Sodium Zirconium Cyclosilicate for the First Line Treatment of Hyperkalaemia (review of TA599)

For zoom – contains redacted information

Technology appraisal committee B [08 October 2025]

Chair: Charles Crawley

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Company: AstraZeneca

Sodium Zirconium Cyclosilicate for the First Line Treatment of Hyperkalaemia (review of TA599)

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Review of TA599

See supplementary appendix for appraisal history

TA599 recommendation: SZC as an option for emergency + optimised outpatient use only (S-K ≥6.0 mmol/L, CKD/HF, non-dialysis) when RAAS inhibitor not optimised

1.1 Sodium zirconium cyclosilicate is recommended as an option for treating HK in adults only if used:

- in emergency care for acute life-threatening HK alongside standard care or
- for people with persistent HK and chronic kidney disease stage 3b to 5 or heart failure, if they: — have a confirmed S-K level of at least 6.0 mmol/litre and — because of HK, are not taking an optimised dosage of renin-angiotensin-aldosterone system (RAAS) inhibitor and — are not on dialysis. [**amended 2022**]

1.2 Stop sodium zirconium cyclosilicate if RAAS inhibitors are no longer suitable. [**amended 2022**]

What this appraisal is about:

- A target review, which expands the population to those with an S-K level of ≥5.5 to <6.0 mmol/L while addressing evidence gaps identified in TA599. Specifically, key uncertainties in
  - ❑ Relationship between S–K levels and long-term clinical outcomes (MACE, hospitalisation, and mortality)
  - ❑ SZC treatment effect in maintaining RAASi therapy in people with HK, independent of S-K levels
  - ❑ Relationship between RAASi treatment dosages and long-term treatment outcomes

CKD, chronic kidney disease; HF, heart failure; HK, hyperkalaemia; MACE, major adverse cardiovascular event; RAAS, renin-angiotensin-aldosterone system; S-K, serum potassium; TA, technology appraisal

Background:

Hyperkalaemia is commonly defined as a serum potassium level above 5.5mmol/L

Hyperkalaemia (HK): abnormally high level of potassium in blood (normal range 3.5 to 5.0 mmol/L); UK Kidney Association Clinical Practice guidelines define HK as a S-K of >5.5 mmol/L

Risk factors

- Advancing age and cardiorenal conditions such as CKD or HF
- Taking inhibitors of RAAS (e.g. angiotensin-converting-enzyme (ACE) inhibitors , angiotensin II receptor blockers and potassium-sparing diuretics)

Epidemiology: prevalence is ~ 6% while incidence is 2.8 cases 100 person-years

Prognosis

- Sub-optimal dosing of RAASi due to HK is associated with an increased risk of adverse cardiorenal outcomes

Management of HK: primary or secondary setting

- S–K of < 6.0 mmol/L: commonly down-titration/discontinuation of RAASi
- S–K of ≥ 6.0 mmol/L: SZC or patiromer recommended by NICE

NICE

CKD, chronic kidney disease; HF, heart failure; HK, hyperkalaemia; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium

Patient perspectives

Based on patient expert statement received during TA599, statements relevant to S-K level of ≥5.5 to <6.0 mmol/L only

- Dietary intervention not adequate, not always effective
    - low potassium diet is very demanding especially as it restricts common items like bananas, coffee and chocolate and alongside other restrictions on dairy food if phosphate levels are too high accompanied by the very common liquid restriction of 500 ml/day
- Living with someone with hyperkalaemia is difficult for partners/carers especially if they are struggling to work out what to buy and cook
- Groups of people who may have particular need:
    - people on dialysis or advanced chronic kidney disease (CKD 5), but not yet on dialysis. People cannot process potassium between dialysis days and are at risk of having a hyperkalaemia event
    - “for [people] on conservative care [in the community] .. reluctance to prescribe specialist drugs by non-specialists so patients can lose out”

CKD, chronic kidney disease; S-K, serum potassium; TA, technology appraisal

Clinical perspectives

SZC can help optimise doses of essential medication such as RAASi therapy

Submissions from UK Kidney Association and 2 clinical experts

- Clinically significant treatment response would be reduction in S-K level to ≤ 5.0 mmol/l and certainly <5.5mmol/L
- Most important outcomes: rate of onset of action, efficacy, ability to optimise RAASi & mineralocorticoid receptor antagonist therapy and tolerability
- SZC facilitates optimisation of essential medication (e.g. RAASi therapy)→ help with management of renal and heart disease and reduce hospital admissions
- Paradoxically, people with renal or heart disease are most susceptible to HK but also stand to gain greatest benefit from RAASi therapy
- SZC could reduce need for strict dietary restrictions
- Unmet need: prior to availability of SZC, only oral option was calcium resonium which is poorly tolerated with unreliable efficacy
- SZC would be useful during periods when dialysis cannot be achieved

In clinical practice, SZC is proving to be efficacious in the acute and chronic setting.

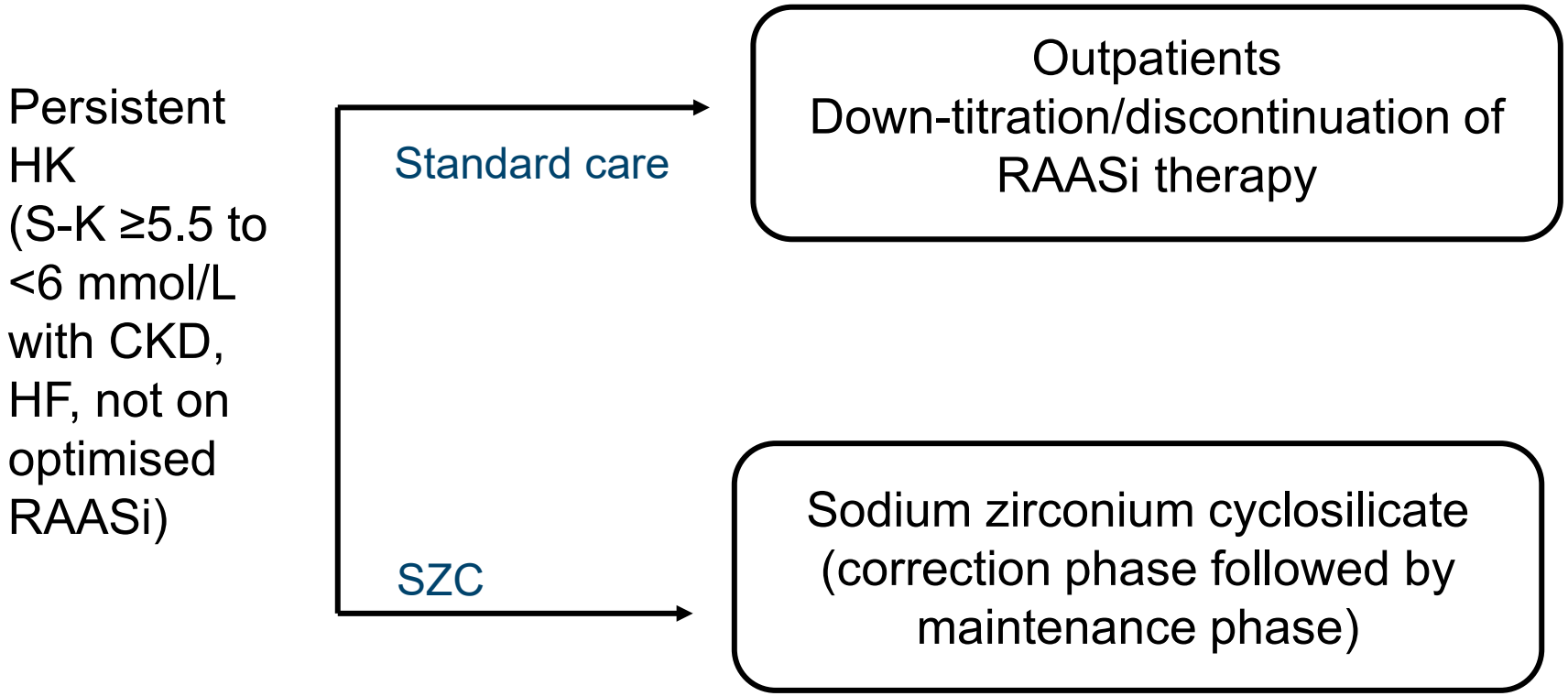
This technology was also crucial during the COVID pandemic in allowing dialysis schedules to be safely reduced to twice weekly.

HK, hyperkalaemia; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, Sodium zirconium cyclosilicate

Treatment pathway

EAG: pathway largely reflects NHS practice, but SZC treatment duration in persistent HK not established and will vary across patients

Treatment pathway and anticipated positioning of SZC



Management of RAASi therapies in persistent setting for standard care:

- Down-titration/ discontinuation of RAASi if S-K ≥5.5 to <6 mmol/L
- Discontinuation of RAASi if S-K ≥6 mmol/L

Is the treatment pathway reflective of NHS clinical practice?
Is down-titration/discontinuation of RAASi therapy the relevant comparator for the company's proposed population?

CKD, chronic kidney disease; HF, heart failure; HK, hyperkalaemia; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

Sodium Zirconium Cyclosilicate (Lokelma, AstraZeneca)

Technology details

Marketing authorisation	• Indicated for the treatment of hyperkalaemia in adult patients • Marketing authorisation from the MHRA in March 2018; subsequently revised in April 2020 to extend indication for treatment of patients receiving chronic dialysis via EMA centralised procedure
Mechanism of action	• Non-absorbed powder, captures potassium throughout GI tract and reduces concentration of free potassium in GI lumen, thereby lowering S-K and increasing faecal potassium excretion
Administration	**Correction phase**: recommended dose 10mg 3 times a day. Max duration 72 hours. When normokalaemia is achieved, maintenance regimen should be followed **Maintenance phase**: starting dose of 5 g once daily is recommended, with possible titration up to 10 g once daily, or down to 5 g once every other day, as needed to maintain normal potassium level. Max dose 10mg once daily
Price	• List price: SZC 5 g = £5.20; SZC 10 g = £10.40 • Patient access scheme not applicable

EMA, European Medicines Agency; GI, gastrointestinal; MHRA, Medicines and Healthcare products Regulatory Agency; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

Key issues

Issue	ICER impact
Consideration of dialysis population	Unknown
Association between persistent HK and adverse outcomes in SPARK study	Small
Generalisability of ZORA study re-analysis results	Unknown
Impact of SZC on RAASi use	Large
SZC treatment duration	Large
Impact of SZC treatment discontinuation	Unknown
SZC treatment if S-K ≥6.0 mmol/L	Unknown
Generalisability of RAASi model algorithm to NHS clinical practice	Unknown
CKD health state costs	Moderate

CKD, chronic kidney disease; ICER, incremental cost effectiveness ratio; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

Equality considerations

Company: excluding people receiving dialysis from recommendation would result in inequitable access across population covered in marketing authorisation

- SZC now licensed in people having chronic dialysis
  - ❑ Population of high unmet need → monthly episode of HK with S-K ≥5.5 mmol/L in about 2/3 of those undergoing dialysis (DIALIZE and ADAPT studies, supplementary appendix)
- SZC previously incorporated into emergency COVID-19 guidelines (NG160) for management of dialysis, allowing delay in dialysis until COVID-19 results are known
  - NICE technical team comment: NG160 withdrawn in May 2022
- Lack of evidence on SZC's longer term outcomes suitable for economic modelling, so population undergoing dialysis not included in this submission
- Restricting access to SZC in this population because of insufficient data demonstrating cost-effectiveness after previously allowing access in NG160 would
  - ❑ preclude small number of people and
  - ❑ result in inequitable access across full population covered in marketing authorisation

HK, hyperkalaemia; S-K, serum potassium; NG, NICE guideline; SZC, sodium zirconium cyclosilicate; TA, technology appraisal

Key issues: Consideration of dialysis population

Marketing authorisation includes people having dialysis but insufficient evidence for robust economic modelling for this population

Background

- SZC marketing authorisation revised in 2020 to include treatment of people having chronic dialysis
- Final scope population includes people with persistent HK who require dialysis

Company

- Currently insufficient evidence for robust economic modelling for people receiving dialysis→ population is not addressed within submission
  - ❑ Reasonable to include this group in positive NICE recommendation: see equality issue slide

EAG:

- Clinical advice to EAG: people with persistent HK requiring dialysis are not generally prescribed potassium binders in practice, as dialysis effectively removes excess potassium from blood

Clinical expert:

- Use of SZC in dialysis population is common (although not routine) in people with persistent HK

What is the proportion of people undergoing dialysis in the NHS whose SK-levels are not adequately controlled so are unable to receive optimised RAASi treatment?
What is the committee's view on including people with persistent HK who require dialysis in consideration?

EAG, External Assessment Group; HK, hyperkalaemia; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

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SLRs and additional real-world evidence

Key studies summary of clinical evidence for SZC from phase 3 clinical trials presented in TA599 provided in supplementary appendix

Company: conducted 2 real-world studies and an SLR to address main area of uncertainties in TA599:

- ❑ Spark study: link between S-K levels and long-term clinical outcomes such as mortality;
- ❑ Zora re-analysis: impact of SZC on reinitiation, up-titration, or maintaining optimised RAASi dosage;
- ❑ SLR(2): the relationship between RAASi dosage and long term clinical outcomes
- Also conducted another SLR(1) assessing efficacy and safety of SZC for patients with persistent HK

EAG: regarding the SLRs

- **Lack of evidence** on effect of **down-titration or stopping** of RAASi on S-K for patients with HF or CKD;
- No new RCT evidence to support the clinical effectiveness of SZC in patients with S-K ≥ 5.5 to < 6.0mmol

Additional real-world evidence

	Spark study	Zora study re- analysis
Objective	to investigate relationship between S-K and hospitalisation, MACE and mortality	To compare the **odds of maintained RAASi** therapy at 6 months in: SZC versus no potassium binder, stratified by S-K levels
Design	Retrospective, observational, longitudinal study using secondary data extracted from CPRD and linked datasets	Observational, longitudinal cohort study conducted using secondary care data from health registers and medical claims

CKD, chronic kidney disease; CPRD, Clinical Practice Research Datalink; EAG, External Assessment Group; HF, heart failure; HK, hyperkalaemia; MACE, major adverse cardiovascular event; RAASi, renin-angiotensin-aldosterone system inhibitor; RCT, randomised controlled trial; S-K, serum potassium; SLR, systematic literature review; SZC, sodium zirconium cyclosilicate; TA, technology appraisal

Real-world studies

See supplementary appendix for:
- SPARK study summary
- ZORA study re-analysis summary

	Spark study	Zora study re- analysis
Population	People aged ≥18 years with a recorded S-K measurement, a **diagnosis of HK and CKD and/or HF**, or a prescription of potassium binder	People aged ≥18 years with a diagnosis of **CKD and/or HF**, and an outpatient prescription for RAASi medication within 6 months prior to indexing
Intervention	No intervention	Sodium zirconium cyclosilicate
Comparator(s)	None	No prescribed potassium binder medication
Treatment duration	N/A	Not reported (minimum 120 days)
Study follow-up	Minimum 12 months of records before index date	Both cohorts (SZC and no potassium binder) were followed for 180 days after the index HK event for outcomes assessment.
Key outcomes	Use of RAASi therapy, hospitalisations, MACE, mortality, kidney function decline	RAASi use: discontinued, down titrated, stabilised or up titrated. Aggregated into: Maintained RAASi, reduced RAASi
Locations	UK-specific	Japan, US, Spain
Used in model?	Yes	Yes (ad-hoc re-analysis of Japan and US data)

CKD, chronic kidney disease; HF, heart failure; HK, hyperkalaemia; MACE, major adverse cardiovascular event; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

See supplementary appendix for SPARK study patient baseline characteristics

SPARK study: key results

Company: results show higher incidence rate of mortality and hospitalisations with CKD or HF with S-K levels ≥5.5 to <6.0 mmol/L vs. S-K of ≥4.5 to <5.0 mmol/L, [redacted]

Adjusted incidence rate ratios, CKD population

Outcome	Adjusted IRR for S-K level of ≥5.5 to <6.0mmol/L vs ≥4.5 to <5.0mmol/L
MACE	[redacted]
Mortality	[redacted]
Hospitalisation	[redacted]

Adjusted incidence rate ratios, HF population

Outcome	Adjusted IRR for S-K level of ≥5.5 to <6.0mmol/L vs ≥4.5 to <5.0mmol/L
MACE	[redacted]
Mortality	[redacted]
Hospitalisation	[redacted]

Company

- Comorbidities and co-medications adjusted results shows a clear 'U-shaped' relationship between S–K and hospitalisation, MACE, and mortality as stratified by S–K levels and eGFR
- Excluded James 2021 study from SLR2 because population having a RAASi did not solely have HF, CKD or diabetic nephropathy; study objectives and methods also differ from SPARK study
  - ❑ In James 2021, lower mortality risk observed in those spending more time with S-K levels ≥5.0mmol/L (see supplementary appendix) may be because benefits from more proactive management
  - Differences in study results likely because: disparities in dataset, exposure definitions, confounding structures, and statistical modelling – see supplementary appendix

CI, confidence interval; CKD, chronic kidney disease; HF, heart failure; IRR, Incident rate ratio; MACE, major adverse cardiovascular event; S-K, serum potassium

Key issues: Association between persistent HK and adverse outcomes in SPARK study

EAG: SPARK study does not provide robust evidence to confirm impact of persistent HK (S-K ≥ 5.5 to < 6.0mmol) on MACE, hospitalisation and mortality

EAG comments

- **SPARK study population may not reflect population with persistent HK**, as single S-K tests may incorrectly identify HK
  - ❑ in cohort with S-K level ≥5.5 to <6.0mmol/L, a proportion of people only had 1 S-K measure and for those who had more than 1 measure, [redacted] and [redacted] in prior CKD cohort and prior HF cohort, respectively, had an S-K level that at least once that fell below their baseline S-K group
  - ❑ analysis that uses time spent with persistent HK (for different S-K groups) as an independent variable may help resolve issue, but no information provided on how long people spent in each S-K group
- James 2021 study provides evidence from a large UK cohort with CKD (n= 297,702) or HF (n=84,210)
  - ❑ Different results from SPARK highlight complexity of relationship between S-K levels and outcomes
- Provided exploratory scenario in which S-K level assumed to have no effect on risk of MACE, hospitalisations and mortality (S-K group incidence rate ratios set equal to 1) → small impact on company base case

Clinical expert:

- RCTs show potassium binders allow RAASi use rather than reducing adverse outcomes directly. But observational data suggest S-K level 5.5 to 6.0mmol/L associated with worsening of outcomes – see supplementary appendix

What is the committee's view on the SPARK study? Is S-K level an appropriate surrogate outcome for mortality or MACE based on the evidence from SPARK study?

CKD, chronic kidney disease; HF, heart failure; HK, hyperkalaemia; MACE, major adverse cardiovascular event; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

ZORA study re-analysis: key results

See supplementary appendix for ZORA study re-analysis patient baseline characteristics (after matching)

EAG: It is unclear if ZORA re-analysis indicated that SZC maintains RAASi therapy after HK

Proportions of patients who discontinued, down titrated, stabilised and up-titrated their RAASi therapy meta-analysed across countries

Subgroup	SZC	Control (no potassium binder)	Odds ratio	p value
≥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]

See supplementary appendix for results stratified by S-K level

EAG comments:

- *Baseline S-K level used for analysis*; no adjustment made in ZORA study re-analysis to account for change in S-K levels during follow up period
  - ❑ Results do not support that SZC impacts the probability of RAASi discontinuation/down-titration independent of S-K levels – see key issue: Impact of SZC on RAASi use

CI, confidence interval; EAG, External Assessment Group; HK, hyperkalaemia; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

Key issues: Generalisability of ZORA study re-analysis results

EAG: differences between baseline characteristics of ZORA study re-analysis and NHS target population may affect generalisability of results

Company

- ZORA study re-analysis: data from Japan and the USA only
- Company's clinical experts: results generalisable to UK population and reflect their clinical experience

EAG comments

- Variation between Japanese and US patients (e.g. receipt of potassium binders, different health care systems)
- Differences in baseline characteristics may affect generalisability of results to NHS patients – see supplementary appendix

Clinical experts:

- ZORA study population not substantially different from those commonly encountered within NHS
- Japanese and US healthcare systems diverse→ makes findings more generalisable to other countries

- Are the ZORA study re-analysis results generalisable to the NHS?
- Does the committee consider ZORA study re-analysis addresses the uncertainties in whether SZC would allow patients to stay on optimal doses of RAAS inhibitors?

EAG, External Assessment Group; RAAS, renin-angiotensin-aldosterone system; SZC, sodium zirconium cyclosilicate

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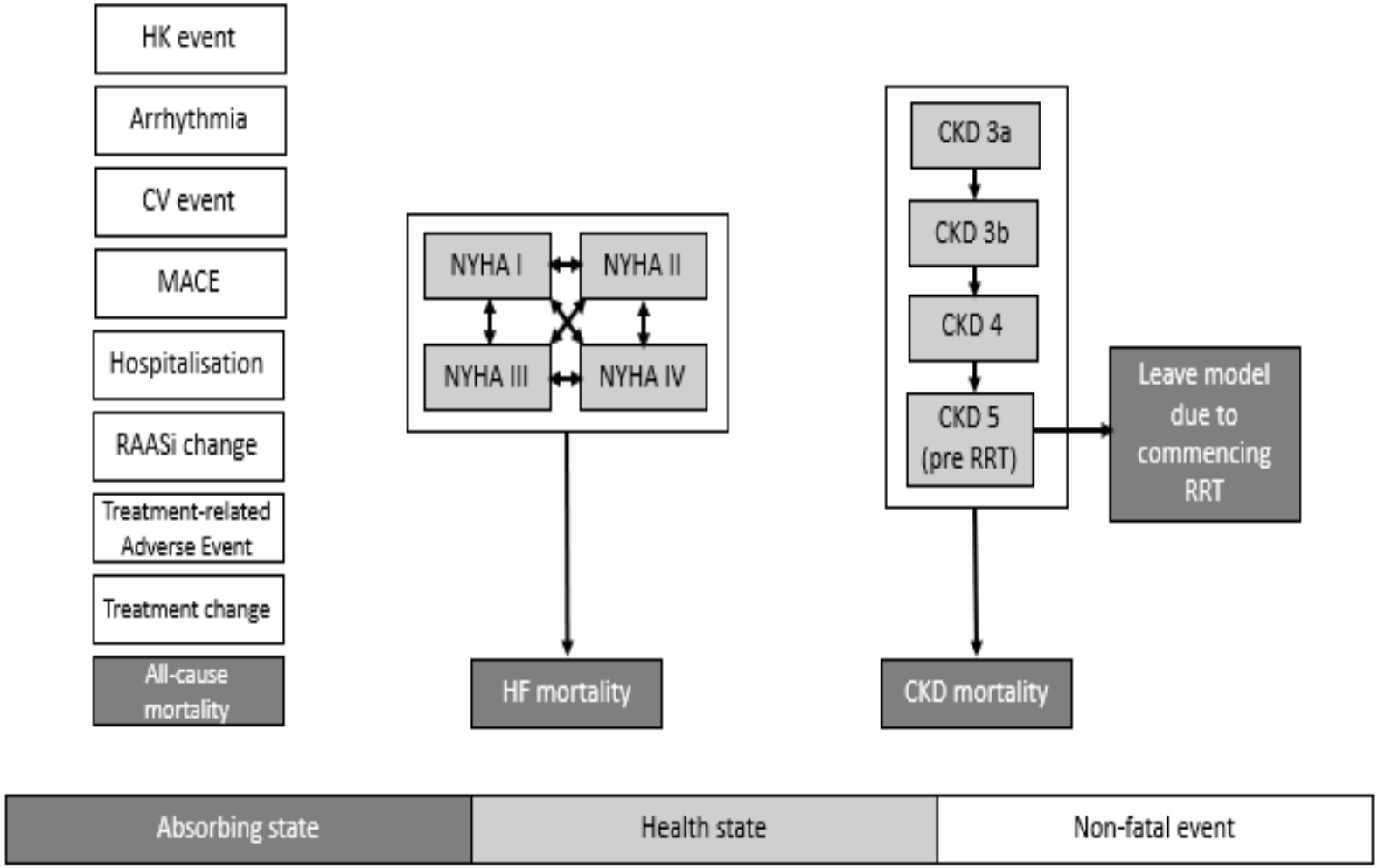
NICE National Institute for Health and Care Excellence

Company's model overview

Company used model previously considered suitable for decision-making by NICE in TA599

Flow diagram summarising model health states (shaded) and events (unshaded)



- **Patient-level**, fixed-time increment stochastic **simulation model**
- disease progression in people with HF represented by movement between NYHA classes I to IV
- disease progression in people with CKD represented by continuous decline in eGFR; tracked until onset of ESRD and initiation of RRT
- Relevant clinical events (e.g. MACE) also incorporated into model through simulation
- People exit model either due to death or on initiation of RRT
- Results presented for **CKD population, HF population and mixed population**

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HF, heart failure; HK, hyperkalaemia; MACE, major adverse cardiovascular event; NYHA, New York Heart Association; RAASi, renin-angiotensin-aldosterone system inhibitor; RRT, renal replacement therapy; S-K, serum potassium

Key Issue: Impact of SZC on RAASi use

Different assumptions used in company and EAG base cases for impact of SZC on down-titrating or discontinuing RAASi treatment

Background

Company model: probability of down-titrating or discontinuing RAASi sourced from ZORA study re-analysis; probabilities dependent on treatment and S-K value *(different probabilities for same S-K level)*

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

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

Company

- Assumed people on SZC less likely to discontinue/down-titrate RAASi independent of S-K levels
- Supported by Zora study re-analysis results – see results slide
- In ZORA re-analysis, subgroup analysis of people stratified by S–K values, [redacted] of SZC in the proportions receiving guideline directed RAASi therapy

EAG, External Assessment Group; RAASi, renin-angiotensin-aldosterone system inhibitor; SE, standard error; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

Key Issue: Impact of SZC on RAASi use

EAG comments

- **Prefers probabilities of RAASi discontinuation/down-titration to be based on S-K group only** and independent of treatment
  - ZORA study reanalysis does not support assumption that people having SZC less likely to discontinue/down-titrate RAASi dose independent of S-K levels, as S-K groups defined using S-K at baseline, and no adjustment made to account for S-K changes over the follow-up period
  - In model, effect of changes to S-K on RAASi use already accounted through different S-K group probabilities and lower average S-K values in SZC arm
  - In EAG base case, 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

Clinical experts:

- SZC effectively maintains potassium within target ranges. This, in turn, enables initiation, continuation, and optimisation of RAASi therapy

Would SZC impact RAASi use in people with the same S-K level?
Is it more appropriate to assume the probability of down-titrating or discontinuing RAASi is dependent on treatment arm and S-K value, or dependent on S-K value only?

- If the latter, is it more appropriate to derive probabilities of down-titration or discontinuation using SZC values or standard care values?

EAG, External Assessment Group; HK, hyperkalaemia; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

Key issue: SZC treatment duration

Company assume SZC treatment duration of 12 weeks; EAG prefer to assume lifetime treatment

Company

- In company model, all people still receiving SZC at 12 weeks discontinue treatment; SZC reinitiated (for 12 weeks) if S-K is ≥5.5 mmol/L - assumption based on company market research

EAG comments

- Clinical advice to EAG: SZC dose reductions may occur in clinical practice but most people would not discontinue treatment as discontinuation expected to increase S-K to level prior to treatment start
- Prefers to assume SZC treatment continues for lifetime (subject to annual discontinuation probability)

Clinical experts:

- For people with progressive CKD or advanced HF who require long-term RAASi therapy, ongoing treatment with SZC may be necessary to sustain S-K control and ensure optimisation of RAASi therapy
- Most underlying causes of chronic / recurrent HK are not reversible (e.g. CKD or HF)→ SZC treatment almost certainly lifelong

Does the committee prefer assuming a 12-week treatment duration for SZC or a lifetime treatment duration (with annual discontinuation probability)?

CKD, chronic kidney disease; EAG, External Assessment Group; HF, heart failure; HK, hyperkalaemia; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

Key Issue: Impact of SZC treatment discontinuation

Company

- SZC probabilities of discontinuing or down-titrating RAASi treatment applied to all people initially having SZC independent of whether patient has discontinued SZC → **treatment discontinuation implicitly captured in SZC cohort of ZORA study re-analysis** since people may have discontinued after 120 days of continuous SZC treatment

EAG comments

- Applying ZORA study re-analysis SZC probabilities to all people initially treated with SZC likely to overestimate benefit of SZC on RAASi use
  - ❑ minimum SZC duration in ZORA study (120 days) is 66.7% (120/180) of study follow up, much higher than the mean SZC treatment duration in company base case, expressed as proportion of expected survival in years (2.3/8.1=28.3%)
  - ❑ If assuming SZC lifetime treatment duration (see previous slide), mean treatment duration expressed as proportion of expected survival is approximately 70%→ more consistent with minimum possible treatment duration in ZORA study re-analysis

Is it appropriate to apply the same probability of discontinuing or down-titrating RAASi treatment to people still taking SZC and people who have discontinued SZC?

EAG, External Assessment Group; RAASi, renin-angiotensin-aldosterone system inhibitor; SZC, sodium zirconium cyclosilicate

Key issue: SZC treatment in standard care arm if S-K ≥6.0 mmol/L

Company: Excluding SZC for standard care arm likely to have minimal impact on model outcomes

Background

- In company model, people on standard care do not have SZC even if S-K level is ≥6.0 mmol/L

Company

- For standard care arm, average S-K assumed constant from day 4+; supported by REVOLUTIONIZE study
- Excluding SZC treatment for people on standard care likely to have a minimal impact on model outcomes since a S-K level of ≥6.0 mmol/L unlikely to occur

EAG comments

- REVOLUTIONIZE study follow-up is only 6 months and model has lifetime time horizon; company hasn't provided evidence to support that S-K value remains constant on standard care
- Clinical advice to EAG: for HK managed by down-titrating or discontinuing RAASi treatment, average S-K levels are likely to increase over time as underlying disease progresses
- SZC treatment would increase costs but reduce S-K levels and allow for optimised RAASi dosages
- Uncertain how many people on standard care are expected to have SZC over modelled time horizon

Clinical expert:

- Unless underlying disease reversed or stabilised, likelihood of recurrent or worsening HK increases over time

What is the committee's view on the impact of excluding SZC treatment for people in the standard care arm if S-K ≥6.0 mmol/L, on cost effectiveness? Is it appropriate?

EAG, External Assessment Group; HK, hyperkalaemia; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

Key issue: Generalisability of RAASi model algorithm to NHS clinical practice

EAG: company's approach to modelling RAASi use does not reflect what would happen in current clinical practice

Background

- As per TA599: in company model, at baseline, all people assumed to be receiving optimal ("max") RAASi dose
- Also assumed that after RAASi discontinuation, people can only return to the optimal RAASi dose
- RAASi status modifies the risk of disease progression and adverse outcomes in model

Company

- Assuming all people at baseline receive optimal RAASi dose is conservative→ likely that higher proportion in standard care arm would already have their RAASi dose proactively down-titrated to avoid a potential HK event *compared* with *SZC arm*
- Assuming that people return to optimal RAASi dose after discontinuation also conservative → people on standard care likely to reinitiate RAASi treatment more cautiously than people receiving SZC

EAG, External Assessment Group; HK, hyperkalaemia; RAASi, renin-angiotensin-aldosterone system inhibitor; SZC, sodium zirconium cyclosilicate; TA, technology appraisal

Key issue: Generalisability of RAASi model algorithm to NHS clinical practice

EAG comments

- Company's reasoning that optimal RAASi dose at baseline is conservative not relevant for cost effectiveness analysis→ baseline values should be same for both treatment arms

- Baseline RAASi use may have large impact on model outcomes
  - ❑ Time spent in "max" RAASi state likely to decrease for all patients if some having a suboptimal RAASi dose at baseline; extent of decrease in time may depend on probability of up-titration

- Up-titration after RAASi discontinuation
  - ❑ Proportion and/or the length of time spent in "max" RAASi state likely overestimated by assuming all people up-titrate to maximum
- Impact of assumptions for baseline RAASi use and up-titration dose depends on probability of up-titration
- Impact on cost-effectiveness results uncertain, *EAG has not made changes to company model*

- Would all, or only a proportion of people have optimal RAASi dose at baseline in clinical practice?
- After RAASi discontinuation, can people only return to the maximum RAASi dose, or can they also reinitiate RAASi at suboptimal dosages and up-titrate over time in clinical practice?

EAG, External Assessment Group; RAASi, renin-angiotensin-aldosterone system inhibitor

Key issue: CKD health state costs

Company and EAG disagree on most appropriate source for CKD health state costs

Background

- In company model, annual costs associated with each CKD stage are sourced from Kent et al. (2015)

Company

- Costs from Kent et al. are more recent than those from NICE CG182 and were accepted in recent NICE appraisals in CKD, such as TA775 and TA937

EAG comments

- Kent et al. costs reported by CKD stage at baseline; 28% of people with CKD stage 4 and 79% of people with CKD stage 5 (not receiving dialysis) at baseline received RRT by end of study period
- In company model, **people exit model on initiation of RRT**→ Kent et al. overestimates cost associated with CKD progression in context of model
- **Prefers using NICE CG182 costs**

Annual CKD costs applied in model

Health state	Annual cost (mean)	
	Company base case (Kent et al)	EAG base case (NICE CG182)
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

Are CKD health state costs from Kent et al. or from NICE CG182 more appropriate?

CG, Clinical guideline; CKD, chronic kidney disease; EAG, External Assessment Group; RRT, renal replacement therapy; TA, technology appraisal

Summary of company and EAG base case assumptions

Assumptions in company and EAG base case

Assumption	Company base case	EAG exploratory base case 1	EAG exploratory base case 2
Probabilities of RAASi down-titration/discontinuation	Dependent on S-K group and treatment arm	Probabilities for each S-K group equivalent by treatment: **SZC values**	Probabilities for each S-K group equivalent by treatment: **standard care values**
SZC treatment duration	12 weeks	Model lifetime	
SZC treatment in standard care arm	No SZC even if S-K level is ≥6.0 mmol/L		
Risk of MACE, hospitalisations and mortality	Modelled using incidence rate ratio derived from SPARK study		

EAG, External Assessment Group; MACE, major adverse cardiovascular event; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

Summary of company and EAG base case assumptions

Assumptions in company and EAG base case

Assumption	Company base case	EAG exploratory base case 1	EAG exploratory base case 2
RAASi model algorithm	At baseline, all people receiving optimal RAASi dose, and after discontinuation return to optimal dose		
CKD health state costs*	Kent et al.	NICE CG182	
Probability of up-titration†	Luo 2016	ZORA study subgroup analysis	
Time for return to "max" RAASi state†	Eligible to return to "max" RAASi state **12 weeks** after discontinuation/down-titration	Eligible to return to "max" RAASi state **4 weeks** after discontinuation/down-titration	

*only applicable for CKD population

† not included as key issues due to less significant impact on results, see supplementary appendix for further details

CG, clinical guideline; CKD, chronic kidney disease; EAG, External Assessment Group; RAASi, renin-angiotensin-aldosterone system inhibitor

Company base case results (1)

Deterministic base case results: CKD population

Technology	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Standard care	£49,669	3.194	-	-	-
SZC	£54,241	3.466	£4,572	0.272	£16,833

Deterministic base case results: HF population

Technology	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Standard care	£17,719	3.187	-	-	-
SZC	£24,224	3.906	£6,506	0.719	£9,053

CKD, chronic kidney disease; HF, heart failure; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year; SZC, sodium zirconium cyclosilicate

Company base case results (2)

Deterministic base case results: mixed CKD and HF population

Technology	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Standard care	£40,234	3.703	-	-	-
SZC	£45,546	4.128	£5,312	0.425	£12,495

Probabilistic base case results: mixed CKD and HF population

Technology	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Standard care	£40,321	3.703	-	-	-
SZC	£45,596	4.126	£5,276	0.423	£12,417

CKD, chronic kidney disease; HF, heart failure; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year; SZC, sodium zirconium cyclosilicate

EAG base case results (1)

Deterministic results for CKD population: SZC versus standard care

Scenario/EAG revisions	SZC		Standard care		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	(£/QALY)
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
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
R2) Lifetime SZC treatment duration	£61,162	3.600	£49,669	3.194	£11,494	0.406	£28,333
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
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
R5) CKD health state costs informed by NICE CG182	£50,331	3.466	£44,875	3.194	£5,456	0.272	£20,089
EAG exploratory base case 1 (R1a, R2-R5)	**£54,893**	**3.478**	**£44,909**	**3.242**	**£9,984**	**0.236**	**£42,351**
EAG exploratory base case 2 (R1b, R2-R5)	**£52,209**	**3.283**	**£43,827**	**3.150**	**£8,382**	**0.133**	**£63,010**

† not included as key issues due to less significant impact on results, see supplementary appendix for further details

CG, clinical guideline; CKD, chronic kidney disease; 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

EAG base case results (2)

Deterministic results for HF population: SZC versus standard care

Scenario/EAG revisions	SZC		Standard care		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	(£/QALY)
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
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
R2) Lifetime SZC treatment duration	£32,979	4.286	£17,719	3.187	£15,260	1.099	£13,892
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
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
EAG exploratory base case 1 (R1a, R2-R5)	**£29,530**	**3.889**	**£17,812**	**3.281**	**£11,717**	**0.607**	**£19,290**
EAG exploratory base case 2 (R1b, R2-R5)	**£26,127**	**3.406**	**£16,664**	**3.075**	**£9,463**	**0.331**	**£28,618**

† not included as key issues due to less significant impact on results, see supplementary appendix for further details

EAG, External Assessment Group; HF, heart failure; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

EAG base case results (3)

Deterministic results for mixed CKD and HF population: SZC vs standard care

Scenario/EAG revisions	SZC		Standard care		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	(£/QALY)
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
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
R2) Lifetime SZC treatment duration	£53,486	4.344	£40,234	3.703	£13,252	0.641	£20,689
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
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
R5) CKD health state costs informed by NICE CG182	£47,159	4.128	£41,017	3.703	£6,142	0.425	£14,446
EAG exploratory base case 1 (R1a, R2-R5)	**£52,573**	**4.131**	**£41,150**	**3.773**	**£11,423**	**0.358**	**£31,898**
EAG exploratory base case 2 (R1b, R2-R5)	**£49,634**	**3.836**	**£39,997**	**3.638**	**£9,637**	**0.198**	**£48,641**

CKD [redacted]%;HF [redacted]%

† not included as key issues due to less significant impact on results, see supplementary appendix for further details

CG, clinical guideline; CKD, chronic kidney disease; EAG, External Assessment Group; HF, heart failure; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

EAG base case results (4)

Due to substantial PSA run time (>24 hours), probabilistic results are only presented for the mixed population to demonstrate similarity with deterministic results

Probabilistic results for mixed CKD and HF population: SZC vs standard care

Scenario/EAG revisions	SZC		Standard care		Incremental		ICER (£/QALY)
	Cost	QALYs	Cost	QALYs	Cost	QALYs	
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**
B2. EAG exploratory base case (R1b, R2-R5)	£49,704	3.844	£40,065	3.638	£9,639	0.206	**£46,761**

CKD, chronic kidney disease; EAG, External Assessment Group; HF, heart failure; ICER, incremental cost effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; SZC, sodium zirconium cyclosilicate

Sodium Zirconium Cyclosilicate for the First Line Treatment of Hyperkalaemia (review of TA599)

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

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Potential uncaptured benefits

Benefits not captured in QALY calculation, as per company submission:

- Impact of SZC treatment on Sodium-glucose cotransporter-2 (SGLT-2) inhibitors
  - In a retrospective analysis of 44 people with heart failure with reduced ejection fraction with a history of HK who were receiving SZC to enable prescription of RAASi therapy, SGLT-2 inhibitor use increased from 66% prior to SZC prescription to 84% after prescription of SZC
  - SGLT-2 use not captured in SZC trials but data from retrospective analysis highlight potential benefit of SZC for people eligible for SGLT-2 inhibitor treatment
- Outcome data from population comorbid with CKD and HF are not available but people simultaneously experiencing both CKD and HF are expected to be at a greater risk of HK events compared to populations experiencing one of these conditions in isolation
- No disutilities were applied to standard care for a low potassium diet
  - literature and clinical expert opinion suggest that this diet impact QoL negatively
  - SZC would prevent the requirement for a low potassium diet

CKD, chronic kidney disease; HF, heart failure; HK, hyperkalaemia; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year; QoL, quality of life; RAASi, renin-angiotensin-aldosterone system inhibitor; SGLT2, sodium-glucose cotransporter-2; SZC, sodium zirconium cyclosilicate

Sodium Zirconium Cyclosilicate for the First Line Treatment of Hyperkalaemia (review of TA599)

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

NICE National Institute for Health and Care Excellence

Key committee questions

Parameter	Key Committee Questions
Treatment pathway and comparator	• Is the treatment pathway reflective of NHS clinical practice? • Is down-titration/discontinuation of RAASi therapy the relevant comparator for the company's proposed population?
Consideration of dialysis population	• What is the proportion of people undergoing dialysis in the NHS whose SK-levels are not adequately controlled so are unable to receive optimised RAASi treatment? • What is the committee's view on including people with persistent HK who require dialysis in consideration?
Association between HK and adverse outcomes	• What is the committee's view on the SPARK study? • Is S-K level an appropriate surrogate outcome for mortality or MACE based on the evidence from SPARK study?
Generalisability of ZORA study re-analysis	• Are the ZORA study re-analysis results generalisable to the NHS? • Does the committee consider ZORA study re-analysis addresses the uncertainties in whether SZC would allow patients to stay on optimal doses of RAAS inhibitors?
Impact of SZC on RAASi use	• Would SZC impact RAASi use in people with the same S-K level? • Is it more appropriate to assume the probability of down-titrating or discontinuing RAASi is dependent on treatment arm and S-K value, or dependent on S-K value only? • If the latter, is it more appropriate to derive probabilities of down-titration or discontinuation using SZC values or standard care values?

Key committee questions (2)

Parameter	Key Committee Questions
SZC treatment duration	Does the committee prefer assuming a 12-week treatment duration for SZC or a lifetime treatment duration (with annual discontinuation probability)?
Impact of SZC treatment discontinuation	Is it appropriate to apply the same probability of discontinuing or down-titrating RAASi treatment to people still taking SZC and people who have discontinued SZC?
SZC treatment in standard care arm if S-K ≥6.0 mmol/L	What is the committee's view on the impact of excluding SZC treatment for people in the standard care arm if S-K ≥6.0 mmol/L, on cost effectiveness? Is it appropriate?
Generalisability of RAASi model algorithm to NHS clinical practice	• Would all, or only a proportion of people have optimal RAASi dose at baseline in clinical practice? • After RAASi discontinuation, can people only return to the maximum RAASi dose, or can they also reinitiate RAASi at suboptimal dosages and up-titrate over time in clinical practice?
CKD health state costs	Are CKD health state costs from Kent et al. or from NICE CG182 more appropriate?
Preferred ICER and threshold	• What is the committee's preferred ICER threshold - and why? • What is the committee's preferred ICER?

Key issues

Issue	ICER impact	Slide (s)
Consideration of dialysis population	Unknown	11
Association between persistent HK and adverse outcomes in SPARK study	Small	16
Generalisability of ZORA study re-analysis results	Unknown	18
Impact of SZC on RAASi use	Large	21, 22
SZC treatment duration	Large	23
Impact of SZC treatment discontinuation	Unknown	24
SZC treatment if S-K ≥6.0 mmol/L	Unknown	25
Generalisability of RAASi model algorithm to NHS clinical practice	Unknown	26, 27
CKD health state costs	Moderate	28

CKD, chronic kidney disease; ICER, incremental cost effectiveness ratio; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

Sodium Zirconium Cyclosilicate for the First Line Treatment of Hyperkalaemia (review of TA599)

Supplementary appendix

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TA 599 appraisal history

ACM1 (Oct 2018)

- ZS-004, ZS-005 trial population with S-K > 5 mmol/L;
- Primary outcome: ↓ S-K at 48h, maintenance of S-K at 3.5–5.0 mmol/L,
- No survival/QoL outcomes
- Invalid model

❌ Not recommended

ACM2 (Apr 2019)

Additional evidence from ZS-003 trial; but still:

- No direct comparison with NHS standard care for outpatient setting
- No outcomes for managing RAAS inhibitors, OS, QoL
- Insufficient evidence of surrogacy between ↓ S-K and improved outcomes such as reduction in mortality/MACE;
- Company's model assumed SZC prolongs life in 2 ways: by lowering S-K levels and by allowing more people to continue RAAS inhibitor treatment
- % of people stop, down-titrate or restart RAASi in model uncertain

⚠ recommended in emergency setting only

ACM3 (Jul 2019)

- Post-hoc analysis of ZS-004 and ZS-005 trials for S-K ≥ 6 mmol/L subgroup;
- Committee preferred to remove the association between S-K levels and outcomes;
- Company addressed decision problem indirectly; provided evidence that RAAS inhibitors associated with delayed disease progression, and therefore improved QoL

✅ Emergency + optimised recommendation

ACM, appraisal committee meeting; HK, hyperkalaemia; MACE, major adverse cardiovascular event; OS, overall survival; QoL, quality of life; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate; TA, technology appraisal

Evidence for SZC in people receiving dialysis

DIALIZE study: double-blind, placebo-controlled, phase 3b multicentre study evaluating the use of SZC 5g once daily on non-dialysis days (titrated towards maintaining normokalaemia over 4 weeks)

- Of 97 people receiving SZC, 41.2% met primary end point of maintaining a pre-dialysis S–K of 4.0 to 5.0 mmol/L during at least 3 of 4 dialysis treatments over a 4-week stable-dose evaluation period (without rescue therapy); compared with 1.0% of 99 people receiving placebo (P<0.001)
- DIALIZE follow up only 10 weeks→ company state not suitable for assessing cost effectiveness

ADAPT study: prospective, randomised, open-label, 2-by-2 crossover study investigating use of SZC alongside a dialysate solution with a higher concentration of potassium in people receiving chronic dialysis as an alternative to use of dialysate solutions with a lower concentration of potassium.

- People receiving SZC had significantly reduced incidence of recorded atrial fibrillation, of other arrhythmias, and of hypokalaemia after dialysis

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

Clinical effectiveness evidence for ZS-004 and ZS-005

ZS-004 and ZS-005 study overview

Study	ZS-004	ZS-005
Study design	Multicentre, multi-phase, multi-dose, prospective, randomised, double-blind, placebo-controlled maintenance Phase 3	Prospective, international, open-label, single-arm Phase 3
Population	People aged >18 years with an i-STAT potassium value ≥5.1 mmol/L	Outpatients aged ≥18 years with HK (defined as an S–K ≥5.1 mmol/L)
Intervention(s)	Sodium zirconium cyclosilicate	Sodium zirconium cyclosilicate. No mandated dietary restrictions or changes in RAASi therapy were required
Comparator(s)	Placebo	None
Key outcomes	S-K levels, use of RAASi therapy, time to normalisation, AE of treatment	S-K levels, use of RAASi therapy, time to normalisation, AE of treatment
Used in model?	Yes	Yes

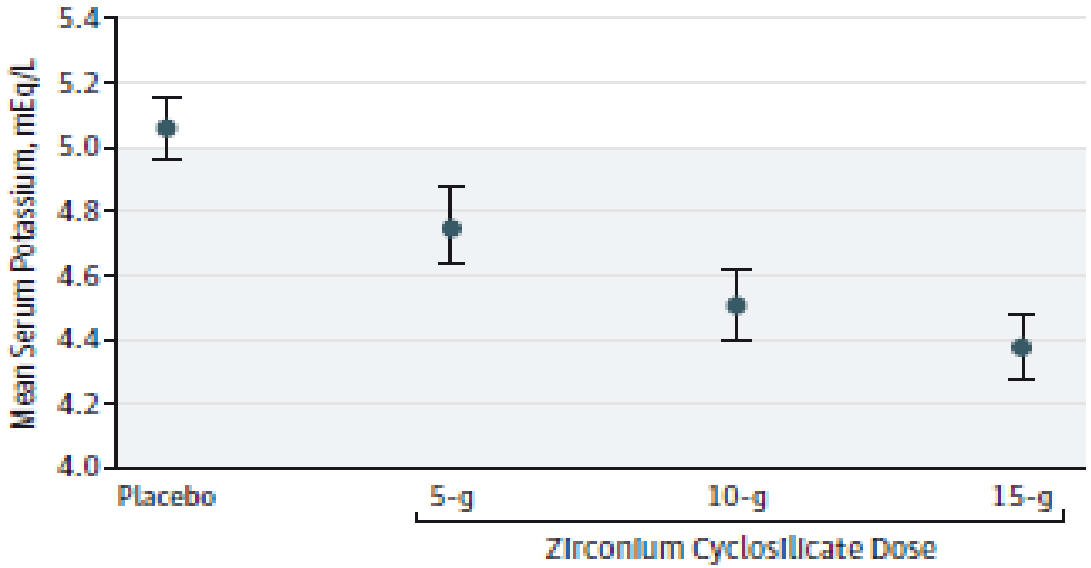
AE, adverse event; HK, hyperkalaemia; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

ZS-004: mean S-K during maintenance phase study days 8 to 29

Mean S-K statistically lower than placebo for each dose

Primary outcome ZS-004: mean S-K levels in randomised phase (days 8–29) Mean S-K

A



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

P<0.001 for all the SZC treatment groups

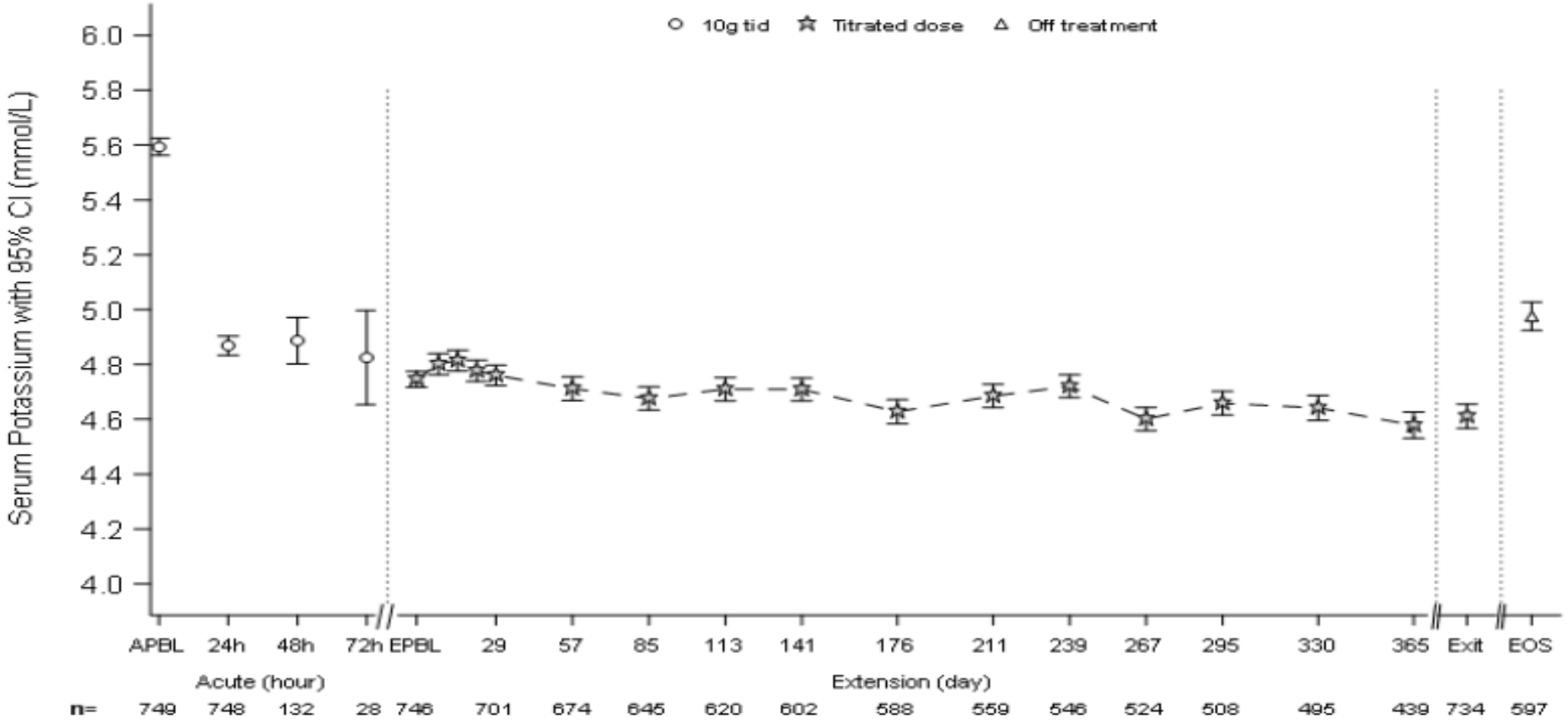
mEq/L, milliequivalents per litre; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

NICE

ZS-005 extended dosing phase: mean S-K over time

Normal S-K maintained on SZC, increases when stopped

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



APBL, acute phase baseline; CI, confidence interval; EPBL, extended phase baseline; EOS, end of study; ITT, intention to treat; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

SPARK study analysis summary

- SPARK investigates the relationship between S–K and hospitalisation, MACE, and mortality, stratified by S–K levels and eGFR. Other objectives:
    - describe patient characteristics and treatment patterns stratified by demography, S-K levels, and comorbidities at baseline – see SPARK study baseline characteristics
    - demonstrate the ability to maintain optimal RAASi dose by S–K level through the use of SZC - sample size of UK SZC users was too small to yield robust results
- Retrospective, observational, longitudinal study using secondary data extracted from CPRD and linked datasets
- Included data from people aged ≥18 years in UK with a recorded S-K measurement, a diagnosis of HK, or a prescription for a potassium binder in their medical records from primary or secondary care
- Multivariable regression models performed to evaluate association between S-K level and clinical outcomes, stratified by variables of interest. A generalised estimating equations model was used to estimate adjusted IRR
- Adjusted by an additional 30+ confounders than studies used to inform TA599, including co-medications, comorbidities and RAASi usage

CPRD, Clinical Practice Research Datalink; eGFR, estimated glomerular filtration rate; HK, hyperkalaemia; IRR, Incidence rate ratio; MACE, major adverse cardiovascular event; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate; TA, technology appraisal

SPARK study: patient baseline characteristics

Characteristics	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	[redacted]	[redacted]
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

SPARK study: key results

CONFIDENTIAL

People with CKD or HF with S-K levels ≥5.5 to <6.0 mmol/L have a statistically significant higher incidence rate of mortality and hospitalisations compared with people with S-K of ≥4.5 to <5.0 mmol/L;

EAG: Analysis done by company do not provide evidence that address NICE committee concerns

Adjusted incidence rate ratios, CKD population

Outcome	Adjusted IRR for S-K level of ≥5.5 to <6.0mmol/L vs ≥4.5 to <5.0mmol/L
MACE	[redacted]
Mortality	[redacted]
Hospitalisation	[redacted]

Adjusted incidence rate ratios, HF population

Outcome	Adjusted IRR for S-K level of ≥5.5 to <6.0mmol/L vs ≥4.5 to <5.0mmol/L
MACE	[redacted]
Mortality	[redacted]
Hospitalisation	[redacted]

Adjusted Incidence rate ratios, CKD population (using the S–K level of ≥4.5 to <5.0 as a reference

[redacted]

Adjusted Incidence rate ratios, HF population (using the S–K level of ≥4.5 to <5.0 as a reference

[redacted]

CKD, chronic kidney disease; CI, confidence interval; EAG, External Assessment Group; HF, heart failure; IRR, incidence rate ratio; MACE, major adverse cardiovascular event; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

Association between persistent HK and adverse outcomes

Clinical expert:

Observational data to support hypothesis that a S-K level in 5.5 to 6.0mmol/L range is associated with worsening of mortality/ MACE/ hospitalisation outcomes:

- Data collected from UK CPRD and HES over 15 years with 1 relevant condition and/or on RAASi therapy explored impact of S-K levels and potassium variability, on clinical outcomes
- Study considered thresholds above 5.0mmol/L, 5.5mmol/L and 6.0mmol/L
- Impact on risk of mortality in this range was uncertain but at all potassium thresholds, risk of MACE for overall cohort and people with CKD, diabetes or resistant hypertension or prescribed RAASi increased rapidly with time spent in a hyperkalaemic state, at least initially.

- In CKD Prognosis Consortium that included UK cohorts, risk relationship between potassium and all-cause mortality demonstrated lowest risk with S-K levels between 4 mmol/L and 4.5 mmol/L and higher risk outside of 3.5 to 5.0 mmol/L range
- Compared with reference of 4.2 mmol/L, overall adjusted HR for all-cause mortality was 1.22 at S-K 5.5 mmol/L
- Risk relationships were similar for CV mortality and progression to end-stage kidney disease.

- TOPCAT trial looking at 'time in target range' defined as a S-K of 4.3 to 4.9mmol/L showed that maintaining S-K levels within therapeutic range of 4.3 to 4.9 mmol/L (i.e <5mmol/L) in people with heart failure preserved ejection fraction was associated with a lower risk of MACE or all-cause mortality.

CKD, chronic kidney disease; CPRD, Clinical Practice Research Datalink; CV, cardiovascular; HES, hospital episode statistics; HF, heart failure; HR, hazard ratio; HK, hyperkalaemia; MACE, major adverse cardiovascular event; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

James 2021 study

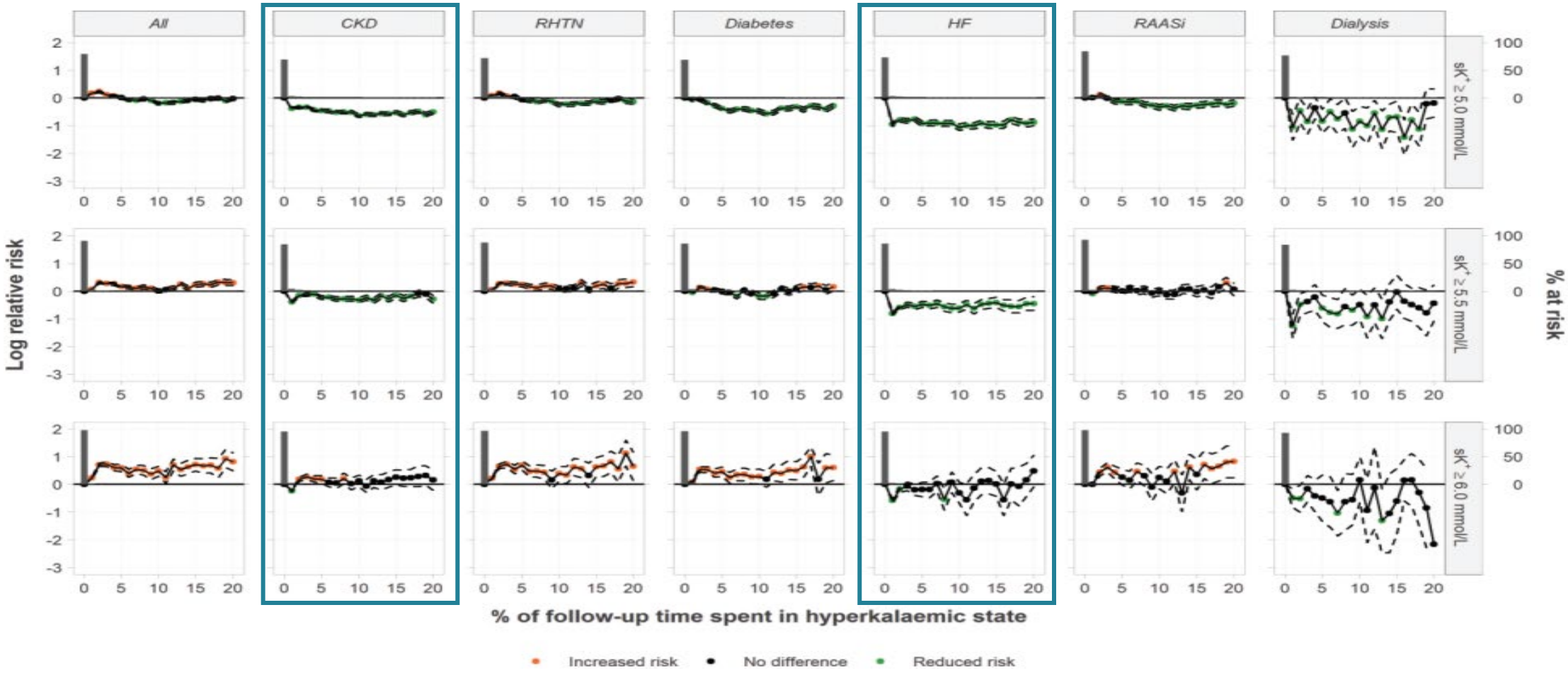
EAG: James 2021 provides information on relationship between time spent in different S-K level groups (i.e. potentially focusing on persistent HK) and adverse outcomes; provides more relevant evidence for this relationship than SPARK

	SPARK study	James 2021
Design & objective	Retrospective cohort (CPRD Aurum+HES); investigates relationship between S–K and hospitalisation, MACE, and mortality, by S–K levels and eGFR	Retrospective cohort (CPRD GOLD+HES); explore impact of length of time spent in an HK state (S-K ≥5.0/5.5/6.0 mmol/L) on adverse outcomes vs. no time in an HK state .
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)
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 vs. 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)
Adjustment	age, sex, comorbidities, medications, and patient-years	Disease-specific cohorts with published risk equations
Outcomes	All-cause mortality, MACE, hospitalisation, healthcare resource use and cost	All-cause mortality, MACE

CPRD, Clinical Practice Research Datalink; eGFR, estimated glomerular filtration rate; GEE, generalised estimating equations; HES, Hospital Episode Statistics; IRR, incidence rate ratio; RHTN, resistant hypertension; SD, standard deviation

James 2021 study: risk of ACM by time spent in an HK state.

Company: at HK threshold of S–K ≥5.0 mmol/L, time spent in an HK state associated with a reduced risk of all-cause mortality across all cohorts including patients with CKD and HF, compared with those spent no time in an HK state. But trend of reduced mortality risk with HK started to reverse at a threshold of S–K ≥5.5 mmol/L

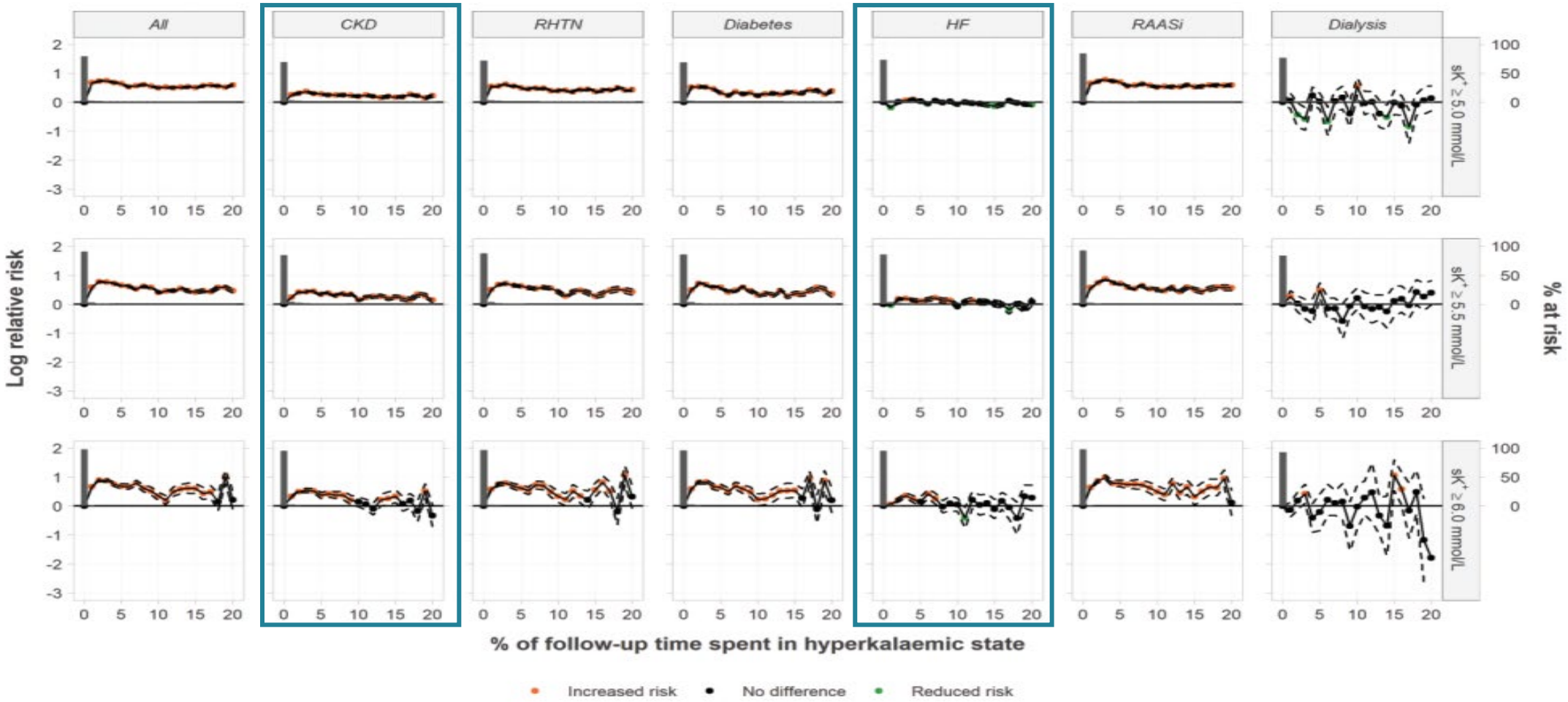


Lines represent the log relative risk, bars represent the number of patients (‘000 000s’) at risk for each time interval. Time is represented as % follow-up time spent in an HK state at the given sK+ threshold, in non-overlapping 1% windows, and is capped at 20%

ACM, all-cause mortality; CKD, chronic kidney disease; HF, heart failure; HK, hyperkalaemia; RAASi: renin-angiotensin-aldosterone system inhibitors; RHTN, resistant hypertension; s-k serum potassium

James 2021 study: risk of MACE by time spent in an HK state

Results: increased risk of MACE associated with increased time spent in an HK state at all HK thresholds in patients with CKD, RHTN, diabetes or prescribed RAASi; but not in those with HF



Lines represent the log relative risk, bars represent the number of patients (‘000 000s’) at risk for each time interval. Time is represented as % follow-up time spent in an HK state at the given S-K threshold, in non-overlapping 1% windows, and is capped at 20%.

MACE, major adverse cardiovascular events; CKD, chronic kidney disease; HF, heart failure; HK, hyperkalaemia; RAASi: renin-angiotensin-aldosterone system inhibitors; RHTN, resistant hypertension; s-k serum potassium

ZORA study re-analysis: key results

Company: re-analysis of ZORA demonstrate that SZC treatment helps facilitate maintenance and guideline-concordant RAASi therapy after an HK event

Proportions of patients who discontinued, down titrated, stabilised and up-titrated their RAASi therapy meta-analysed across countries

Subgroup	SZC	Control (no potassium binder)	Odds ratio	p value
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; HK, hyperkalaemia; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

ZORA study re-analysis summary

- ZORA study investigated real-world usage of RAASi medication in people with CKD and/or HF who are experiencing HK (published by Rastogi et al. [2024])
- Included people aged ≥18 years with an index HK event, comorbid with CKD and/or HF receiving RAASi therapy
- Observational, cohort study programme performed using secondary data extracted from health registers and hospital medical records from the US, Japan, and Spain (re-analysis uses data from US and Japan only)
- ZORA re-analysis aims to address whether SZC allows a greater proportion of people to receive guideline dosages of RAASi drugs compared with those not treated with SZC, irrespective of S-K levels (additional subgroup analysis stratified by S-K levels also conducted)
- Propensity score matching conducted based on stratified groups to achieve balance between the SZC cohort and no potassium binder based on 33 potential confounders identified a priori through subject matter knowledge – see next slide for patient baseline characteristics after propensity score matching

CKD, chronic kidney disease; HF, heart failure; HK, hyperkalaemia; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

ZORA re-analysis baseline characteristics (after PSM)

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	[redacted]							
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; HF, heart failure; HK, hyperkalaemia; PSM, propensity score matching; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SD, standard deviation; SZC, sodium zirconium cyclosilicate

ZORA study re-analysis: key results

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]
Stabilised	[redacted]	[redacted]	[redacted]	[redacted]
Up titrated	[redacted]	[redacted]	[redacted]	[redacted]

CI, confidence interval; SZC, sodium zirconium cyclosilicate

Model input: source and evidence

Factor	Chosen values	
	TA599 (chronic setting)	Current Appraisal
Population	>6.0mmol/L	5.5 to 6.0mmol/L
Baseline demographics	Pooled from ZS-004 and ZS-005	
Intervention	SZC	
Comparator	Managing RAASi	Standard care (i.e. managing RAASi)
Relationship between S-K levels and clinical outcomes	Published literature	SPARK
SZC impact on RAASi optimisation	Clinical expert input	ZORA study re-analysis
Time horizon	Lifetime (80 years from first event), unless RRT is initiated in which case model ends at RRT	
Cycle length	28 days after the first 5 cycles (initial management has various cycle lengths)	
Discount of 3.5% for utilities and costs	Yes	
Perspective (NHS/PSS)	UK NHS PSS	
utilities	sourced from published literature	
costs	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.	

BNF, British National Formulary; PSS, personal social services; RAASi, renin-angiotensin-aldosterone system inhibitor; RRT, renal replacement therapy; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

Other issues

Issue	Overview
Probability of up-titration	**Company:** assumed probability of returning to "max" RAASi state is 49.7% for people receiving SZC or standard care (value used in TA599 and sourced from Luo 2016). ZORA study re-analysis not appropriate to estimate probability of up-titration because not known how many people up-titrated to an optimal RAASi dose or reinitiated RAASi therapy following discontinuation **EAG:** several limitations also with Luo 2016 estimate so unclear whether this provides more robust estimates than ZORA study re analysis. Due to a lower average S-K level, people receiving SZC likely to have higher probability of RAASi up-titration than people receiving standard care→ prefers using ZORA study re-analysis treatment-specific estimates
Time constraint for return to "max" RAASi state	**Company:** assumed people only eligible to return to the "max" RAASi state if 12 weeks have elapsed since RAASi treatment was discontinued or down-titrated (based on clinical expert input from TA599) **EAG:** Clinical advice to EAG is that clinicians would consider re-initiating or up-titrating RAASi treatment 4 weeks after discontinuation or down-titration. EAG considers 4 weeks more representative of current NHS clinical practice and is consistent with clinical guidelines.

EAG, External Assessment Group; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

NICE health technology evaluations: the manual, 2022, 3 level of evidence considered in validation of surrogate outcomes

- ❑ **Level 3**: **biological plausibility** of relation between surrogate and final outcomes.
- ❑ **Level 2**: **consistent association between surrogate and final outcomes**. ...usually be derived from **epidemiological or observational studies.**
- ❑ **Level 1**: treatment effect on surrogate corresponds to commensurate effect on the final outcome as shown in **randomised controlled trials** (RCTs).

- Validation of surrogate outcome specific to **population** and **technology** under consideration. Justify if different;
- Borrowing information from similar class of treatment, population, settings allowed for meta-analysis recommended;

Other related NICE guidance and resources:

Report: Surrogate endpoints in cost-effectiveness analysis for use in health technology assessment

Scenario analysis

Deterministic cost effectiveness results for mixed CKD and HF population: SZC vs standard care

Scenario/EAG revisions	SZC		Standard care		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	(£/QALY)
Company base case	**£45,546**	**4.128**	**£40,234**	**3.703**	**£5,312**	**0.425**	**£12,495**
Scenario (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
EAG exploratory base case 1	**£52,573**	**4.131**	**£41,150**	**3.773**	**£11,423**	**0.358**	**£31,898**
EAG exploratory base case 2	**£49,634**	**3.836**	**£39,997**	**3.638**	**£9,637**	**0.198**	**£48,641**
Scenario (s1) applied to EAG exploratory base case 1	£54,305	4.320	£43,183	4.035	£11,123	0.285	£39,012
Scenario (s2) applied to EAG exploratory base case 2	£51,351	4.028	£42,051	3.900	£9,300	0.127	£73,033

CKD, chronic kidney disease; EAG, External Assessment Group; HF, heart failure; ICER, incremental cost effectiveness ratio; MACE, major cardiovascular adverse event; S-K, serum potassium; QALY, quality-adjusted life year; SZC, sodium zirconium cyclosilicate

TA599 committee considerations/conclusion

ACM3: no clinical evidence showing that having SZC improved length of life or QoL or allowed patients to stay on optimal doses of renin-angiotensin-aldosterone system (RAAS) inhibitors

ACM3: company model and assumptions	Committee consideration/conclusion
• Patient-level simulation model; • SZC prolongs life in 2 ways: by level of S-K and by whether the patient on a RAAS inhibitor	• Model appropriate for decision making; • Company's approach of modelling association between RAAS inhibitor and outcomes (ORs from NMAs including clinical trials) appropriate; *but data not*; • Company's scenario removing association between S-K and outcomes appropriate;

Committee's recommendation for research

- valuable to have studies comparing:
  - SZC + standard care vs. standard care alone in people with confirmed H-K of 6.0 mmol/litre and above, and that these should investigate:
    - ❑ Mortality, disease progression, patterns of RAAS inhibitor use, healthcare utilisation, and health-related quality of life.

ACM, appraisal committee meeting; HK, hyperkalaemia; NMA, network meta-analysis; OR, odds ratio; QoL, quality of life; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate TA, technology appraisal