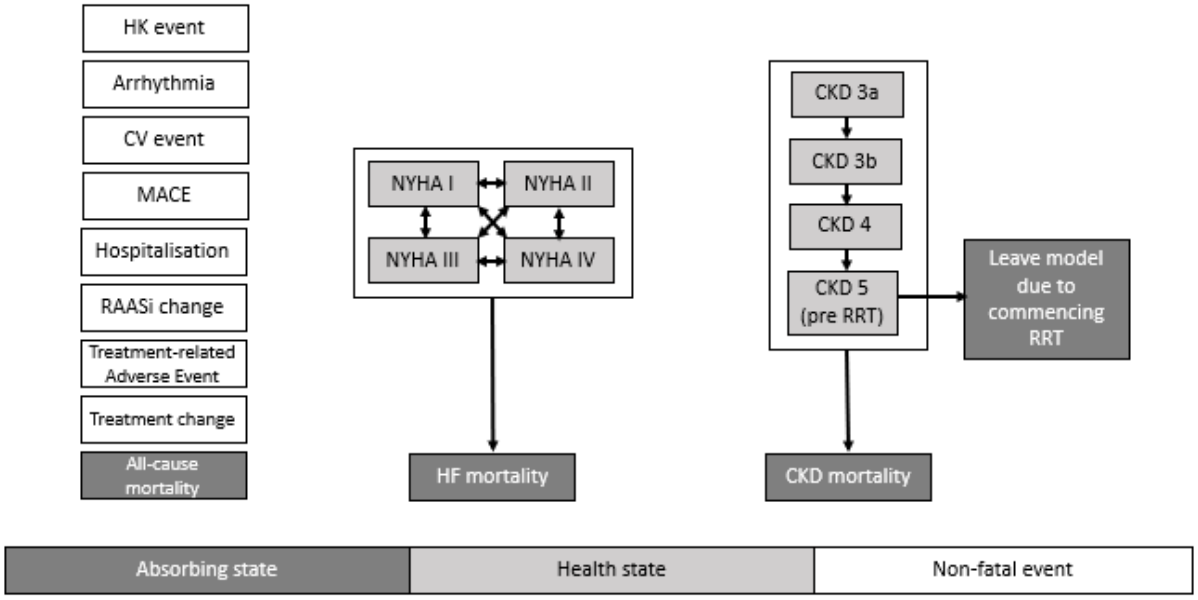

Figure 4 Company model structure

Health states are shaded; events are unshaded
CKD=chronic kidney disease; CS=company submission; CV=cardiovascular; HF=heart failure; HK=hyperkalaemia; MACE=major adverse cardiac event; NYHA=New York Heart Association; RAASi=renin-angiotensin-aldosterone system inhibitor; RRT=renal replacement therapy
Source: CS, Figure 12

4.2.3 Population

The modelled population comprises adults with persistent HK with an S-K level of ≥5.5 to <6.0mmol/L. Patients in the model have a co-diagnosis of HK and an underlying condition, either:

- CKD: stage 3b-5 in the base case (CS, Table 30) and stage 3a-5 in a scenario analysis or
- HF: NYHA class I to IV (CS, Table 31)

Results were also presented for the mixed population of patients with CKD and patients with HF, although results for patients with comorbid HF and CKD were not presented. Cost effectiveness results for patients who require dialysis were also not presented.

Patients are assumed to enter the model with an S-K level of [redacted]mmol/L, reflecting the pooled mean S-K level of the ZS-004 and ZS-005 trial S-K ≥5.5 to <6.0mmol/L cohorts. Model baseline characteristics also reflected ZS-004 and ZS-005 trial data (CS, Table 34) or, where trial data were not available, real-world observational study data (CS, Table 35).

For the mixed population analysis, based on the SPARK[14] study distribution, the cohort was stratified by disease, CKD ([redacted]%) and HF ([redacted]%).[14] These values were used to calculate weighted average baseline characteristics for the mixed patient population. All patients were assumed to be eligible for RAASi therapy; this assumption is consistent with the TA599[1] NICE recommendation that SZC is a treatment option when HK prevents patients from receiving an optimised RAASi dosage.

4.2.4 Interventions and comparators

The company model compares the cost effectiveness of SZC versus standard care. SZC is administered as a 5g or 10g powder (oral suspension); the recommended starting dose is 10g three times daily for up to 72 hours (correction phase), followed by 5g once daily (maintenance phase). In the maintenance phase, to maintain normokalaemia, SZC dose can be up-titrated to 10g once daily or down-titrated to 5g every other day. Standard care was assumed to consist of down-titration or discontinuation of RAASi therapy. Treatment with SZC or standard care includes lifestyle and dietary advice to help manage S-K levels.

4.2.5 Perspective, time horizon and discounting

The model perspective was reported as NHS and Personal Social Services (PSS). A 4-week cycle length was used; this aligns with the ZS-004[6-8] and ZS-005[10-12] trial dosing schedules. To capture granular changes in S-K levels and SZC dosing during the initial treatment phase, the first 4-week period was divided into shorter cycles (Table 15).

The model time horizon was lifetime (80 years), unless RRT was initiated. The 80-year time horizon reflects a maximum age cap of 100 years; all patients aged over 20 year who enter the model transition to an absorbing state within the time horizon. Costs and outcomes were discounted at a rate of 3.5% per annum.

Table 15 Model cycle lengths applied from start of simulation

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

CS=company submission
Source: CS, Table 32

4.2.6 Treatment effectiveness

S-K levels over time

The company model estimates individual patient S-K levels using mixed-effects regression models fitted to ZS-003,[3-5] ZS-004[6-8] and ZS-005[10-12] trial data (Table 16 and Table 17). The regression models consist of four components:

- a fixed component that represents the population-averaged mean S-K level over the trial follow-up period
- a time-dependent component that reflects the daily change in S-K level observed in the trial correction phase (applied in Days 0 to 3 only)
- a patient-specific component that reflects the mean S-K level for an individual patient; a value is drawn from a normal distribution on Day 0 and on Day 4
- an observational component that reflects random variation over time; a value is drawn from a normal distribution in each model cycle.

Table 16 Pre-defined S-K profile for patients treated with SZC: mean values (mmol/L) for mixed-effects model parameters

Model cycle	Fixed component	Time-dependent component	Patient component (SD)	Observation component (SD)	Source
Day 0 to 3	[redacted]	[redacted]	[redacted]	[redacted]	Pooled ZS-004 and ZS-005 trial SZC arm: S-K ≥5.5 to <6.0mol/L subgroup data
Day 4 to 14	[redacted]	[redacted]	[redacted]	[redacted]	
Day 15 to 28	[redacted]	[redacted]	[redacted]	[redacted]	
Day >28	[redacted]	[redacted]	[redacted]	[redacted]	

CS=company submission; N/A=not applicable; SD=standard deviation; S-K=serum potassium
Source: CS, Table 36

Table 17 Pre-defined S-K profile for patients treated with standard care: mean values (mmol/L) for mixed-effects model parameters

Model cycle	Fixed component	Time-dependent component	Patient component (SD)	Observation component (SD)	Source
Day 0 to 3	[redacted]	[redacted]	[redacted]	[redacted]	ZS-003 trial placebo arm: S-K ≥5.5 to <6.0mmol/L subgroup data
Day 4 to 14	[redacted]	[redacted]	[redacted]	[redacted]	
Day 15 to 28	[redacted]	[redacted]	[redacted]	[redacted]	
Day >28	[redacted]	[redacted]	[redacted]	[redacted]	

CS=company submission; N/A=not applicable; SD=standard deviation; S-K=serum potassium
Source: CS, Table 37

For patients receiving standard care, the 48-hour absolute reduction in S-K observed in the ZS-003 trial placebo arm was applied to Day 2 of the S-K trajectory and linearly extrapolated to Day 3 as a conservative assumption; this is in line with the approach preferred by the NICE AC in TA599[1].

The average S-K value is assumed to remain constant from Day 29 onwards for patients treated with SZC and from Day 4 onwards for patients receiving standard care. Upon discontinuation of SZC, a patient's S-K value is calculated using the standard care fixed component (Day 29 onwards) in each subsequent cycle. If a patient reinitiates treatment with SZC, a patient's S-K value is calculated using the SZC fixed component (Day 29 onwards).

The company model generates a new S-K value for each patient in every cycle and this determines the patient's risk of MACE, mortality and hospitalisation (estimated using SPARK study results).

RAASi status change

The company categorises the level of RAASi therapy use as follows:

- RAASi "max", which corresponds to RAASi dosages recommended by clinical guidelines[49]
- RAASi "sub-max", which reflects imperfect RAASi therapy use and is based on the mean dose at baseline observed in the SPARK study
- No RAASi use

All patients enter the model in the "max" RAASi state and can down-titrate or discontinue treatment in the first model cycle. The probabilities of down-titrating or discontinuing RAASi are estimated from the ZORA study re-analysis and vary by S-K group and treatment (Table 18). The probabilities of discontinuing RAASi are assumed equivalent for patients in the "max" or "sub-max" RAASi therapy states.

Table 18 RAASi discontinuation and down-titration by S-K category

S-K category (mmol/L)	SZC				Standard care				Source
	Proportion of patients discontinuing		Proportion of patients down-titrating		Proportion of patients discontinuing		Proportion of patients down-titrating		
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	
<5.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Assumption
5.0–5.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ZORA subgroup analysis
5.5–5.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
≥6.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

CS=company submission; RAASi=renin-aldosterone system inhibitor; SE=standard error; S-K=serum potassium;
Source: CS, Table 38

The probability of returning to the "max" RAASi state is 49.7% for patients receiving SZC or standard care; this probability was used in TA599. [1] The probability of up-titration was sourced from a study of patients with CKD who had discontinued RAASi therapy;[43] the company assumed that the probability of up-titration was the same regardless of underlying disease (HF or CKD) and prior RAASi therapy status (no RAASi or "sub-max" RAASi).

Patients were only eligible to return to the “max” RAASi state if they were in the maintenance phase (Day 29 onwards), had not exited the model due to death or RRT and at least 3 cycles (12 weeks) had elapsed since RAASi discontinuation or down-titration. The timing requirement was informed by the published literature[50] and the value of 12 weeks was based on clinical expert input during TA599.[1]

The steps used in the company model to determine changes in RAASi therapy are shown in Figure 5. Only one change to RAASi therapy is permitted in each model cycle.

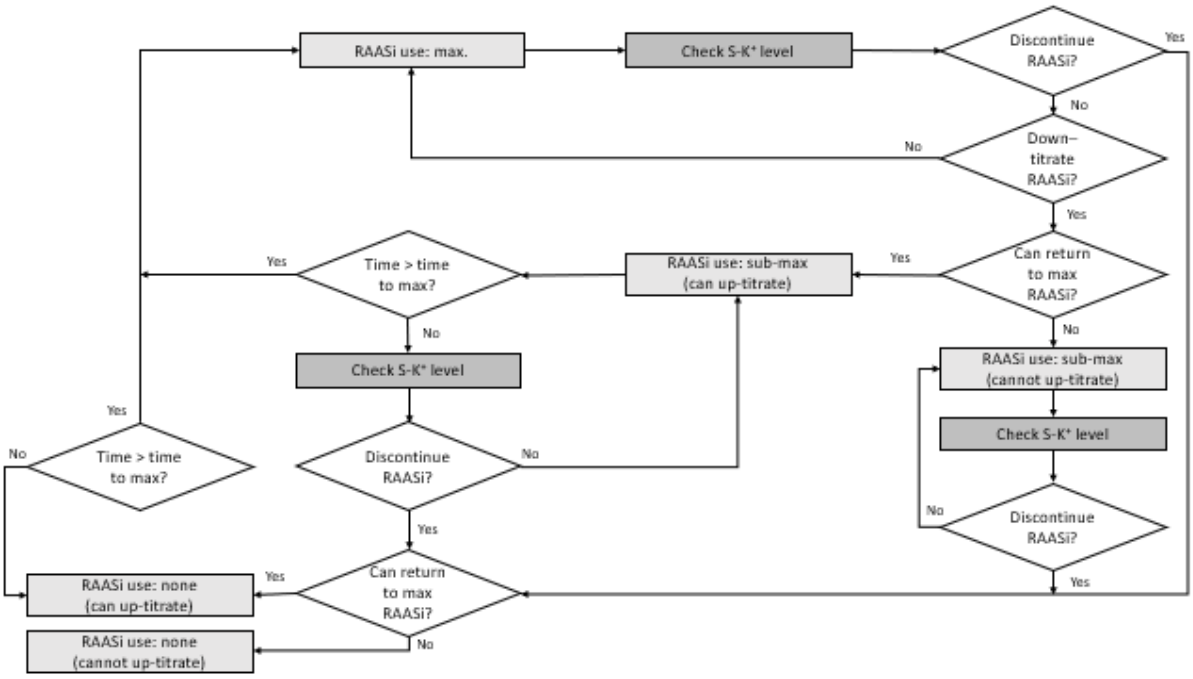

Figure 5 Company model algorithm to determine change in RAASi use

CS=company submission; RAASi=renin-angiotensin-aldosterone system inhibitor; S-K=serum potassium
Source: CS, Figure 14

4.2.7 Disease progression and adverse events

Chronic kidney disease

In the company model, patients with CKD who have discontinued RAASi therapy have a higher risk of disease progression (greater eGFR decline) than patients who remain on RAASi therapy (CS, Table 40). RRT is initiated when eGFR falls to ≤8.5 mL/min/1.73 m²; this is in line with Renal Association recommendations.[51]

The risks of clinical outcomes (MACE, mortality and hospitalisation) occurring are determined by eGFR/CKD stage, S-K values and RAASi use (CS, Figure 15).

Heart failure

NYHA classification transition probabilities were sourced from the literature[52] and were assumed to be independent of RAASi use (CS, Table 44). Event risks for the HF population were determined by RAASi use, NYHA stage and S-K level (CS, Figure 16).

The company used the Seattle Heart Failure Model,[53] a multivariate Cox model, to estimate mortality risk for patients with HF. Hazard ratios were applied to adjust the all-cause mortality risk (CS, Table 47).

Treatment-related adverse events

All AEs with an incidence of ≥5% in the ZS-005 trial were included in the company model (Table 19); as a conservative assumption, the company assumed these were TRAEs. The company assumed that no patients treated with standard care experienced TRAEs.

Table 19 Proportion of cohort experiencing treatment-related adverse events

Treatment-related adverse event	SZC (while on treatment)		Distribution	Source
	Mean	SE		
Oedema	0.116	0.012	Beta	ZS-005 trial
Worsening hypertension	0.109	0.011	Beta	
Constipation	0.064	0.009	Beta	
Diarrhoea	0.044	0.007	Beta	
Nausea	0.075	0.010	Beta	
Hypomagnesaemia	0.012	0.004	Beta	
Hypokalaemia	0.015	0.004	Beta	
Urinary tract infection	0.079	0.010	Beta	

CS=company submission; SE=standard error
Source: CS, Table 39

Other-cause mortality

In the company model, patients are at risk of condition-specific mortality and other-cause mortality. The company estimated other-cause mortality using the ONS life tables.[54] When the probability of death due to comorbidities is lower than the probability of all-cause mortality, the latter is applied to maintain clinical plausibility. No patient was assumed to live past 100 years.

4.2.8 Health-related quality of life

Health state utility values

No HRQoL data were collected as part of the ZS-004 and ZS-005 trials and therefore the utility values used in the company model were sourced from the published literature. The company defined a patient's health state utility as the product of the general population baseline utility (Table 20) and a condition-specific utility value (Table 21), with disutilities associated with adverse events subtracted. Utility was assumed to remain constant over the course of the disease for a given disease state; this approach was used in TA599.[1]

Table 20 Company model baseline utility values

Age (years)	Male		Female		Distribution	Source
	Mean	SE	Mean	SE		
0	0.000	0.007	0.000	0.007	Normal	Szende 2014[55]
1 to 24	0.934	0.007	0.934	0.007	Normal	
25 to 34	0.922	0.005	0.922	0.005	Normal	
35 to 44	0.905	0.005	0.905	0.005	Normal	
45 to 54	0.849	0.010	0.849	0.010	Normal	
55 to 64	0.804	0.010	0.804	0.010	Normal	
65 to 74	0.785	0.010	0.785	0.010	Normal	
75 to 100	0.734	0.013	0.734	0.013	Normal	

CS=company submission; SE=standard error
Source: CS, Table 50

Table 21 Company model disease-specific utility values

Health state	Utility	SE	Distribution	Source
NYHA I	0.855	0.005	Beta	Göhler 2009[56]
NYHA II	0.771	0.005	Beta	
NYHA III	0.673	0.006	Beta	
NYHA IV	0.532	0.027	Beta	
CKD 3a	0.800	0.080	Beta	TA599
CKD 3b	0.800	0.080	Beta	
CKD 4	0.740	0.074	Beta	
CKD 5 (pre-RRT)	0.710	0.071	Beta	

CKD=chronic kidney disease; CS=company submission; NYHA=New York Heart Association; RRT=renal replacement therapy; SE=standard error
Source: CS, Table 51

Adverse event disutilities

Event disutilities were estimated using utility values identified from the published literature (Table 22). No disutility was applied for a low potassium diet. Disutilities were applied as decrements to baseline utility values; they were conditional on AE occurrence and duration varied by AE type. Total disutility was assumed to be equal across treatment arms to account

for the potential of multiple AE events in the shorter-duration standard care arm; this approach is consistent with the approach used in TA599.[1]

Table 22 Adverse event disutilities applied in company model

Adverse event	No. cycles applied	Utility	SE	Dist	Source
Oedema	13 (1 year)	−0.0029	0.000	Beta	Sullivan 2011[57]
Constipation	13 (1 year)	−0.0056	0.001	Beta	Sullivan 2011[57]
Diarrhoea	13 (1 year)	−0.0008	0.001	Beta	Kristiansen 1999[58]
Nausea	13 (1 year)	−0.0037	0.001	Beta	Nafees 2008[59]
Hypomagnesaemia	13 (1 year)	−0.0028	0.002	Beta	Sullivan 2011[57]
Anorexia	13 (1 year)	−0.0029	0.001	Beta	Sullivan 2011[57]
Hypokalaemia	13 (1 year)	0.0000	0.000	Beta	Assumption – no study identified
Urinary tract infection	13 (1 year)	−0.0004	0.001	Beta	Sullivan 2011[57]
MACE event	1	−0.050	0.040	Beta	Kent 2013[60]
Hospitalisation	1	−0.024	0.007	Beta	Göhler 2009[56]

CS=company submission; Dist=distribution; MACE=major adverse cardiac event; SE=standard error
Source: CS, Table 52

4.2.9 Resources and costs

Intervention and comparators costs

The list price for a 5g sachet of SZC is £5.20 and the list price for a 10g sachet is £10.40. The cost of a course of SZC was estimated as the cost per sachet multiplied by the actual doses given over the first 84 days of the ZS-005 trial for patients with an S-K of ≥5.5 to <6.0mmol/L (Table 23).

One SZC treatment course includes the correction phase (Days 1 to 3) followed by the maintenance phase (Days 4 to 28 and two additional 4-week cycles). In the company model, the total cost per treatment course is £[redacted] without wastage, and £[redacted] when a wastage assumption of 2 days per 28 days is applied (in the maintenance phase only).

Table 23 Dosing schedule for SZC applied in company model

Day	5g daily	10g daily	10g three times a day	Cost/day
1	[redacted]%	[redacted]%	[redacted]%	£[redacted]
2	[redacted]%	[redacted]%	[redacted]%	£[redacted]
3	[redacted]%	[redacted]%	[redacted]%	£[redacted]
Day	**5g every other day**	**5g daily**	**10g daily**	**Cost/day**
4+	[redacted]%	[redacted]%	[redacted]%	£[redacted]

CS=company submission
Source: CS, Table 56

In the company base case analysis, patients receiving SZC are assumed to discontinue treatment after 12 weeks, or on initiation of RRT. Patients may also discontinue SZC for other reasons; the company applied an annual probability of discontinuation (37.5%); based on ZS-005 trial data. Patients can re-initiate SZC treatment if their S-K level is ≥5.5mmol/L. No costs were directly associated with the prescription of SZC; the company assumed that prescription costs were included within the cost of managing a HK event (via outpatient visit).

The company assumed that patients receiving standard care do not incur costs related to the treatment of persistent HK. No costs were included for low potassium diets.

RAASi therapy costs

RAASi therapy includes angiotensin-converting-enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs). The company stated that the inclusion of MRAs within RAASi therapy drug costs was intended to align with national guidelines and considered a conservative assumption.[49] However, MRAs were not considered as part of RAASi therapy in the Xie et al.[61] study used in the company model to inform the risk of death and MACE by RAASi status (CS, Table 43). Drug costs were estimated separately for the "max" and "sub-max" RAASi therapy states for the CKD population and the HF population (Table 24).

Table 24 RAASi therapy costs

RAASi therapy state	Drug class (drug costed)	Population		Average daily dose (mg)	Cost per mg	Source
		CKD	HF			
Max	ACEi (ramipril)	90%	90%	10.00	£0.0058	ESC recommendations[49]
	ARB (candesartan cilexetil)	10%	10%	32.00	£0.0036	ESC recommendations[49]
	MRA (spironolactone)	50%	70%	50.0	£0.0026	ESC recommendations[49]
Sub-max	ACEi (ramipril)	90%	90%	5.99	£0.0058	CPRD mean dose at baseline (SPARK study)
	ARB (candesartan cilexetil)	10%	10%	10.06	£0.0036	CPRD mean dose at baseline (SPARK study)
	MRA (spironolactone)	30%	50%	44.59	£0.0026	CPRD mean dose at baseline (SPARK study)

ACEi=angiotensin-converting-enzyme inhibitor; ARB=angiotensin II receptor blocker; CKD=chronic kidney disease; CPRD=Clinical Practice Research Datalink; CS=company submission; ESC=European Society of Cardiology; HF=heart failure; MRA=mineralocorticoid-receptor antagonist; RAASi=renin-angiotensin-aldosterone system inhibitor
Source: CS, Table 59, Table 60, Table 61 and Table 62

The cost of a change to RAASi therapy (down-titration, discontinuation or up-titration) is applied as a one-off cost. The resource use associated with each possible change was verified by clinical expert input[62] (CS, Table 65 and Table 66). The company assumed that i) for patients who discontinue or down-titrate RAASi therapy, 50% occur in primary care and 50% occur in secondary care and ii) that up-titration occurred exclusively in primary care.

Health state costs and resource use

CKD and HF management costs are presented in Table 25 and have been inflated to the current cost year using the PSS Pay and Prices Index.[63]

Table 25 Disease health state costs

Disease severity	Annual cost		Distribution	Source
	Mean	SE		
Chronic kidney disease				
Stage 3a	£1,354.02	£59.04	Gamma	Kent 2015[64]
Stage 3b	£1,354.02	£59.04	Gamma	
Stage 4	£4,741.00	£107.81	Gamma	
Stage 5 (pre-RRT)	£16,623.00	£237.43	Gamma	
Heart failure				
NYHA I	£106.89	£10.69	Gamma	Ford 2012[65]
NYHA II	£123.15	£12.31	Gamma	
NYHA III	£159.72	£15.97	Gamma	
NYHA IV	£170.46	£17.05	Gamma	
S-K (all levels)	£0.00	£0.00	N/A	Assumption – no literature source found

CS=company submission; N/A=not applicable; NYHA=New York Heart Association; SE=standard error; S-K=serum potassium
Source: CS, Table 58

Adverse event costs

The company model included two types of HK events:

- an emergency HK event (patient's S-K level ≥6.5mmol/L) that required hospital admission
- a less severe HK event (patient's S-K level ≥5.5 to <6.5mmol/L) that was managed via a single outpatient visit

The cost of an emergency HK event was informed by clinical expert input[62] and varied by treatment (Table 26). The resource use associated with a less severe HK event was informed by clinical expert input[62] (CS, Table 64). The cost of a MACE and hospitalisation were sourced from the published literature (Table 26). Each event cost was applied in the cycle that the event occurred.

Table 26 Adverse event costs applied in the company model

Event	Annual cost		Dist	Source
	Mean	SE		
Less severe HK event	£379.93	£37.99	Gamma	Clinical expert input[66]
Emergency HK event - SZC	£2,749.39	£274.74	Gamma	Clinical expert input[66]
Emergency HK event – standard care	£3611.87	£361.19	Gamma	Clinical expert input[66]
MACE	£5,817.39	£822.37	Gamma	Kent 2013[64]
Hospitalisation	£2,962.16	£296.22	Gamma	Colquitt 2014[67]

CS=company submission; Dist=distribution; HK=hyperkalaemia; MACE=major adverse cardiovascular event; SE=standard error
Source: CS, Table 67 and Table 68

The average per-patient TRAE cost was calculated by combining the proportion of patients expected to experience each TRAE with the annual cost of the TRAE, conditional on occurrence. The company sourced TRAE unit costs from NHS Cost Collection 2022-2023[68] (CS, Table 67).

5 COST EFFECTIVENESS RESULTS

5.1 Base case analysis

The company's base case deterministic cost effectiveness results are presented in Table 27 for the mixed CKD and HF population, Table 28 for the CKD population, and Table 29 for the HF population.

Table 27 Deterministic base case results: mixed CKD and HF population

Technology	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
SZC	£45,546	4.128	£5,312	0.425	£12,495
Standard care	£40,234	3.703	-	-	-

CKD=chronic kidney disease; CS=company submission; HF=heart failure; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
Source: CS, Table 78

Table 28 Deterministic base case results: CKD population

Technology	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
SZC	£54,241	3.466	£4,572	0.272	£16,833
Standard care	£49,669	3.194	-	-	-

CKD=chronic kidney disease; CS=company submission; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
Source: CS, Table 79

Table 29 Deterministic base case results: HF population

Technology	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
SZC	£24,224	3.906	£6,506	0.719	£9,053
Standard care	£17,719	3.187	-	-	-

CS=company submission; HF=heart failure; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year;
Source: CS, Table 80

A summary of clinical outcomes for the three populations is provided in Table 30. The company attributed the higher number of MACE, hospitalisations, and RAASi down-titration/discontinuation events in the SZC arm to increased life expectancy resulting in more S-K-unrelated events.

Table 30 Company base case disaggregated clinical outcomes per patient

Events	Cumulative events per patient					
	Mixed CKD and HF		CKD		HF	
	SZC	Standard care	SZC	Standard care	SZC	Standard care
HK event	12.141	16.621	10.252	14.314	12.096	14.764
MACE	1.194	1.129	1.238	1.218	0.929	0.768
Hospitalisation	4.652	4.378	4.978	4.749	3.260	2.799
RAASi discontinuation/ down-titration	2.720	2.451	2.576	2.431	2.732	2.426
Mortality within 5 years of first HK event	0.272	0.329	0.341	0.381	0.380	0.506

CS=company submission; CKD=chronic kidney disease; HF=heart failure; HK=hyperkalaemia; MACE=major adverse cardiac event
Source: CS, Table 81

The company conducted a probabilistic sensitivity analysis (PSA) with 100 iterations for the mixed CKD and HF population (Table 31); these results are similar to the company's deterministic cost effectiveness results for the mixed population.

Table 31 Probabilistic base case results: mixed CKD and HF population

Technology	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
SZC	£45,596	4.126	£5,276	0.423	£12,417
Standard care	£40,321	3.703	-	-	-

CS=company submission; CKD=chronic kidney disease; HF=heart failure; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
Source: CS, Table 82

5.2 Sensitivity analysis

The company varied model parameter input values individually in one-way sensitivity analyses (OWSA). Upper and lower CI were sourced from the literature, where available, or derived from the predefined probabilistic distributions assigned to each parameter. Where standard errors were not available to calculate confidence intervals, a standard error equal to 10% of the mean was assumed.

Among the parameters tested, the S-K threshold for repeat treatment had the greatest influence on cost effectiveness results (CS, Table 83).

5.3 Scenario analysis

The company conducted scenario analyses exploring alternative model settings and structural uncertainties (CS, Table 84). The company base case cost effectiveness results were most sensitive to assumptions about long-term outcomes for patients treated with a RAASi and the proportion of CKD patients entering the model with stage 3a disease.

5.4 Model validation

The company validated modelling assumptions and clinical inputs by consulting clinical and health economic experts. The submitted company model was based on a version originally developed by an external consultancy and further refined to incorporate NICE TA599[1] AC-preferred assumptions, additional real-world evidence and updated clinical validation. The model structure and methodological approach were reviewed and validated by academic health economics researchers and external consultancy experts.

6 EAG CRITIQUE OF COMPANY ECONOMIC MODEL

The company submitted an economic model developed in Microsoft® Excel to generate cost effectiveness results for the comparison of SZC versus standard care (patients who would otherwise manage HK by down-titration or discontinuation of RAASi) for the treatment of HK for patients with a S-K between ≥5.5 and <6.0mmol/L.

The main benefit of SZC is to enable patients to maintain or up-titrate their RAASi dosages which in turn reduces the risk of disease progression and adverse outcomes. The EAG critique therefore focusses on the modelling of RAASi use and assumptions relating to the impact of SZC on RAASi use.

6.1 Overview of modelling issues identified by the EAG

The EAG reviewed the company model to check that calculations were accurate and that parameter values matched the values presented in the CS. There were small discrepancies between the SPARK study S-K group IRRs for mortality and MACE used in the company model and those presented in the CS (Appendix M, Table 90 and Table 91); the EAG assessed the impact of using Appendix M values on cost effectiveness results and found that it was minimal. A summary of the EAG critique is presented in Table 32.

Table 32 Summary of EAG critique of company cost effectiveness model

Aspect considered	EAG comment	Section of EAG report
Model structure	The company model structure and time horizon are appropriate.	N/A
Population	No cost effectiveness evidence was presented for patients comorbid with HF and CKD or those who require dialysis.	N/A
Impact of SZC on RAASi use	ZORA study subgroup re-analysis results do not support the assumption that SZC impacts the probability of RAASi discontinuation/down-titration for patients in the same S-K group. The minimum possible SZC treatment duration in the ZORA study is longer in relative terms than the average SZC treatment duration in the company base case. Applying SZC-specific probabilities to patients who have discontinued SZC will overestimate the benefit of SZC on RAASi use.	6.2
Comparator	In the company model, patients receiving standard care do not receive SZC if their S-K ≥6.0 mmol/L. If average S-K values are expected to increase over time, it is plausible that a substantial proportion of patients would be eligible to receive SZC.	6.4
SZC treatment duration	In the company model. all patients receiving SZC at 12 weeks discontinue treatment and re-initiate if S-K ≥ 5.5 mmol/L. The EAG has used a lifetime treatment duration.	6.3

Aspect considered	EAG comment	Section of EAG report
Relationship between S-K and adverse outcomes	The EAG has concerns that SPARK study S-K group IRRs may not reflect a causal effect of S-K on the risk of adverse outcomes. In an explanatory scenario, the EAG assumes that S-K has no effect on the risk of MACE, hospitalisations and mortality.	6.5
Modelling of RAASi up-titration	The EAG has used ZORA study re-analysis estimates to inform the probabilities of up-titration in the company model to be consistent with the data source used for the probabilities of down-titration/discontinuation.	6.6
Generalisability of RAASi model algorithm	The algorithm used to model changes in RAASi use may not accurately reflect what would happen in NHS clinical practice and may overestimate the proportion of patients and/or length of time patients spend in the “max” RAASi state.	6.7
Healthcare resource use	Annual costs associated with CKD health states are likely to be overestimates since patients received RRT in the follow-up period of the Kent study[64]. The EAG has applied the cost estimates used in TA599.	6.8
Health-related quality of life	Disease-specific HSUVs were multiplied by general population utility values; the age-related decline in patient HRQoL is likely to be overestimated particularly for earlier disease states. As patients treated with SZC are less likely to experience disease progression due to more optimal RAASi use, the EAG considers this approach is conservative.	N/A
Drug costs	Drug costs have been calculated appropriately.	N/A
Adverse events	The approach to modelling AEs is appropriate.	N/A
Severity modifier	The company did not present evidence to support the application of a severity modifier. The EAG agrees that a severity modifier should not be applied.	N/A
PSA	The PSA took a substantial time to run (>24 hours) therefore results are presented for the mixed population only. It was not clear why risk parameters were excluded from the PSA.	N/A

AE=adverse event; CKD=chronic kidney disease; HF=heart failure; HRQoL=health-related quality of life; HSUV=health state utility value; IRR=incidence rate ratio; MACE=major adverse cardiac event; N/A=not applicable; PSA=probabilistic sensitivity analysis; RAASi=renin–angiotensin–aldosterone system inhibitors; RRT=renal replacement therapy; S-K=serum potassium

6.2 Impact of SZC on RAASi use

In the company model, the probabilities of down-titrating or discontinuing RAASi were sourced from the ZORA study re-analysis. The probabilities applied in each model cycle depend on a patient’s treatment and their S-K value (Table 18). This means that, in the company model, two patients with the same S-K value will have different probabilities of discontinuing/down-titrating RAASi treatment if one of the patients is treated with SZC. Therefore, SZC has both a direct (conditional on S-K) and indirect (through changes in S-K) impact on the probability of discontinuing or down-titrating RAASi treatment.

6.2.1 Appropriateness of treatment-specific RAASi down-titration/discontinuation probabilities for patients in the same S-K group

When carrying out the ZORA study re-analysis, "…the SZC and control (no potassium binder) cohorts were stratified by HK severity (defined by the maximum S-K level recorded in the 2 weeks prior to the index date) among those with available data on S-K" (CS, p68). As S-K subgroups were defined using baseline S-K values, the EAG asked the company to provide information on whether, within each subgroup, S-K values changed over the study follow-up period (clarification question A2). In response to this question (company clarification response, Table 2), the company presented data that showed:

[redacted]The EAG highlights that no adjustment was made in the ZORA study re-analysis to account for changes in S-K levels during the follow-up period. Whilst the magnitude of change in S-K values for each cohort is not known, [redacted]. In the ZORA study re-analysis, [redacted] is likely to be explained by the decrease in S-K after treatment initiation, as opposed to any effect that is independent of S-K. The effect of changes to S-K on RAASi use is already accounted for in the model through the different S-K group probabilities and lower average S-K values for patients treated with SZC.

The EAG considers that the ZORA study re-analysis does not support the company assumption that, conditional on S-K group, [redacted]. For each S-K group, the EAG has set the probabilities of RAASi discontinuation or down-titration to be the same for patients treated with SZC and for patients receiving standard care. It is not clear which probabilities (SZC or standard care) would be most representative of NHS clinical practice; therefore, the EAG has presented two alternative base cases, one populated with SZC probabilities and one populated with standard care probabilities. This EAG revision removes the direct impact of SZC on RAASi treatment; however, the indirect impact (i.e., impact due to changes in S-K level) remains.

6.2.2 Accounting for SZC treatment discontinuation

In each model cycle, the SZC probabilities of discontinuing or down-titrating RAASi treatment are applied to all patients initially treated with SZC, independent of whether the patient has discontinued SZC. In response to clarification question B4, the company considered that treatment discontinuation was implicitly captured in the SZC cohort of the ZORA study re-analysis since patients may have discontinued after 120 days of continuous SZC treatment.

The company did not provide the mean SZC treatment duration or number of ZORA study re-analysis patients who discontinued SZC. The EAG highlights that the minimum SZC treatment duration in the ZORA study (assuming all patients discontinued after 120 days of treatment) expressed relative to the length of follow-up is 66.7% (120/180). This estimate is substantially higher than the company base case mean SZC treatment duration, which is expressed as a proportion of expected survival in years (2.3/8.1=28.3%). The EAG therefore considers that applying ZORA study re-analysis SZC probabilities to all patients initially treated with SZC is likely to overestimate the benefit of SZC on RAASi use (i.e., underestimate the proportion of patients who discontinue or down-titrate RAASi treatment).

In an EAG scenario in which a lifetime SZC treatment duration is assumed (see Section 6.3), mean treatment duration expressed as a proportion of expected survival is approximately 70%; this proportion is more consistent with the minimum possible treatment duration in the ZORA study re-analysis. The EAG also assumed that SZC had no impact on RAASi use conditional on S-K (Section 6.2.1). Both revisions adjust for the overestimation of the benefit of SZC on RAASi use in the company base case.

6.3 SZC treatment duration

In the company model, all patients still receiving SZC at 12 weeks discontinue treatment; the company reports that this modelling decision was taken based on clinical expert opinion[66] and market research.[69] The market research showed that, for patients with HK, median treatment duration was [redacted] days between October and December 2022 and [redacted] days between July and August 2023. In the company model, SZC is reinitiated (for 12 weeks) if a patient's S-K is ≥5.5 mmol/L. In the company base case analysis, a patient remains on SZC treatment for an average of 2.30 years over the model time horizon as patients frequently discontinue and re-initiate SZC treatment.

The EAG considers the evidence provided by the company to support a treatment duration of 12 weeks is weak. During the company advisory board meeting,[66] only one clinician (of five consulted by the company) expressed a view consistent with a short treatment duration, stating that [redacted]

[redacted]". The market research data[69] were only collected over [redacted] ([redacted]); in each period, clinicians were asked to provide [redacted]. There is also no information about whether patients were being treated for acute or persistent HK, their S-K level when treatment was initiated and why treatment with SZC was stopped.

Clinical advice to the EAG is that whilst SZC dose reductions may occur in clinical practice, most patients would not discontinue treatment with SZC as discontinuation would be expected to result in S-K increasing to the level prior to SZC treatment initiation. The EAG therefore considers that the frequent discontinuation and re-initiation of SZC that occurs in the company model likely does not reflect future NHS clinical practice. Furthermore, during the company advisory board meeting[66] it was noted that, "[redacted]". The EAG highlights that, in the company model, SZC discontinuation increases a patient's S-K level and this increases the probability of RAASi treatment discontinuation or down-titration; this effect is not consistent with the primary objective of initiating SZC treatment. The EAG has run a scenario in which, once initiated, treatment with SZC continues for the remainder of that patient's lifetime (but is subject to an annual probability of treatment discontinuation from the ZS-005 trial).

6.4 Standard care

6.4.1 S-K levels over time

In the company model, for patients receiving standard care, the mean S-K level is assumed to remain constant from Day 4 onwards. In response to clarification question B1, the company considered this assumption was supported by the REVOLUTIONIZE I study[70] where patient S-K levels associated with recurrent HK events were generally comparable to S-K levels associated with the patient's initial HK event. The EAG considers that the REVOLUTIONIZE I study[70] provides evidence that S-K remains relatively stable in the short-and medium-term (study follow-up was 6 months); however, the model time horizon is lifetime and the company has not provided any evidence to support the assumption that the mean S-K value remains constant indefinitely for patients receiving standard care. Clinical advice to the EAG is that for patients whose S-K level is managed by down-titrating or discontinuing RAASi treatment, average S-K levels are likely to increase over time as their underlying disease progresses, particularly for patients with CKD. The EAG notes that disease progression (eGFR decline

and NYHA progression) is included in the model; however, these metrics have no effect on S-K levels. If average S-K levels are expected to increase over time, a substantial proportion of patients may be eligible to receive SZC (Section 6.4.2).

6.4.2 SZC treatment if S-K ≥6.0 mmol/L

In the company model, patients receiving standard care do not receive SZC (or another potassium binder) if their S-K level is ≥6.0 mmol/L. In response to clarification question B1, the company stated that the exclusion of SZC treatment for patients receiving standard care was likely to have a minimal impact on model outcomes since a S-K level of ≥6.0 mmol/L was unlikely to occur. The EAG considers that the small number of model patients with S-K levels ≥6.0 mmol/L is a consequence of the company assumption that average S-K level remains constant over time, which is not consistent with clinical advice to the EAG (Section 6.4.1). Whilst treatment with SZC will increase costs for patients receiving standard care, a substantial reduction in S-K would also be expected based upon the reduction modelled in TA599.[1] As a result, patients would be able to maintain and optimise their RAASi dosages for longer, reducing their risk of disease progression and adverse outcomes. The impact on cost effectiveness results is uncertain as it is not known how many patients receiving standard care are expected to receive SZC over the time horizon of the model.

6.5 Relationship between S-K and adverse outcomes

In the company model, the risks of MACE, hospitalisation and mortality depend on a patient's S-K level, RAASi state (off treatment, "sub" and "max" dosages) and disease stage (CKD or HF). SPARK study IRRs for each outcome are applied in each model cycle and vary according to a patient's S-K level (for patients with CKD, the risk of hospitalisation also varies by eGFR value).

As discussed in section 3.4.5, the EAG considers that the SPARK study does not provide robust evidence to confirm the association between persistent HK (S-K level ≥5.5 to <6.0mmol/L) and MACE and mortality outcomes; evidence from James 2021[41] shows that the relationship is complicated and persistent HK (S-K level ≥5.5 to <6.0mmol/L) may be protective against mortality. Furthermore, if the association between S-K and the risk of adverse outcomes reflects underlying disease progression and/or changes to RAASi dosages, applying SPARK study S-K group IRRs may overestimate the risk of adverse outcomes as these effects are included in the model.

The EAG has run a scenario in which S-K level is assumed to have no effect on the risk of MACE, hospitalisations and mortality (S-K group IRRs set equal to one); this has a small impact on company base case cost effectiveness results. The EAG considers that this is due

to [redacted] (after accounting for changes in RAASi use).

6.6 Modelling RAASi up-titration

6.6.1 Data source used to estimate the probability of up-titration

In the company model, the probability of returning to the "max" RAASi state is 49.7% for patients receiving SZC or standard care. This value, which was used in TA599,[1] was sourced from Luo 2016[43] and reflects the proportion of patients with CKD who reinitiated RAASi treatment after having previously discontinued (defined as ≥14-day gap in drug supply).

The ZORA study re-analysis includes estimates of the proportion of patients who up-titrated RAASi by treatment and S-K group and, in the company model, the probabilities of down-titrating or discontinuing RAASi treatment are sourced from the ZORA study re-analysis. The EAG asked the company to explain why data from Luo 2016[43] was preferred to ZORA study re-analysis data and to update the company model so that the probability of up-titration was informed by ZORA study re-analysis estimates (clarification question B7).

In response to clarification B7, the company considered that it was not appropriate to use ZORA study re-analysis estimates because it is not known how many patients up-titrated to an optimal RAASi dose or reinitiated RAASi therapy following discontinuation. Furthermore, since the baseline ZORA study re-analysis population was not disaggregated by patients receiving an optimal versus suboptimal RAASi dose, the company considered that up-titration may not have been possible for a large proportion of patients. The company also considered their approach was conservative since the ZORA study re-analysis estimates suggest that, for all S-K groups, the probability of RAASi up-titration is higher for patients in the SZC cohort than for patients in the no potassium binder cohort.

The EAG acknowledges that there are limitations and uncertainties with the ZORA study re-analysis but highlights that several assumptions were made in the company model when using the Luo study[43] estimate:

- all patients are assumed to return to optimised RAASi treatment but in the Luo study[43] it is not known how many patients up-titrated to an optimal RAASi dose (as with the ZORA study re-analysis)
- the probability of up-titration is applied to patients in the model who are receiving a suboptimal RAASi dose but the Luo study[43] estimate only relates to patients who reinitiated RAASi treatment having previously discontinued
- the probability of up-titration is applied to patients regardless of underlying disease but the Luo study[43] only included patients with CKD

It is therefore not clear to the EAG that Luo 2016[43] provides more robust estimates than the ZORA study re-analysis. As discussed in Section 6.2.1, the EAG does not consider that results from the ZORA study re-analysis support the assumption that SZC impacts RAASi use conditional on S-K group. However, the EAG considers that due to a lower average S-K level, patients treated with SZC are likely to have a higher probability of RAASi up-titration than patients receiving standard care. Since the probability of RAASi up-titration is applied to all patients independent of their S-K level, the EAG has run a scenario using ZORA study re-analysis treatment-specific estimates (Table 33).

Table 33 Probability of RAASi up-titration applied in company model

Model analysis	SZC	Standard care	Source
Company base case	49.7%	49.7%	Luo 2016[43]
EAG base case	[redacted]	[redacted]	ZORA study re-analysis (any baseline S-K group)

Source: CS, Table 24

The EAG highlights that the Luo 2016[43] estimate is substantially higher than the ZORA study re-analysis estimates. It is therefore not clear that the company's approach is conservative as, in the company base case, patients treated with SZC who return to the "max" RAASi state [redacted].

6.6.2 Time constraint to be eligible for return to "max" RAASi state

In the company model, patients are only eligible to return to the "max" RAASi state if 12 weeks have elapsed since RAASi treatment was discontinued or down-titrated. A value of 12 weeks was based upon clinical expert input from TA599.[1]

Clinical advice to the EAG is that clinicians would consider re-initiating or up-titrating RAASi treatment 4 weeks after discontinuation or down-titration. The EAG considers that 4 weeks is more representative of current NHS clinical practice than 12 weeks and that a period of 4 weeks is consistent with clinical guidelines[18,24] which emphasise the importance of optimising RAASi treatment and minimising time spent not receiving a RAASi (CS, p16). The impact on the ICER per QALY gained of using a period of 4 weeks rather than a period of 12 weeks is small (<£200).

6.7 Generalisability of RAASi model algorithm to NHS clinical practice

The EAG considers that the company's approach to modelling RAASi use may not accurately reflect NHS clinical practice and is likely to overestimate the proportion of patients and/or length of time that is spent in the "max" RAASi state. The EAG concerns relate to baseline

RAASi use (Section 6.7.1) and up-titration after RAASi discontinuation (Section 6.7.2). The impact of changing these model parameters on cost effectiveness results is uncertain and may depend on the probability of up-titration applied in the model; the EAG has not made any changes to the company model.

6.7.1 Baseline RAASi use

In the company model, at baseline, all patients are assumed to be in the "max" RAASi state and the probabilities of discontinuation/down-titration are applied in the first model cycle. The EAG considers that two patient cohorts are eligible for SZC treatment in this appraisal: patients currently receiving a suboptimal RAASi dose (as per the TA599[1] recommendation) and patients receiving an optimal RAASi dose who, without SZC treatment, would have to discontinue or down-titrate their RAASi dose; the company model only includes the latter population at baseline.

In response to clarification question B5, the company considered that their approach was conservative as, compared to patients treated with SZC, at baseline, a greater proportion of patients receiving standard care may have already down-titrated their RAASi dose. The EAG does not consider that this argument is relevant to the cost effectiveness analysis; patient baseline values should be the same for both treatments.

Since a patient's RAASi status modifies the risk of disease progression and adverse outcomes, baseline RAASi use may have a large impact on model outcomes. If the model includes a proportion of patients receiving a suboptimal RAASi dose at baseline, the time spent in the "max" RAASi state is likely to decrease for all patients. The extent of this decrease and the subsequent impact on cost effectiveness results may depend on the probability of up-titration (Section 6.6.1). In the company base case analysis, patients quickly return to the "max" RAASi state so the change in cost effectiveness results may be small. In contrast, [redacted] and if these probabilities are used in the company model, patients will spend longer in the "sub" RAASi state; the change in cost effectiveness results may be substantial.

6.7.2 Up-titration after RAASi discontinuation

In the company model, after discontinuing RAASi treatment, patients may return to the "max" RAASi state but not the "sub-max" RAASi state. Clinical advice to the EAG is that patients re-initiating RAASi treatment will start at a suboptimal dosage and up-titrate over time. In response to clarification question B6, the company stated that they considered that this was a conservative approach since patients receiving standard care were likely to reinitiate RAASi treatment more cautiously (i.e., at a lower dose) than patients treated with SZC. However, the

company acknowledged that there is a lack of data on patients reinitiating RAASi and it is not known whether speed of up-titration is affected by whether a patient is being treated with SZC.

By assuming all patients up-titrate to the maximum RAASi dosage, the proportion of patients and/or the length of time that is spent in the "max" RAASi state are likely to be overestimated. As with baseline RAASi use (Section 6.7.1), the impact on cost effectiveness results may depend on the probability of up-titration used in the model.

6.8 CKD health state costs

In the company model, annual costs associated with each CKD stage are sourced from Kent 2015[64] (Table 34). At clarification, the EAG noted that these costs were substantially different from those used in TA599[1] (sourced from NICE CG182[71]). In response to clarification question B14, the company stated that costs from the Kent 2015[64] were applied since they had been used in recent NICE appraisals of CKD.[72,73]

Table 34 CKD health state costs applied in the company model Annual cost (mean)

Health state	Annual cost (mean)	
	Company base case (Kent 2015[64])	EAG base case (NICE CG182[71])
CKD stage 3a	£1,354.02	£3,510.96
CKD stage 3b	£1,354.02	£3,510.96
CKD stage 4	£4,741.00	£3,510.96
CKD stage 5 (pre-RRT)	£16,623.00	£5,477.78

CG=clinical guideline; CKD=chronic kidney disease; RRT=renal replacement therapy
Source: Company clarification response, Table 9

The EAG highlights that Kent 2015[64] costs are reported by CKD stage at baseline; 28% of patients with CKD stage 4 and 79% of patients with CKD stage 5 (not receiving dialysis) at baseline went on to receive RRT by the end of the study period. Since patients exit the model on initiation of RRT, the EAG considers that using estimates from the Kent 2015[64] overestimates the cost associated with CKD progression (up to but not including RRT). The EAG has therefore run a scenario that uses the NICE CG182 costs.[71]

6.9 Impact of EAG revisions on company base case cost effectiveness results

The EAG has made the following revisions to the company base case cost effectiveness analysis:

- probabilities of RAASi down-titration or discontinuation for each S-K group equivalent by treatment using either SZC values (R1a) or standard care values (R1b)
- lifetime SZC treatment duration (R2)

- probability of up-titration informed by ZORA study subgroup re-analysis (R3)
- eligible to return to "max" RAASi state 4 weeks after discontinuation/down-titration (R4)
- CKD health state costs informed by NICE CG182[71] (R5)

The EAG has also presented results for the following exploratory scenario:

- assumes S-K level has no effect on the risk of MACE, hospitalisation or mortality (S1)

Model instructions for the EAG revisions to the company model are presented in Section 8.3 of this EAG report. Deterministic results for the CKD, HF and mixed populations are presented in Table 35, Table 36 and Table 37 respectively. Due to the substantial PSA run time (>24 hours), probabilistic results are only presented for the mixed population (Table 38) to demonstrate similarity with deterministic results. The EAG considers that subgroup results should be used for decision-making as: patients are identifiable; HK is usually treated at different S-K thresholds in clinical practice; the effectiveness of RAASi, and therefore the cost effectiveness of SZC, differs between the populations.

Table 35 Deterministic cost effectiveness results for CKD population: SZC versus standard care

Scenario/EAG revisions	SZC		Standard care		Incremental		ICER (£/QALY)	Change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Company base case	**£54,241**	**3.466**	**£49,669**	**3.194**	**£4,572**	**0.272**	**£16,833**	**-**
R1a) Probabilities of RAASi down-titration/discontinuation for each S-K group equivalent by treatment: SZC values	£54,241	3.466	£50,906	3.337	£3,335	0.128	£25,972	£9,139
R1b) Probabilities of RAASi down-titration/discontinuation for each S-K group equivalent by treatment: standard care values	£52,485	3.275	£49,669	3.194	£2,816	0.082	£34,551	£17,718
R2) Lifetime SZC treatment duration	£61,162	3.600	£49,669	3.194	£11,494	0.406	£28,333	£11,500
R3) Probability of up-titration informed by ZORA study subgroup analysis	£52,606	3.368	£48,883	3.150	£3,723	0.217	£17,131	£298
R4) Eligible to return to “max” RAASi state 4 weeks after discontinuation/down-titration	£54,350	3.475	£49,682	3.194	£4,668	0.280	£16,654	-£179
R5) CKD health state costs informed by NICE CG182[71]	£50,331	3.466	£44,875	3.194	£5,456	0.272	£20,089	£3,256
S1) S-K has no effect on the risk of MACE, hospitalisation or mortality	£56,660	3.598	£52,583	3.356	£4,077	0.242	£16,832	-£1
B1. EAG exploratory base case (R1a, R2-R5)	**£54,893**	**3.478**	**£44,909**	**3.242**	**£9,984**	**0.236**	**£42,351**	**£25,518**
B2. EAG exploratory base case (R1b, R2-R5)	**£52,209**	**3.283**	**£43,827**	**3.150**	**£8,382**	**0.133**	**£63,010**	**£46,177**
C1. B1+S1	**£56,369**	**3.591**	**£46,691**	**3.406**	**£9,678**	**0.185**	**£52,254**	**£35,421**
C2. B2+S1	**£53,624**	**3.393**	**£45,569**	**3.308**	**£8,056**	**0.085**	**£94,676**	**£77,843**

CG=clinical guideline; CKD=chronic kidney disease; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; MACE=major adverse cardiovascular event; QALYs=quality-adjusted life year; RAASi=renin–angiotensin–aldosterone system inhibitors; S-K=serum potassium; SZC=sodium zirconium cyclosilicate

Table 36 Deterministic cost effectiveness results for HF population: SZC vs standard care

Scenario/EAG revisions	SZC		Standard care		Incremental		ICER (£/QALY)	Change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Company base case	**£24,224**	**3.906**	**£17,719**	**3.187**	**£6,506**	**0.719**	**£9,053**	**-**
R1a) Probabilities of RAASi down-titration/discontinuation for each S-K group equivalent by treatment: SZC values	£24,224	3.906	£19,885	3.546	£4,339	0.360	£12,059	£3,006
R1b) Probabilities of RAASi down-titration/discontinuation for each S-K group equivalent by treatment: standard care values	£21,079	3.403	£17,719	3.187	£3,360	0.216	£15,569	£6,516
R2) Lifetime SZC treatment duration	£32,979	4.286	£17,719	3.187	£15,260	1.099	£13,892	£4,839
R3) Probability of up-titration informed by ZORA study subgroup analysis	£21,788	3.598	£16,655	3.074	£5,133	0.524	£9,799	£746
R4) Eligible to return to “max” RAASi state 4 weeks after discontinuation/down-titration	£24,372	3.922	£17,833	3.195	£6,539	0.727	£8,993	-£60
S1) S-K has no effect on the risk of MACE, hospitalisation or mortality	£25,964	4.274	£20,028	3.663	£5,936	0.611	£9,712	£659
B1. EAG exploratory base case (R1a, R2-R4)	**£29,530**	**3.889**	**£17,812**	**3.281**	**£11,717**	**0.607**	**£19,290**	**£10,237**
B2. EAG exploratory base case (R1b, R2-R4)	**£26,127**	**3.406**	**£16,664**	**3.075**	**£9,463**	**0.331**	**£28,618**	**£19,565**
C1. B1+S1	**£31,379**	**4.221**	**£20,096**	**3.761**	**£11,283**	**0.460**	**£24,545**	**£15,492**
C2. B2+S1	**£28,123**	**3.761**	**£18,983**	**3.551**	**£9,140**	**0.211**	**£43,360**	**£34,307**

CG=clinical guideline; HF=heart failure; ICER=incremental cost effectiveness ratio; EAG=External Assessment Group; MACE=major adverse cardiovascular event; QALYs=quality-adjusted life year; RAASi=renin–angiotensin–aldosterone system inhibitors; S-K=serum potassium; SZC=sodium zirconium cyclosilicate

Table 37 Deterministic cost effectiveness results for mixed CKD and HF population: SZC vs standard care

Scenario/EAG revisions	SZC		Standard care		Incremental		ICER (£/QALY)	Change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Company base case	**£45,546**	**4.128**	**£40,234**	**3.703**	**£5,312**	**0.425**	**£12,495**	**-**
R1a) Probabilities of RAASi down-titration/discontinuation for each S-K group equivalent by treatment: SZC values	£45,546	4.128	£41,722	3.921	£3,824	0.208	£18,391	£5,895
R1b) Probabilities of RAASi down-titration/discontinuation for each S-K group equivalent by treatment: standard care values	£43,526	3.832	£40,234	3.703	£3,292	0.129	£25,529	£13,034
R2) Lifetime SZC treatment duration	£53,486	4.344	£40,234	3.703	£13,252	0.641	£20,689	£8,193
R3) Probability of up-titration informed by ZORA study subgroup analysis	£43,736	3.959	£39,384	3.638	£4,352	0.321	£13,546	£1,050
R4) Eligible to return to “max” RAASi state 4 weeks after discontinuation/down-titration	£45,658	4.141	£40,342	3.711	£5,316	0.430	£12,365	-£130
R5) CKD health state costs informed by NICE CG182[71]	£47,159	4.128	£41,017	3.703	£6,142	0.425	£14,446	£1,951
S1) S-K has no effect on the risk of MACE, hospitalisation or mortality	£47,808	4.343	£42,971	3.967	£4,837	0.375	£12,884	£389
B1. EAG exploratory base case (R1a, R2-R5)	**£52,573**	**4.131**	**£41,150**	**3.773**	**£11,423**	**0.358**	**£31,898**	**£19,403**
B2. EAG exploratory base case (R1b, R2-R5)	**£49,634**	**3.836**	**£39,997**	**3.638**	**£9,637**	**0.198**	**£48,641**	**£36,146**
C1. B1+S1	**£54,305**	**4.320**	**£43,183**	**4.035**	**£11,123**	**0.285**	**£39,012**	**£26,517**
C2. B2+S1	**£51,351**	**4.028**	**£42,051**	**3.900**	**£9,300**	**0.127**	**£73,033**	**£60,538**

CG=clinical guideline; CKD=chronic kidney disease; EAG=External Assessment Group; HF=heart failure; ICER=incremental cost effectiveness ratio; MACE=major adverse cardiac event; QALY=quality adjusted life year; RAASi=renin–angiotensin–aldosterone system inhibitor; S-K=serum potassium; SZC=sodium zirconium cyclosilicate

Table 38 Probabilistic results for mixed CKD and HF population: SZC vs standard care

Scenario/EAG revisions	SZC		Standard care		Incremental		ICER (£/QALY)	Change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Company base case	**£45,596**	**4.126**	**£40,321**	**3.703**	**£5,276**	**0.423**	**£12,417**	**-**
B1. EAG exploratory base case (R1a, R2-R5)	**£52,626**	**4.136**	**£41,228**	**3.777**	**£11,398**	**0.359**	**£31,718**	**£19,301**
B2. EAG exploratory base case (R1b, R2-R5)	**£49,704**	**3.844**	**£40,065**	**3.638**	**£9,639**	**0.206**	**£46,761**	**£34,344**

CKD=chronic kidney disease; EAG=External Assessment Group; HF=heart failure; ICER=incremental cost effectiveness ratio; QALYs=quality-adjusted life year; SZC=sodium zirconium cyclosilicate

6.10 Cost effectiveness conclusions

The SPARK and ZORA studies are new sources of clinical evidence presented by the company to address key uncertainties identified in TA599.[1] In the cost effectiveness model, the health benefit of SZC is dependent on the ZORA study re-analysis results and to a lesser extent, the SPARK study results. The EAG is concerned that the SPARK study does not provide robust evidence on the risk of adverse outcomes for patients with persistent HK (S-K ≥5.5 to <6.0mmol/L). The EAG is also concerned that the ZORA study re-analysis results may not be generalisable to the NHS. If the SPARK and ZORA studies do not provide reliable evidence on the risk of adverse outcomes for patients with persistent HK or the impact of SZC on RAASi use then the economic modelling undertaken by the company cannot be considered reliable.

Cost effectiveness results are most sensitive to assumptions on how SZC impacts RAASi use and how long patients remain on SZC treatment. The EAG considers that the ZORA study re-analysis does not provide evidence that [redacted]. The EAG also considers that a lifetime treatment duration is more appropriate for patients with persistent HK.

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8 APPENDICES

8.1 Appendix 1: Quality assessment of the company's SLR

Table 39 Quality assessment of the company's SLR

Quality assessment item	EAG assessment	EAG comment
Did the research question and inclusion criteria for the review include the components of PICO?	Yes	CS, Appendix K, K.1.1.2 and Table 1 of the company SLR report
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review? Were any significant deviations justified?	Yes	The company SLR report (Section 2.1) states that the review methods were agreed a priori in a study protocol. The company has reported (CS, Appendix K, Table 66) the methodological differences in between the 2019 SLR and the 2024 update. The EAG considers the differences reported are acceptable
Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Company SLR report (Table 1)
Did the review authors use a comprehensive literature search strategy?	Yes	CS, Appendix K, K.4.2
Did the review authors perform study selection in duplicate?	Partially	CS, Appendix K, Table 66 The study selection in the 2019 SLR was conducted in duplicate. Study selection in the 2024 update was conducted by one reviewer and a second reviewer checked 20% of exclusions
Did the review authors perform data extraction in duplicate?	Partially	CS, Appendix K, Table 66 The data extraction in the 2019 SLR was conducted in duplicate. Extraction in the 2024 update was conducted by one reviewer and 20% of inputs was checked by a second reviewer
Did the review authors provide a list of excluded studies and justify the exclusion?	Yes	CS, Appendix K, K.8.1.3
Did the review authors describe the included studies in adequate detail	Partially	Studies included in the 2024 SLR are listed in CS, Appendix K6 with basic detail. For the 2018 SLR, full details are available in the Excel data extraction file provided by the company
Did the review authors use a satisfactory technique for assessing the risk of bias in the individual studies that were included in the review?	Yes	CS, Appendix K, K.5.3 Quality (risk of bias) assessment (QA) of RCTs was conducted using the seven-criteria NICE checklist described in PMG24[35] Quality assessment of systematic reviews was conducted using the AMSTAR2[36] checklist

Quality assessment item	EAG assessment	EAG comment
Did the review authors report on the sources of funding for the studies included in the review?	Yes	CS, Appendix K6
If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	NA	The results in the 2024 SLR were described narratively
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	NA	No meta-analyses were conducted in the 2024 SLR
Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes	CS, Appendix K, Section K5.6.5 All studies and systematic reviews included in the 2024 SLR were considered to be of high quality
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Heterogeneity was measured and discussed in the 2019 SLR. Heterogeneity is not applicable to the narrative update of the review
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	NA/No	Publication bias was not assessed
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The SLRs were funded by the company (Astra Zeneca)

CSR=Clinical Study Report; NA=not applicable; RoB=risk of bias
Source: AMSTAR2[36] quality assessment tool for systematic reviews

8.2 Appendix 2 Key findings from the company's SLR

Table 40 Overview of the company 2024 SLR results for chronic kidney disease

	Number and type of study	Summary
Question 1: What are the long-term outcomes in patients discontinuing/down-titrating RAASi?	5 SLRs 1 RCT	• RAASi discontinuation was associated with a significantly increased risk of CV events, all-cause mortality (including in patients discontinuing due to hyperkalaemia), and MACE.
Question 2: What are long-term clinical benefits (CV events, mortality, hospitalisation) of taking RAASi	21 SLRs 6 RCTs	• The most consistently reported outcomes were CV events, all-cause and CV mortality, composite CV outcomes including CV death, and HF hospitalisation • A consistent numerical advantage in favour of RAASi therapy was seen with statistically significant differences also reported, particularly for composite CV outcomes including CV death and HF hospitalisation
Question 3: What changes occur in S–K with RAASi down-titration and discontinuation?	None	• No publications were identified
Question 4: Is there disease progression in patients with RAASI?	25 SLRs 13 RCTs	• Meta-analyses reported that RAASi prevented disease progression in patients with CKD (depending on the outcome measured) with statistically significant reductions in both progression to end-stage kidney disease/kidney failure and decrease in eGFR as well as prevention of composite renal endpoints and renal death • There was inconsistency in the findings between publications for other outcomes

CS=company submission; CV=cardiovascular; eGFR=estimated glomerular filtration rate; HF=heart failure; RAASi=renin-angiotensin-aldosterone system inhibitors; RCTs=randomised controlled trials; SLRs=systematic literature reviews
Source: Summary of CS, Appendix K, p243

Table 41 Overview of the company's 2024 SLR results for heart failure

	Number and type of study	Summary
Question 1: What are the long-term outcomes in patients discontinuing/down-titrating RAASi?	5 SLRs 1 RCT	• One publication highlighted that RAASi discontinuation following an episode of hyperkalaemia was associated with a 31% increase in all-cause mortality (Siddiqui 2022[74]) • Discontinuation of RAASi was also associated with an increased risk of all-cause mortality and CV mortality or HF hospitalisation • Publications addressing RAASi dose reduction showed a significant increase in the risk of all-cause mortality, with inconsistency in findings between publications for other outcomes
Question 2: What are long-term clinical benefits (CV events, mortality, hospitalisation) of taking RAASi	26 SLRs 8 RCTs	• The most consistently reported relevant MA outcomes were CV events, all-cause and CV mortality, HF hospitalisation and CV death, and/or HF hospitalisation • The majority of data identified consistently showed a numerical advantage in favour of RAASi therapy • Statistically significant differences were also frequently reported across most outcomes and particularly for HF hospitalisation and CV death and/or HF hospitalisation
Question 3: What changes occur in S–K with RAASi down-titration and discontinuation?	1 RCT	• Increased potassium levels for patients randomised to spironolactone 50mg versus 25mg
Question 4: Is there disease progression in patients with RAASI?	11 SLRs 3 RCTs	• RAASi reduced the rate of disease progression in patients with HF depending on outcome measured and led to significant improvement in E/e', left ventricular mass index, left atrial volume index, and New York Heart Association class when compared to placebo in the majority of analyses • For renal outcomes, RAASi slowed the decline in eGFR compared to placebo.

CS=company submission; CV=cardiovascular; eGFR=estimated glomerular filtration rate; HF=heart failure; MA=meta-analysis; RAASi=renin-angiotensin-aldosterone system inhibitors; RCTs=randomised controlled trials; SLRs=systematic literature reviews
Source: CS, Appendix K, p243

8.3 Appendix 3: EAG company model revisions

Table 42 Details of EAG company model revisions

EAG revisions	Implementation instructions
R1) Probabilities of RAASi down-titration/discontinuation equivalent	In Sheet 'Front End' In cell D55 enter "R1*" Name cell E55 "EAG_R1" Set value in cell E55=1 In cell C62 enter "*0=company base case; 1= SZC values; 2 = standard care values" In Sheet 'Inputs' Copy range M129:M140 and paste values into range V129:V140 Copy range S129:S140 and paste values into range W129:W140 Set value in cell M129 =IF(EAG_R1=2,W129,V129) Copy formula in cell M129 to range M129:M140 Set value in cell S129 =IF(EAG_R1=1,V129,W129) Copy formula in cell S129 to range S129:S140
R2) Lifetime SZC treatment duration	In Sheet 'Front End' In cell D56 enter "R2" Name cell E56 "EAG_R2" Set value in cell E56=1 Remove data validation from cells E8 and E10 Set value in cell E8 =IF(EAG_R2=1,"Lifetime","User-defined") Copy formula in cell E8 and paste to cell E10
R3) Probability of up-titration informed by ZORA study estimates (any S-K group)	In Sheet 'Front End' In cell D57 enter "R3" Name cell E57 "EAG_R3" Set value in cell E57=1 In Sheet 'Inputs' Set value in cell M91 =IF(EAG_R3=1,0.106,S91) Copy cell M91 and paste formula in cell M92 Set value in cell S91 =IF(EAG_R3=1,0.059,0.497) Copy cell S91 and paste formula in cell S92
R4) Eligible to return to max RAASi dosages 4 weeks after discontinuation/down-titration	In Sheet 'Front End' In cell D58 enter "R4"

<table>
<tr><th>EAG revisions</th><th>Implementation instructions</th></tr>
<tr><td></td><td>Name cell E58 “EAG_R4”
Set value in cell E58=1

<u>In Sheet ‘Inputs’</u>
Set value in cell S93 =IF(EAG_R4=1,4,12)
Copy cell S93 and paste formula in cell S94</td></tr>
<tr><td>R5) CKD costs informed using NICE CG182</td><td><u>In Sheet ‘Front End’</u>
In cell D59 enter “R5”
Name cell E59 “EAG_R5”
Set value in cell E59=1

<u>In Sheet ‘Inputs’</u>
Copy range S121:T124 and paste values into range V121:W124
Copy the table below and paste values into range X121:Y124
<table><tr><td>3510.96</td><td>351.1</td></tr><tr><td>3510.96</td><td>351.1</td></tr><tr><td>3510.96</td><td>351.1</td></tr><tr><td>5477.78</td><td>547.78</td></tr></table>
Set value in cell S121 =IF(EAG_R5=1,X121,V121)
Copy cell S121 and paste formula into range S121:T124

Set value in cell M121 =S121
Copy formula in cell M121 to range M121:N124</td></tr>
<tr><td>S1) S-K level has no effect on the risk of MACE, hospitalisation or mortality</td><td><u>In Sheet ‘Front End’</u>
In cell D60 enter “S1”
Name cell E60 “EAG_S1”
Set value in cell E60=1

<u>In Sheet ‘Inputs 2’</u>
Copy range AA30:AA71 and paste values into range AF30:AF71
Set value in cell AA30 =IF(EAG_S1=1,1,AF30)
Copy cell AA30 and paste formula into range AA30:AA71

Copy range AA111:AA159 and paste values into range AF111:AF159
Set value in cell AA111 =IF(EAG_S1=1,1,AF111)
Copy cell AA111 and paste formula into range AA111:AA159</td></tr>
</table>

CG=clinical guidelines; CKD=chronic kidney disease; EAG=External Assessment Group; MACE=major adverse cardiac event; RAASi=renin-angiotensin-aldosterone system inhibitors; S-K=serum-potassium; SZC=sodium zirconium cyclosilicate

Single Technology Appraisal

Sodium zirconium cyclosilicate for treating hyperkalaemia (partial review of TA599) [ID6439]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by the end of **8 July 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Decision problem

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 10: 'In the final scope issued by NICE, the description of the population includes people with persistent HK who require dialysis. The company has not provided clinical effectiveness evidence to support treating this group of patients with SZC.'	Please amend as follows: 'In the final scope issued by NICE, the description of the population includes people with persistent HK who require dialysis. ~~The company has not provided clinical effectiveness evidence to support treating this group of patients with SZC.~~ Evidence for the clinical effectiveness of SZC in this population is provided from the DIALIZE study. However, the company states (CS, pg33) patients in DIALIZE were followed for a total of 10 weeks, and as such this study is not suitable for assessing the cost-effectiveness of treatment with SZC in patents receiving chronic haemodialysis.'	Data from the DIALIZE study investigating SZC as a treatment for pre-dialysis HK is presented in CS Section 1.3.8. While the data presented are not suitable for economic assessment due to an insufficient length of follow-up, it is inaccurate to say that clinical evidence is not available in this population.	This is not a factual inaccuracy. The company has not presented clinical effectiveness evidence to support treating people with persistent HK who require dialysis with SZC. No changes have been made to the EAG report.
Page 26: 'Lifestyle interventions aimed at maintaining S-K levels within the normal range are an important part of HK management; these	Please amend as follows: 'Lifestyle interventions aimed at maintaining S-K levels within the normal range are an important part of HK management; ~~these interventions~~	Low K^+ diets are no longer the main treatment for patients with persistent HK with an S-K of ≥5.5–<6.0 mmol/L.	Section 2.5.4 has been amended as follows: Lifestyle interventions aimed at maintaining S-K levels within the normal range are an

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
interventions typically include a low-potassium diet.'	~~typically include a low-potassium diet.~~ historically this may have included low K^+ diets, but these are now considered not to be clinically effective and are associated with decreased patient QoL. The primary intervention in England for those with persistent HK with an S-K of ≥5.5–<6.0 mmol/L is modification of concomitant RAASi therapy.'		important part of HK management. Clinical advice to the EAG is that patients with HK are referred to specialist dieticians for dietary advice; however, it is difficult to follow a healthy low-potassium diet, and adherence to such a diet is typically low. Clinical advice to the EAG was also that, for patients with S-K levels between ≥5.5 to <6.0mmol/L, RAASi therapy doses may be adjusted or down-titrated. However, this approach often results in suboptimal RAASi therapy dosing, potentially compromising the clinical benefits associated with these agents.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 27: 'SGLT-2 inhibitors reduce S-K level, which may allow better use of RAASi therapy. The company states (CS, Table 1) that it has been demonstrated that treatment with SZC can increase the proportion of patients receiving SGLT-2 treatment.'	Please amend as follows: SGLT-2 inhibitors reduce S-K level, which may allow better use of RAASi therapy. ~~The company states (CS, Table 1) that it has been demonstrated that treatment with SZC can increase the proportion of patients receiving SGLT-2 treatment~~. However, in the UK, SGLT-2 inhibitors are not indicated for HK and are not used by clinicians with the aim of lowering patient S–K levels. Furthermore, UK clinical guidelines state that patients should only initiate SGLT-2 inhibitors if they are in receipt of an optimised RAASi dose. SZC facilitates maintenance of an optimised RAASi dosage, meaning that SZC has the potential to enable more patients to be eligible for SGLT-2 inhibitors than standard care.	Amendment requested to reflect the clarification provided by the Company in response to clarification question A1.	The EAG report has been amended to include the wording suggested by the company and to acknowledge the company's response to clarification question 1.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 27: 'During TA599,[1] the company presented data showing that treatment with SZC is associated with hypokalaemia and stated that hypokalaemia is associated with life-threatening arrhythmias. The company explained that treating HK at ≥6.0mmol/L was less likely to cause hypokalaemia than treating HK at lower S-K levels. The risk of hypokalaemia associated with treating patients with S-K levels of ≥5.5 to <6.0mmol/L with SZC is not known'	AstraZeneca request that this paragraph is removed.	As discussed in TA599, the dose of SZC should be up- or down-titrated as per the SmPC to maintain an appropriate S-K.[1] If patients become hypokalaemic, therapy should be discontinued. As such, hypokalaemia is unlikely to be a frequent adverse event in UK clinical practice, given the low rate of hypokalaemia in the post-hoc analysis of the SZC trials. Nevertheless, data on the incidence of hypokalaemia for patients with S-K levels of ≥5.5 to <6.0mmol/L treated with SZC in ZS-005 are provided in Table 20, Appendices of the CS. These demonstrate the low rates of hypokalaemia in patients with S-K levels of ≥5.5–<6.0mmol/L treated with SZC during extended phase days 85–365 of the ZS-005 trial	The EAG report has been amended as follows: 'The risk of hypokalaemia associated with treating NHS patients with S-K levels ≥5.5 to <6.0mmol/L with SZC is not known. However, ZS-005 trial data (CS, Appendix E, Table 20) show that rates of hypokalaemia in patients with S-K levels of ≥5.5 to <6.0mmol/L treated with SZC during extended phase days 85 to 365 were low (0.0%; 95% confidence interval: 0.0%, 1.3%).

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
		(0.0%; 95% confidence interval: 0.0%, 1.3%).	
Page 50: 'The modelled population comprises adults with persistent HK; persistent HK is defined as an S-K level of ≥5.5 to <6.0mmol/L.'	Please amend as follows: 'The modelled population comprises adults with persistent HK~~; persistent HK is defined as~~ with an S-K level of ≥5.5 to <6.0mmol/L.'	This is an incorrect definition of persistent HK. HK is generally described as any S–K level above normal (i.e. ≥5.0 mmol/L). Persistent HK differs from acute HK in its presentation, with acute HK an immediately life-threatening event characterised by electrocardiogram (ECG) changes, whereas persistent HK may have non-specific symptoms or be asymptomatic. There is no consensus on the magnitude, duration and frequency of elevated S-K levels that define persistency. The description should be revised for accuracy.	The text has been amended as suggested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 50: 'Patients in the model have a co-diagnosis of HK and an underlying condition, either: CKD: stage 3b-5 (CS, Table 30) or'	Please amend as follows: 'Patients in the model have a co-diagnosis of HK and an underlying condition, either: CKD stage 3a–5 (CKD stage 3b–5 in the base case; CS, Table 30)'	The model does consider patients with stage 3a CKD in scenario analyses.	The text has been amended as suggested.
Page 51: 'Treatment with SZC or standard care includes lifestyle and dietary interventions to manage S-K levels.'	AstraZeneca request that this sentence is removed.	As low K^+ diets are now considered not to be clinically effective and are not routinely used in clinical practice, no costs were included for low K^+ diet intervention. As acknowledged Document B of the CS (Section B.3.5.4) this may result in an underestimation of the standard care costs.	The EAG has amended the text as follows: Treatment with SZC or standard care includes lifestyle and dietary advice to help manage S-K levels.

Issue 2 Association between S-K and adverse outcomes

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 11, 69: 'evidence from James 2021 shows that the relationship is complicated and persistent HK (S-K level ≥5.5 to 6.0mmol/L) may be protective against mortality'	At present, the data in the James study is reported inaccurately. Therefore please amend as follows: '~~evidence from James 2021 shows that the relationship is complicated and persistent HK (S-K level ≥5.5 to 6.0mmol/L) may be protective against mortality.~~ The James 2021 study investigated the impact of HK variability and suggests that not only the absolute S–K level, but also how much it fluctuates is important in predicting adverse cardiovascular events. James 2021 suggests that mortality risk was lower in those spending more time with S–K levels ≥5.0 mmol/L. In response to clarification A8 the company state that this may have been attributable to these patients benefitting from more proactive management.	Oversimplification of the conclusions of the James 2021 study. As described in company's clarification response, the methodology and objectives of the James 2021 study differ significantly from the SPARK study. As noted in the publication, both CKD and HF cohorts had the highest frequency of potassium testing (expressed as rate per patient years) and therefore may have been subject to additional treatment or intervention.	The EAG report has been amended as follows: …evidence from James 2021 shows that the relationship is complicated and persistent HK (S-K level ≥5.0 or ≥5.5mmol/L) may be protective against mortality.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 33: 'Only data from objective 2 have been used to populate the company model.'	Please amend as follows: 'Data from objectives 1 and 2 have been used to populate the company model.'	Data from objective 1 are also used in the model.	The EAG report has been amended to include the wording suggested by the company.
Page 33: 'The company completed the NICE DataSAT'	Please amend as follows: 'The company **conducted SPARK in line with the NICE RWE Framework and** completed the NICE DataSAT'	It is important to acknowledge that that Company followed best practice guidance as provided by the NICE RWE framework.	The EAG report has been amended in line with the wording suggested by the company.
Page 33: 'The aim of the company SPARK study was to address NICE TA599[1] AC concerns about the association between persistent HK and adverse clinical outcomes.'	Please amend as follows: 'The aim of the company SPARK study was to specifically address NICE TA599[1] AC concerns about the association between ~~persistent HK~~ **increased S–K levels** and adverse clinical outcomes, whilst remaining consistent with the evidence presented previously to NICE in TA599, and being conducted in line with the NICE RWE framework.	The SPARK study was conducted among patients with any of a reported S-K measurement, a diagnosis of HK and/or K^+ binder use. The SPARK study was specifically designed to remain consistent with the evidence presented previously to NICE in TA599, whilst being conducted in line with NICE RWE framework and addressing the specific concerns raised by committee.	The EAG report has been amended to include the wording suggested by the company.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 35: 'The company explained that whilst the James 2021 study had been identified by the company 2024 SLR2 searches, the study had been excluded from SLR2 because the population treated with a RAASi did not only have HF, CKD or diabetic nephropathy.'	AstraZeneca request the following amendment: 'The company explained that whilst the James 2021 study had been identified by the company 2024 SLR2 searches, it was excluded on the basis that the population taking RAASi was not solely HF, CKD, or diabetic nephropathy (DN) as outlined in the SLR protocol. Out of the 931,460 patients included in the analysis, only 32% (n=297,702) had CKD, 9% (n=84,210) had HF and 31% (n=288,871) had diabetes. In the company response to clarification A8 the company state that additionally the methodology and objectives of the James 2021 study were substantially different from the SPARK study and not aligned with the requirements of the economic model or the NICE RWE framework. James 2021 investigated the impact of HK variability and suggests that not only the absolute S–K level, but also how much it fluctuates is important in	AstraZeneca provided a detailed explanation as to why James 2021 was not suitable for inclusion in the economic model in clarification question A8. Request that the full explanation of the relevance of the James 2021 study to the NICE decision problem as described in clarification response A8 is referred to in the EAG report	The following text has been added to the EAG report: The company provided a full explanation of the relevance of the James 2021 study in response to clarification question A8.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
	predicting adverse cardiovascular events. Furthermore, it noted that James 2021 does not present the relative risk of mortality for patients with S–K ≥5.5 mmol/L compared with those with S–K ≤5.5 mmol/L.'		
Page 36: 'The company has provided more detailed baseline characteristics in CS, Appendix M; in CS, Appendix M, data are presented for 18 different patient groups; the characteristics assessed are standard baseline characteristics (age, gender, body mass index (BMI) and smoking status), five laboratory parameters, 23 medical conditions and 12 different types of treatment.'	Please amend as follows: 'The company has provided more detailed baseline characteristics in CS, Appendix M; in CS, Appendix M, data are presented for 18 different patient groups; the characteristics assessed are standard baseline characteristics (age, gender, body mass index (BMI) and smoking status), ~~five~~ **four** laboratory parameters, 23 medical conditions and 12 different types of treatment.	Data inaccuracy in the number of laboratory parameters and medical conditions reported.	Typographical error noted and corrected.

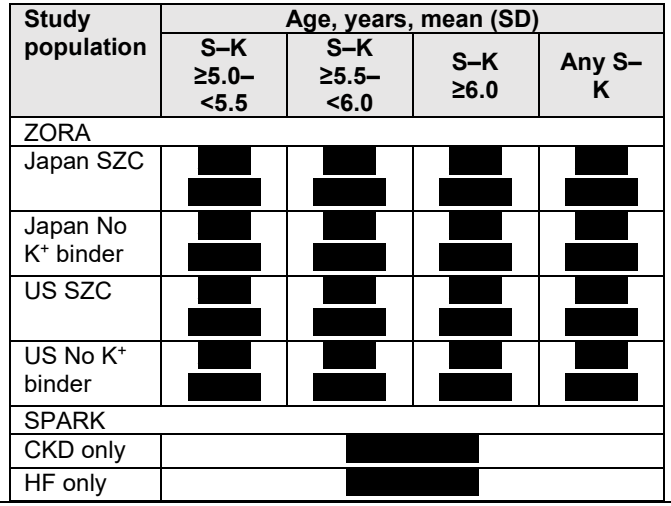
Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 36: 'The analyses carried out by the company were extensive; however, much of the detail is not presented in a way that directly informs the decision problem.'	Please provide additional clarification regarding the presentation of SPARK analyses.	Additional clarification is requested to understand the EAG's concern of the relevance of the SPARK study analyses to the NICE decision problem.	The EAG comment relates only to objective 1. No changes have been made to the EAG report.
Page 36: 'To describe the association between S-K levels and clinical outcomes, the company ran multivariable regression models; these were stratified by variables of interest to account for confounding variables.'	Please amend as follows: 'To describe the association between S-K levels and clinical outcomes, the company ran multivariable regression models; these were stratified by variables of interest to account for confounding variables, **and an analysis was conducted to account for unknown confounding factors using e-values**.'	An analysis was conducted to account for unknown confounding factors using e-values.	The EAG report has been amended to include the wording suggested by the company.
Page 37: 'GEE models are only robust to data that are missing completely at random (MCAR); in the observational context, missing data are unlikely to be entirely MCAR. The	Please amend as follows: 'GEE models are only robust to data that are missing completely at random (MCAR); in the observational context, missing data are unlikely to be entirely MCAR. The company states, "…Missing data were quantified for all	Whilst missing data were not imputed, missing values were included by categorising the relevant data. There were no missing S-K data as this was the definition of the index event.	The EAG welcomes the company clarification; however, as this information was not included in the CS no changes have been made to the EAG report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
company states, "…Missing data were quantified for all study variables, but no attempts were made to impute them" (CS, p49), the EAG therefore concludes that no attempt was made to handle missing data'	study variables, but no attempts were made to impute them" (CS, p49)~~, the EAG therefore concludes that no attempt was made to handle missing data~~. However, missing values were included by categorising the relevant data and there were no missing S-K data given that this was the definition of the index event.'		

Issue 3 RAASi therapy

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 24: 'ii) that the use of SZC allows reinitiation/up-titration of optimum RAASi dosage (ZORA study).'	Please amend as follows: 'ii) that the use of SZC allows ~~reinitiation~~ **maintenance**/up-titration of optimum RAASi dosage (ZORA study).'	The outcome measured in the ZORA study was RAASi maintenance, defined as: having post-index prescriptions for at least the same number of RAASi classes as pre-index; this category encompassed stabilized RAASi (use of the same	The EAG report has been amended to include the wording suggested by the company.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
		number of RAASi classes and doses)	
Page 31: 'The company acknowledged that there was a lack of data evidencing the effects of down-titration or discontinuation of RAASi on outcomes for patients with HF or CKD'.	Please amend as follows: 'The company acknowledged that there was a lack of data evidencing the effects of down-titration or discontinuation of RAASi on ~~outcomes~~ S–K for patients with HF or CKD'.	This SLR provides a comprehensive overview of the latest research relevant to the use of RAASi in patients with CKD or HF in terms of long-term effects on CV events, mortality, and hospitalisation and also markers of disease progression (e.g. LVEF, NYHA functional status for HF and change in eGFR and progression to ESRD for CKD). The identified evidence suggests that RAASi is an effective treatment for patients with HF and CKD, with findings consistently showing benefits across assessed outcomes. However, the company acknowledge that less evidence was	The EAG report has been amended to include the wording suggested by the company.

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG comment</th></tr>
<tr><td></td><td></td><td>identified reporting on the effect of RAASi treatment on S–K level.</td><td></td></tr>
<tr><td>Page 41: ‘Age: US and Japanese ZORA study re-analysis patients are older than SPARK study patients.’</td><td>Please amend as follows:
‘Age: US and Japanese ZORA study re-analysis patients are older than SPARK study patients; the re-analysis patients are a similar age to the CKD-only and HF-only cohorts of the SPARK study’.
 
<table><tr><th>Study population</th><th colspan="4">Age, years, mean (SD)</th></tr><tr><th></th><th>S–K ≥5.0–<5.5</th><th>S–K ≥5.5–<6.0</th><th>S–K ≥6.0</th><th>Any S–K</th></tr><tr><td>ZORA</td><td colspan="4"></td></tr><tr><td>Japan SZC</td><td></td><td></td><td></td><td></td></tr><tr><td>Japan No K+ binder</td><td></td><td></td><td></td><td></td></tr><tr><td>US SZC</td><td></td><td></td><td></td><td></td></tr><tr><td>US No K+ binder</td><td></td><td></td><td></td><td></td></tr><tr><td>SPARK</td><td colspan="4"></td></tr><tr><td>CKD only</td><td colspan="4"></td></tr><tr><td>HF only</td><td colspan="4"></td></tr></table></td><td>This statement is misleading as the CKD and HF cohorts in the SPARK study are of a similar age to the ZORA study re-analysis patients.</td><td>The EAG report has been amended as follows:

• Age: US and Japanese ZORA study re-analysis patients are a similar age to the CKD-only and HF-only cohorts of the SPARK study.</td></tr>
<tr><td>Page 41: after PS matching the size of the groups</td><td>AstraZeneca request that this sentence is clarified as size of groups is due to the</td><td>The size of the respective groups is due to propensity</td><td>This is not a factual inaccuracy. No</td></tr>
</table>

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
decreased by 88.5% and 98.0% respectively	methodology used, and not an interpretation of the strength of matching.	score matching, which uses a matching ratio of up to 1:4 (SZC:no K+ binder) in each dataset, with excess controls discarded, as described in the Rastogi publication.[2]	changes have been made to the EAG report.
Page 41: 'The EAG highlights that whilst the purpose of the ZORA study re-analysis was to identify the relationship between SZC and RAASi does adjustment, clinical advice to the EAG is that whilst HK is one reason to down-titrate RAASi dose, other reasons include worsening renal function, symptomatic hypotension and drug-related adverse events (AEs).'	Please update as follows: 'The EAG highlights that whilst the purpose of the ZORA study re-analysis was to identify the relationship between SZC and RAASi ~~does~~ **dose** adjustment, clinical advice to the EAG is that whilst HK is one reason to down-titrate RAASi dose, other reasons include worsening renal function, symptomatic hypotension and drug-related adverse events (AEs). However, this would be expected to effect both the SZC and no K^+ binder cohorts.'	The impact of down-titration of RAASi for reasons other than HK would impact both arms of the ZORA study and therefore would not be anticipated to have an unbalanced effect on the data. A typographical correction is also requested.	The statement in the EAG report is not a factual inaccuracy. Typographical error noted and corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 64: 'The minimum possible SZC treatment duration in the ZORA study is longer than the average SZC treatment duration in the company base case'	This sentence is incorrect therefore AstraZeneca request that this sentence is removed.	This is incorrect. In the model, if a patient's S-K remains above 5.5 mmol/L, patients will begin treatment again for another 84 day cycle. Within the model, the average treatment duration is 2.3 years. It is a model limitation that patients discontinue treatment for one cycle before continuation of treatment, but the impact of this is limited due to low S-K in the maintenance phase.	The EAG has amended the text as follows: "The minimum possible SZC treatment duration in the ZORA study is longer **in relative terms** than the average SZC treatment duration in the company base case analysis"
Page 65: 'The EAG has used ZORA study re-analysis estimates to inform the probabilities of up-titration in the company model to be consistent with the data source used for the probabilities of down-titration/discontinuation'	Request the paragraph be amended as followed to provide the detailed explanation as described in clarification response B7: The EAG has used ZORA study re-analysis estimates to inform the probabilities of up-titration in the company model to be consistent with the data source used for the probabilities of down-titration/discontinuation. The company state in its response to	The company provided a detailed explanation of the appropriateness of using ZORA re-analysis data to inform RAASi up-titration in clarification question B7. Request that the full explanation of the appropriateness using	The following text has been added to the EAG report (p70): "In response to clarification question B7, the company considered that it

	clarification B7 that this is not appropriate because ZORA does not investigate if up-titration resulted in the patient achieving optimised treatment nor the proportion of patients reinitiate RAASi therapy following discontinuation Furthermore, the baseline population is not disaggregated by patients on max vs non-max RAASi doses meaning that a large percentage of patients may not have been able to up-titrate. Therefore, the percentages of patients up-titrating in the ZORA re-analysis are not applicable to the full population in the economic model.	ZORA re-analysis data to inform RAASi up-titration as described in clarification response B7 is referred to in the EAG report.	was not appropriate to use ZORA study re-analysis estimates because it is not known how many patients up-titrated to an optimal RAASi dose or reinitiated RAASi therapy following discontinuation. Furthermore, since the baseline ZORA study re-analysis population was not disaggregated by patients receiving an optimal versus suboptimal RAASi dose, the company considered that up-titration may not have been possible for a large proportion of patients. The company also considered their approach was

			conservative since the ZORA study re-analysis estimates suggest that, for all S-K groups, the probability of RAASi up-titration is higher for patients in the SZC cohort than for patients in the no potassium binder cohort. The EAG acknowledges that there are limitations and uncertainties with the ZORA study re-analysis but highlights that several assumptions were made in the company model when using the Luo study[43] estimate:

			•all patients are assumed to return to optimised RAASi treatment but in the Luo study[43] it is not known how many patients up-titrated to an optimal RAASi dose (as with the ZORA study re-analysis) •the probability of up-titration is applied to patients in the model who are receiving a suboptimal RAASi dose but the Luo study[43] estimate only relates to patients who reinitiated RAASi treatment having previously discontinued •the probability of up-titration is applied to patients regardless of

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
			underlying disease but the Luo study[43] only included patients with CKD It is therefore not clear to the EAG that Luo 2016[43] provides more robust estimates than the ZORA study re-analysis.
Page 70: The EAG highlights that the Luo 2016 estimate is substantially higher than the ZORA study re-analysis estimates. It is therefore not clear that the company's approach is conservative as, in the company base case, patients treated with SZC who return to the "max" RAASi state [redacted]	Please update as follows: The EAG highlights that the Luo 2016 estimate is substantially higher than the ZORA study re-analysis estimates. It is therefore not clear that the company's approach is conservative as, in the company base case, patients treated with SZC who return to the "max" RAASi state [redacted]. The company do not consider the ZORA reanalysis data suitable for use in the model due to the baseline	The appropriateness of using ZORA re-analysis data to inform RAASi up-titration was discussed in clarification question B7. For the proportion of patients identified as up-titrating RAASi therapy in the ZORA analysis, it is not known if up-titration resulted in the patient achieving optimised treatment. It is also	The EAG report has been amended in response to the comment above.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
[redacted]	population is not disaggregated by patients on max vs non-max RAASi doses meaning that a large percentage of patients may not have been able to up-titrate. Furthermore, there is a lack of certainty regarding whether patients up-titrating RAASi in ZORA achieved an optimal dose'.	unknown from this analysis what proportion of patients reinitiate RAASi therapy following discontinuation. Furthermore, the baseline population is not disaggregated by patients on max vs non-max RAASi doses meaning that a large percentage of patients may not have been able to up-titrate. Therefore, the percentages of patients up-titrating in the ZORA re-analysis are not applicable to the full population in the economic model.	
Page 71: 'patients currently receiving a suboptimal RAASi dose (as per the TA599[1] recommendation) and patients receiving an optimal RAASi dose who, without SZC treatment, would have to discontinue or down-titrate their RAASi dose; the	Please amend as follows: 'patients currently receiving a suboptimal RAASi dose (as per the TA599[1] recommendation) and patients receiving an optimal RAASi dose who, without SZC treatment, would have to discontinue or down-titrate their RAASi dose; the company model	The company model captures patients on suboptimal RAASi on the first cycle (day 1). This is a limitation of the model.	The EAG report has been amended in line with the company suggestion.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
company model only includes the latter population.'	only includes the latter population **at baseline**.'		
Page 78: 'The EAG is also concerned that the ZORA study re-analysis results may not be generalisable to the NHS.'	Please amend as follows: 'The EAG is also concerned that the ZORA study re-analysis results may not be generalisable to the NHS despite clinical advice given to the Company concluding that the ZORA study results are generalisable to the NHS patients.'	Clinical advice given to the Company was that the ZORA study was generalisable to the UK population. This difference in clinical opinion should be reflected in the report.	This is not a factual inaccuracy. The difference in clinical opinion has been clarified elsewhere in the EAG report. No changes have been made to the EAG report.

Issue 4 Clinical advice

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 10, 25, 28, 45: 'Clinical advice to the EAG is that in NHS clinical practice patients with persistent HK who require haemodialysis are not generally prescribed potassium binders as	Please amend to: 'Clinical advice to the EAG is that in NHS clinical practice patients with persistent HK who require haemodialysis are not generally prescribed potassium binders as dialysis effectively removes excess potassium from the blood. This is	Additional clarification requested to acknowledge that patients undergoing haemodialysis are overall a high-risk and complex patient group, and haemodialysis is often highly individualised for each patient. Whilst for many	This is not a factual inaccuracy. No changes have been made to the EAG report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
dialysis effectively removes excess potassium from the blood.'	consistent with the company submission (CS, pg 34), which also notes there will be some patients on haemodialysis where this may not be clinically appropriate, such as those known to be at high risk of hypokalaemia after dialysis.'	patients it may be possible to manage S–K levels though modification of dialysate K^+ concentration, there will some individuals on haemodialysis where this may not be clinically appropriate, such as those known to be at high risk of hypokalaemia after dialysis. Conversely, whilst dialysis can be effective in managing HK temporarily, some patients will remain at risk of persistent HK during the long interdialytic window.	
Page 11 and page 24: 'Clinical advice to the EAG is that differences in the baseline characteristics of UK, Japan and US patients may affect the generalisability of ZORA study re-analysis results to NHS patients.'	Please amend as follows: 'Clinical advice to the EAG is that differences in the baseline characteristics of UK, Japan and US patients may affect the generalisability of ZORA study re-analysis results to NHS patients (Section 3.4.1). This differs to the clinical advice provided by the Company (CS, pg 75) which considered the results are generalisable to the UK population and	Clinical advice given to the Company was that the ZORA study was generalisable to the UK population. Given the difference in clinical opinion AstraZeneca request that the EAG refer to the company submission and provided clinical expert interviews to provide context for the committee.	This is not a factual inaccuracy. No changes have been made to the EAG report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
	the results reflect their clinical experience.[3]'		
Page 12: 'Clinical advice to the EAG is that most patients with persistent HK would not discontinue treatment with SZC as on discontinuation S-K would likely increase to the level prior to SZC treatment initiation for these patients'	Please amend as follows: 'Clinical advice to the EAG is that most patients with persistent HK would not discontinue treatment with SZC as on discontinuation S-K would likely increase to the level prior to SZC treatment initiation for these patients. This differs to clinical advice provided by the Company (CS, pg 102) which suggest that patients would discontinue SZC in clinical practice.'	The treatment durations utilised in TA599 were underpinned by clinical assumptions based on Market Research and are aligned with further clinical expert opinion gathered during the development of this appraisal. Given the difference in clinical opinion AstraZeneca request that the EAG refer to the company submission and provided clinical expert interviews and Market Research to provide context for the committee.	This is not a factual inaccuracy. No changes have been made to the EAG report.
Page 25: 'Clinical advice to the EAG is that some patients find the taste and/or the gritty texture of this mixture unpleasant and that there can be treatment	Please update as follows: 'Clinical advice to the EAG is that some patients find the taste and/or the gritty texture of this mixture unpleasant and that there can be treatment compliance issues due to fluid retention. However, clinical opinion regarding this issue is	AstraZeneca do not have any data, HCP, or patient insights to suggest that unpleasant taste, gritty texture, or oedema, are frequent	This is not a factual inaccuracy. No changes have been made to the EAG report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
compliance issues due to fluid retention'.	varied and the rate of fluid retention events reported in the SZC SmPC is low (5.7%)'.	concerns affecting compliance. The SmPC for SZC states the following: oedema related events, including fluid retention, generalised oedema, hypervolaemia, localised oedema, oedema, oedema peripheral and peripheral swelling, were reported by 5.7% of Lokelma patients. However of note, the 15g dose in which oedema was more commonly seen is higher than the 10g licensed maintenance dose for non-haemodialysis patients in the UK. Furthermore most events (53%) were managed by initiating a diuretic or adjusting a diuretic dose; the remainder did not require treatment. Therefore AstraZeneca do not consider fluid retention impacts	

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
		compliance in clinical practice.[1]	
Page 25: 'Clinical advice to the EAG is that an S-K level of ≥5.5 to <6mmol/L is often tolerated in patients with CKD as these patients frequently have chronically elevated potassium levels, and their cardiac and neuromuscular systems adapt to the higher potassium.'	Please update as follows: 'Clinical advice to the EAG is that an S-K level of ≥5.5 to <6mmol/L is often tolerated in patients with CKD as these patients frequently have chronically elevated potassium levels, and their cardiac and neuromuscular systems adapt to the higher potassium. Conversely, published literature has shown that patients with CKD with an S–K level of ≥5.5–<6.0 mmol/L are at greater risk of a range of adverse clinical outcomes, including hospitalisation, mortality and MACE than those with normokalaemia.[4-10]'	There is a recognised and widely accepted body of evidence that demonstrates that an S-K level of ≥5.5–<6.0 mmol/L, including among patients with CKD, is associated with adverse outcomes in terms of morbidity and mortality.[7, 8, 11-13] Furthermore, an S-K level of ≥5.5–<6.0 mmol/L in patients with CKD commonly results in the down-titration or discontinuation of RAASi therapies,[14, 15] despite RAASi therapy being a mainstay guideline-recommended treatment for CKD.[16-18] This down-titration or discontinuation of RAASi therapies in CKD due to HK has been associated with	This is not a factual inaccuracy. No changes have been made to the EAG report.

		increased morbidity and mortality.[19-23] The KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (CKD), in discussing HK in CKD, does acknowledge that 'observationally, the risk of death from the same degree of HK is lower in more advanced CKD stages. This may suggest that there are adaptive mechanisms that render better tolerance to elevated levels of potassium in circulation.' However, despite this, this guideline still advises actions to manage HK (S-K >5.5 mmol/L) in CKD: firstly to address correctable factors (such as non-RAASi medications and diet), secondly to consider medications (such as diuretics, and potassium exchange agents) and thirdly to reduce or discontinue RAASi as a last resort.[16]	

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
		AstraZeneca is not aware of any CKD guidelines that recommend a 'no management' approach to an S-K level of ≥5.5–<6.0 mmol/L due to a presumed tolerance, nor any robust evidence to support this as a safe approach.	

Issue 5 Resource costs

Description of problem	Description of proposed amendment	Justification for amendment	
Page 58: 'RAASi therapy includes angiotensin-converting-enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs). The company stated that the inclusion of MRAs as part of RAASi therapy was intended to align with national guidelines.[49] However,	Please amend as follows: 'RAASi therapy includes angiotensin-converting-enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs). The company stated that the inclusion of MRAs as part of RAASi therapy was intended to align with national guidelines.[49] ~~However,~~ MRAs were not considered as part of RAASi therapy in the Xie et	The current phrasing is unclear that MRA drug costs are considered in the model.	The EAG has amended the EAG report as follows: The company stated that the inclusion of MRAs within RAASi therapy drug costs was intended to align with national guidelines and considered a conservative

MRAs were not considered as part of RAASi therapy in the Xie et al.[61] study used in the company model (CS, Table 43).'	al.[61] study used in the company model (CS, Table 43). **However, the cost of RAASi in the model includes an MRA component as a conservative assumption (CS, Tables 59–62)**.'		assumption.[49] However, MRAs were not considered as part of RAASi therapy in the Xie et al.[61] study used in the company model to inform the risk of death and MACE by RAASi status (CS, Table 43).
Page 65: 'Annual costs associated with CKD health states are likely to be overestimates since patients received RRT in the follow-up period of the Kent study[64]. The EAG has applied the cost estimates used in TA599.'	Please amend as follows: '**The company updated CKD costs to those used in recent NICE evaluations TA775 and TA937.[23-24]** Annual costs associated with CKD health states are likely to be ~~overestimates~~ **overestimated** since patients received RRT in the follow-up period of the Kent study[64] **used to inform recent CKD TAs.[24, 25]** The EAG has applied the cost estimates used in TA599.	Whilst the costs are from Kent 2015, these have been updated because they have been used in recent CKD TAs (TA775 and TA937) and represent the most recent committee preferred costs.[24, 25]	This is not a factual inaccuracy. The company rationale for using Kent 2015 estimates is stated elsewhere in the EAG report (p73). No changes have been made to the EAG report.
Page 72: 'In response to clarification question B14, the company stated that costs from the Kent 2015[64] were applied since they had	Please amend as follows: 'In response to clarification question B14, the company stated that costs from the Kent 2015[64] were applied since they ~~had been used in recent~~	Costs from Kent 2015 have been accepted in recent CKD TAs and represent current clinical thinking.[24, 25]	This is not a factual inaccuracy. No changes have been made to the EAG report.

been used in recent NICE appraisals of CKD.[72, 73]'	~~NICE appraisals of CKD.~~ are consistent with accepted values from recent appraisals in the CKD indication, such as TA775.[72, ~~73~~]		

Issue 6 Treatment duration

Description of problem	**Description of proposed amendment**	**Justification for amendment**	
Pages 66–67: 'In response to clarification question B4, the company considered that treatment discontinuation was implicitly captured in the SZC cohort of the ZORA study re-analysis since patients may have discontinued after 120 days of continuous SZC treatment.'	Please amend as follows: 'In response to clarification question B4, the company considered that the CS develops the EAG preferred approach in TA599, in that the proportion of patients discontinuing and down-titrating RAASi depends on the RAASi dose and S-K levels as in TA599, plus SZC treatment status. This addition is a result of the real-world evidence now available from the multi-national observational ZORA study, which provides different RAASi discontinuation rates for the same S–K levels, for people receiving SZC versus standard care in the real-world. Treatment discontinuation was implicitly captured in the SZC cohort of the ZORA study re-analysis since	Further rationale around the probabilities of discontinuing or down-titrating RAAS inhibitors was provided in response to clarification question B4.	This is not a factual inaccuracy. No changes have been made to the EAG report.

Description of problem	Description of proposed amendment	Justification for amendment	
	patients may have discontinued after 120 days of continuous SZC treatment.		
Pages 67–68: 'The market research data[69] were only collected over [redacted]) and there is no information about whether patients were being treated for acute or persistent HK, their S-K level when treatment was initiated and why treatment with SZC was stopped.'	Please amend as follows: 'The market research data[69] were ~~only~~ collected over [redacted]. There is no information about whether patients were being treated for acute or persistent HK, their S-K level when treatment was initiated and why treatment with SZC was stopped.'	The market research was conducted over [redacted], however the data collected considered patients treated with SZC over the previous [redacted], and clinicians considered the total actual or expected duration of treatment. Please amend the description for clarity.	The EAG has amended the EAG report as follows: The market research data[69] were only collected over [redacted]; in each period, clinicians were asked to provide [redacted]
Page 68: 'Furthermore, during the company advisory board meeting[66] it was noted that, [redacted]". '	Please amend as follows: 'Furthermore, during the company advisory board meeting[66] it was noted that, "[redacted]"	This is a selectively abbreviated quote from the advisory board meeting which does not accurately represent the discussions.	This is not factual inaccuracy. However, for completeness the EAG report has been amended as suggested by the company.

Description of problem	Description of proposed amendment	Justification for amendment	
	[redacted]		

Issue 7 Typographical and minor amendments

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 11, 19, 24, 25, 28, 34, 40, 45, 64, 69	Please amend S-K level definition throughout to '**≥**5.5 to **<**6.0mmol/L' and '**≥**6.0mmol/L', as necessary.	Exclusion of the ≥ and/or < descriptors in the S-K level range for the decision problem population is inaccurate.	The EAG has made changes to the EAG report in line with the company suggestions
Page 15: <table><tr><th rowspan="2">Scenario/EAG revisions</th><th colspan="2">Incremental</th><th rowspan="2">ICER (£/QALY)</th><th rowspan="2">Change from A1</th></tr><tr><th>Cost</th><th>QALYs</th></tr><tr><td>A1. Company base case</td><td>£4,572</td><td>0.441</td><td>£16,833</td><td>-</td></tr></table>	Please amend as follows: <table><tr><th rowspan="2">Scenario/EAG revisions</th><th colspan="2">Incremental</th><th rowspan="2">ICER (£/QALY)</th><th rowspan="2">Change from A1</th></tr><tr><th>Cost</th><th>QALYs</th></tr><tr><td>A1. Company base case</td><td>£4,572</td><td>0.441 0.272</td><td>£16,833</td><td>-</td></tr></table>	The reported incremental QALYs are incorrect.	Typographical error noted and corrected.
Page 18: 'Stop sodium zirconium cyclosilicate if +- are no longer suitable'	Please amend to: 'Stop sodium zirconium cyclosilicate if +- RAASi are no longer suitable'	Typographical error in the current SZC recommendations.	Typographical error noted and corrected.
Page 19: 'In 2022, the NICE AC was unable to recommend SZC as a treatment option for patients with CKD or HF who had a	Please amend as follows: 'In ~~2022~~ **2019**, the NICE AC was unable to recommend SZC as a	TA599 was published on 4th September 2019. The update in 2022 was	Typographical error noted and corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
confirmed S-K level ≥5.5 to <6mmol/L'	treatment option for patients with CKD or HF who had a confirmed S-K level ≥5.5 to <6mmol/L'	unrelated to the S-K threshold.	
Pages 19–20: 'SZC and patiromer are two potassium binders currently recommended by NICE[1, 31] as treatment options for patients with S-K levels ≥6mmol/L.'	Please amend as follows: 'SZC and patiromer are two potassium binders currently recommended by NICE[1, 31] as treatment options for patients with ~~S-K levels ≥6mmol/L~~ persistent HK and CKD stage 3b–5 or HF if they have S-K levels ≥6.0 mmol/L, are not taking an optimised dosage of RAASi and are not on dialysis.'	The complete criteria in the current recommendations should be included.	The EAG report has been amended to: SZC and patiromer are two potassium binders currently recommended by NICE. Patiromer was recommended by NICE in 2020; the NICE patiromer recommendation reflects the NICE SZC recommendation (Box 1).
Page 20: 'It is available in 5mg and 10mg sachets and is administered orally as a water-based suspension'	Please amend as follows: 'It is available in 5~~mg~~ **g** and 10~~mg~~ **g** sachets and is administered orally as a water-based suspension	Typographical error in the pack size of SZC.	Typographical error noted and corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 20: 'The Medicines and Healthcare Products Regulatory Agency[32] recommends that S-K levels should be monitored regularly during treatment. Based on the ZS-005[10-12] trial (conducted over 12 months). The UK Kidney Association suggests that blood monitoring should be performed weekly for the first month and then monthly thereafter'	Please amend as follows: 'The Medicines and Healthcare Products Regulatory Agency[32] recommends that S-K levels should be monitored regularly during treatment. Based on the ZS-005[10-12] trial (conducted over 12 months**), the** UK Kidney Association suggests that blood monitoring should be performed weekly for the first month and then monthly thereafter'	Updating the typographical error will make the paragraph easier to interpret correctly.	Typographical error noted and corrected.
Page 20: 'No more than 10g once daily should be used for maintenance therapy.'	Please amend as follows: 'No more than 10 g once daily should be used for maintenance therapy for patients who are not on haemodialysis. For patients on dialysis, the dose could be adjusted at intervals of one week in increments of 5 g up to 15 g once daily on non-dialysis days.'	It is inaccurate to state that SZC cannot be given at a dose of more than 10 g daily without caveating that a different dose is recommended for patients on haemodialysis.	Typographical error noted and corrected.
Page 24: 'The ZS trial efficacy data used to populate the	Please amend as follows:	Different data from the ZS trials were used to inform the	Typographical error noted and corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
company economic model are the same data that were used to populate the company TA599[1] economic model.'	'The ZS trial efficacy data were used to populate the company economic model, as per the approach taken in TA599.[1] However, a data-cut for the population of patients with S-K ≥5.5–<6.0 mmol/L specifically was used to inform the economic model in the CS.	economic models in the CS and TA599. Data for the subgroup of patients with S-K ≥5.5–<6.0 mmol/L from the ZS trials were used to inform the economic model in the CS. This is in line with the committee preferred approach in TA599.	
Page 28: 'The company model inputs for these subgroups differ by baseline characteristics (age, eGFR, statin usage, sodium, cholesterol, haemoglobin and lymphocytes), risk of adverse outcomes by S-K and RAASi use, utility values and healthcare resource use.'	Please amend as follows: 'The company model inputs for these subgroups differ by baseline characteristics (age, eGFR, statin usage and other concomitant therapies, sodium, cholesterol, haemoglobin and lymphocytes, proportion female, weight, SBP, WBC count, comorbidities and smoking history), risk of adverse outcomes by S-K and RAASi use, utility values and healthcare resource use.'	The list of baseline characteristics which differ by subgroup is not exhaustive and is therefore misleading.	Typographical error noted and corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 29: 'The data used to populate the company economic analysis were sourced from ZS-002, ZS-003, ZS-004, ZS-004E and ZS-005'	Please amend as follows: 'The data used to populate the company economic analysis were sourced from ~~ZS-002,~~ ZS-003, ZS-004, ~~ZS-004E~~ and ZS-005'	Incorrect list of studies informing the economic model.	Typographical error noted and corrected.
Page 34: Table 5 'patients with ≥1 S-K measures'	Please amend text as follows: 'patients with **≥>**1 S-K measures'	Please correct this error. AstraZeneca acknowledge this is a typographical error that appeared in the clarification question responses.	Typographical error noted and corrected.
Page 40: 'Source: CS, Figure 9'	Please amend as follows: 'Source: CS, **Figure 10**'	Incorrect cross-reference to the CS.	Typographical error noted and corrected.
Page 46: 'To support the original appraisal (TA599[1]), the company undertook SLR1 in June 2018 to identify and appraise: i) published cost effectiveness evaluations, ii) HRQoL data, and iii) cost and resource use data relevant to the decision problem.'	Please amend as follows: 'To support the original appraisal (TA599[1]), the company undertook SLR1 in ~~June~~ **April** 2018 to identify and appraise: i) published cost effectiveness evaluations, ii) HRQoL data, and iii) cost and resource use data relevant to the decision problem.'	Typographical error in the date of SLR1.	Typographical error noted and corrected.

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG comment</th></tr>
<tr><td>Page 52: ‘For patients receiving standard care, the 48-hour absolute reduction in S-K observed in the ZS-003 trial placebo arm was linearly extrapolated to Day 3;’</td><td>Please amend as follows:
‘For patients receiving standard care, the 48-hour absolute reduction in S-K observed in the ZS-003 trial placebo arm was applied to Day 2 of the S-K trajectory and linearly extrapolated to Day 3, as a conversative assumption from TA599.’</td><td>Additional clarification to aid interpretation.</td><td>The EAG report has been amended as suggested by the company.</td></tr>
<tr><td>Page 59:<table><tr><th>Disease severity</th></tr><tr><td>NYHA I</td></tr><tr><td>NYHA II</td></tr><tr><td>NYHA II</td></tr><tr><td>NYHA IV</td></tr></table></td><td>Please update as follows:<table><tr><th>Disease severity</th></tr><tr><td>NYHA I</td></tr><tr><td>NYHA II</td></tr><tr><td>NYHA <s>II</s> III</td></tr><tr><td>NYHA IV</td></tr></table></td><td>Please correct this error. AstraZeneca acknowledge this is a typographical error that appeared in the CS.</td><td>Typographical error noted and corrected.</td></tr>
</table>

Location of incorrect marking	Description of incorrect marking	Amended marking
NA	NA	NA

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