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

For Zoom – contains redacted information

Technology appraisal committee B [14 January 2026]

Chair: Charles Crawley

External assessment group: Liverpool Reviews & Implementation Group (LRiG)

Technical team: Janet Boadu, Mary Hughes, Emily Crowe

Company: AstraZeneca

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

- ✓ **Background and ACM1 summary**
- ❑ Consultation responses
- ❑ Key issues
- ❑ Cost effectiveness results

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Overview (1/2)

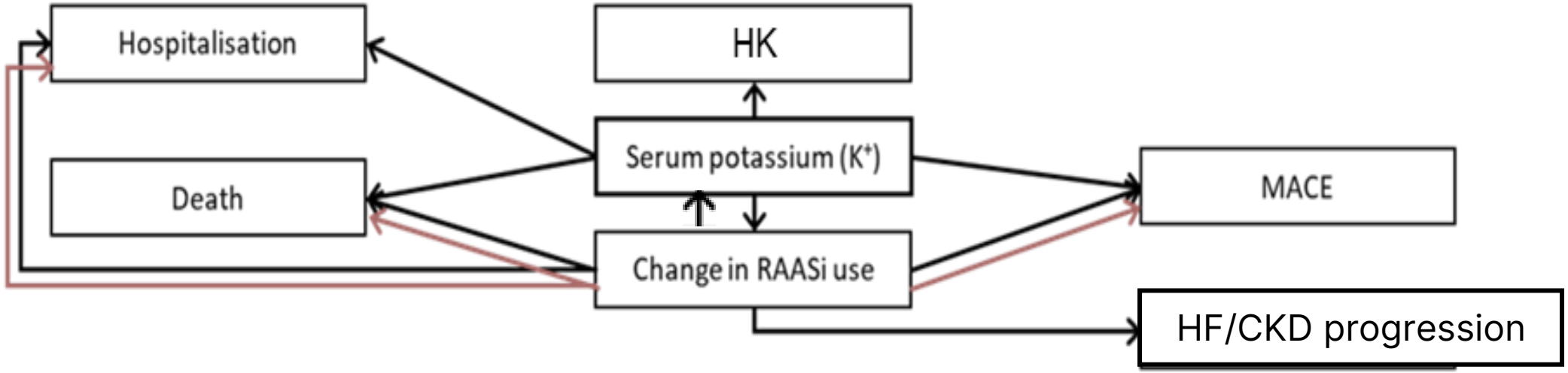
This appraisal is a partial review of TA599 to evaluate SZC in people with persistent serum potassium 5.5 to 5.9 mmol/L

- Risk factors for persistent hyperkalaemia (high serum potassium) are:
  - Advancing age and cardiovascular renal conditions such as CKD or heart failure
  - RAAS inhibitors (medications used to lower blood pressure and manage CKD and HF)
- Hyperkalaemia treated by:
  - Down-titrating or stopping optimal dose of RAASi to lower S-K or
  - Potassium binder (SZC or patiromer)
- SZC currently recommended in TA599, patiromer recommended in TA623:
  - for people with acute life-threatening hyperkalaemia or
  - people with persistent hyperkalaemia and stages 3b to 5 chronic kidney disease or heart failure if
    - S-K ≥6.0 mol/L and
    - are not taking, or have a reduced dosage of a RAASi because of hyperkalaemia and
    - are not on dialysis

Abbreviations: CKD, chronic kidney disease; HF, heart failure; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate; TA, technical appraisal

Overview (2/2)

- No evidence on adverse outcomes (MACE, hospitalisation, death) from SZC trials so these were modelled to be dependent on S-K levels and change in RAASi use (down-titrating or stopping optimal dose)
- Complexity of this topic is that there are interacting factors in the model:
  - relationship between S-K and RAASi dose (which company suggests is also dependent on treatment arm) and RAASi dose and S-K
  - Change in RAASi and S-K modelled to affect risk of adverse outcomes independently, but S-K also impacts adverse outcomes via change in RAASi use



Adapted from figures 15 and 16 in company submission. Red arrows: relationships that may be modelled according to level of RAASi use (maximum versus sub-maximum); Black arrows: modelled relationships between outcomes and variables

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

Draft guidance recommendation– October 2025

Sodium zirconium cyclosilicate should not be used to treat hyperkalaemia in adults when it is persistent and S-K levels between 5.5 mmol/litre and 5.9 mmol/litre

Why the committee made this recommendation:

- Uncertainty in the clinical evidence:
  - SPARK study (evidence on relationship between S-K levels and adverse outcomes) and
  - ZORA reanalysis study (evidence on maintaining RAASi on SZC vs no potassium binder)
- Uncertainties in the economic model assumptions – uncertain how sodium zirconium cyclosilicate affects RAAS inhibitor treatment, and how serum potassium levels are linked to adverse outcomes
- Uncertainties mean it is not possible to determine the most likely cost-effectiveness estimates for sodium zirconium cyclosilicate.

Consultation comments received from:

- AstraZeneca (company)
- Stakeholders (UK Kidney Association, NHS Renal and Cardiac CRG, Renal Pharmacy Group, clinical expert, patient expert)
- 1 web comment (manufacturer of patiromer – potassium binder)

Abbreviations: ACM, appraisal committee meeting; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

ACM1 conclusions for consideration today (1/2)

Issue	Committee conclusion at ACM1	Provided by company?	Results in changes to company base case?
Impact of SZC on RAASi use	• Requested evidence justifying differential stopping or down titration of RAASi treatment between 2 arms • Requested an analysis of rates of stopping or down titrating RAASi treatment per time-unit spent in each S-K category, rather than per baseline S-K category (accounting for individuals switching categories over time)	• Yes • No	No
Treatment duration with SZC	• Preferred EAG assumption of lifelong treatment duration for SZC (subject to an annual stopping rate) to company's 12-week duration with reinitiation if needed	No	No
Relationship between S-K and adverse outcomes	• Requested evidence justifying correlation between S-K levels and risk of adverse outcomes, independent of RAASi use	No	No

Abbreviations: ACM, appraisal committee meeting; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

ACM1 conclusions for consideration today (2/2)

Issue	Committee conclusion at ACM1	Provided by company?	Results in changes to company base case?
SZC treatment in standard care arm	• Preferred to assume people in SoC arm had SZC if S-K levels was ≥ 6.0 mmol/litre • Requested this analysis or scenario where maximum S-K level capped at 6.0 mmol/litre	Yes	Provided scenario
CKD health state costs	• Preferred costs for CKD stages 3a and 3b from Kent et al • Costs for CKD stage 4 and 5 unsuitable because cost of RRT included • Requested removal of RRT costs from Kent et al. (2015) for CKD stage 4 and 5 or exploration of other suitable sources (including NHS reference costs) to populate health state costs for CKD that does not include RRT costs	Yes	Provided scenario

Abbreviations: ACM, appraisal committee meeting; CKD, chronic kidney disease; RRT, renal replacement therapy; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

Sodium Zirconium Cyclosilicate (Lokelma, AstraZeneca)

Technology details

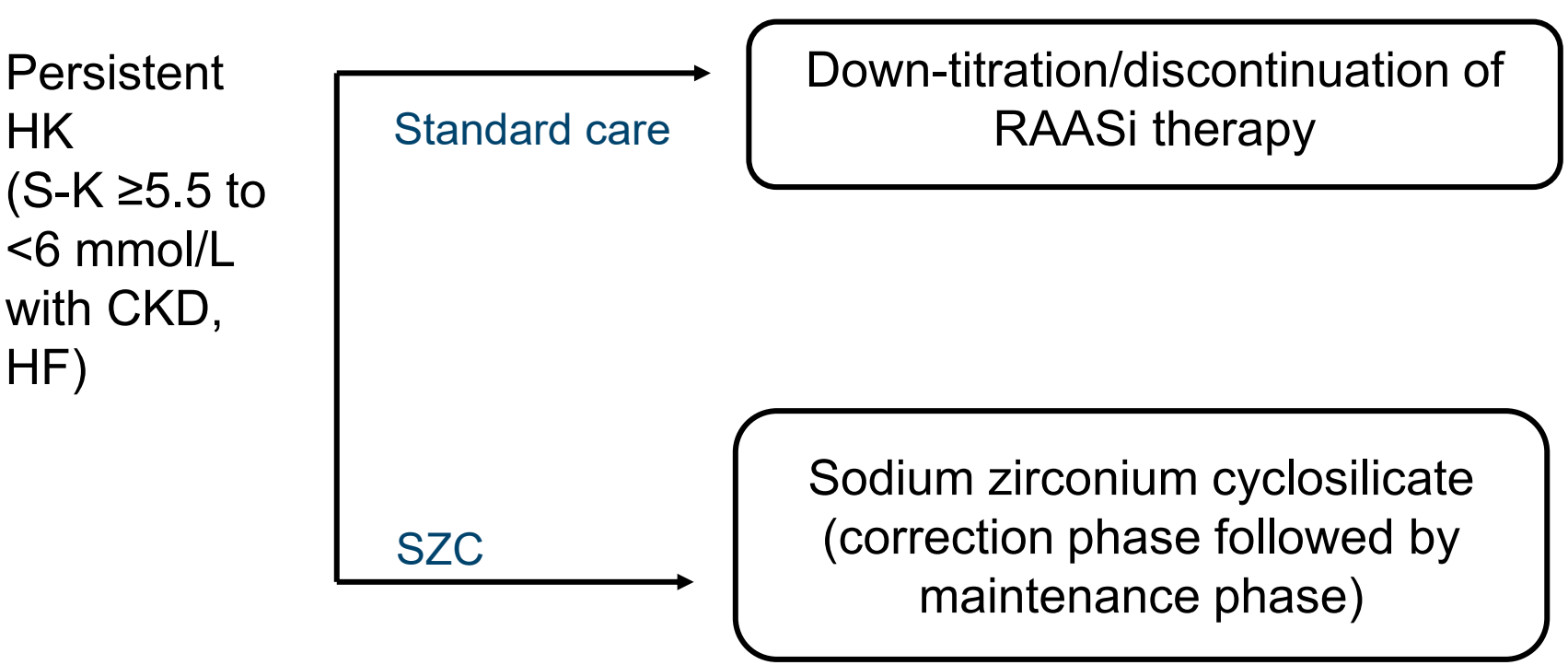
Marketing authorisation	• Indicated for the treatment of hyperkalaemia in adult patients • Marketing authorisation from the MHRA in March 2018; subsequently revised in April 2020 to extend indication for treatment of patients receiving chronic dialysis via EMA centralised procedure
Mechanism of action	• 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 10 g 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 10g once daily
Price	• List price: SZC 5 g = £5.20; SZC 10 g = £10.40 • Patient access scheme not applicable

Abbreviations: EMA, European Medicines Agency; GI, gastrointestinal; MHRA, Medicines and Healthcare products Regulatory Agency; 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

Committee concluded that standard care, (including down titrating or stopping RAAS inhibitors), is the appropriate comparator

Abbreviations: 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 for the First Line Treatment of Hyperkalaemia (review of TA599)

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Consultation comments – Company overview

- ZORA study, clinical experts and additional new evidence demonstrate that people are less likely to down-titrate or discontinue RAASi therapy if they are prescribed SZC versus people without a potassium binder
- Reiterated SPARK study and other literature, demonstrates association between S-K levels and risk of adverse outcomes independent of RAASi use
- No updated company base case but provided two scenario analyses requested by committee:
    - SZC in SoC (S-K level capped at 6.0 mmol/litre)
    - Alternative CKD costs (excluding RRT costs)
- Disagrees with assuming lifelong treatment duration because treatment duration with SZC is varied in NHS clinical practice
    - Presented Prescribing Episode Statistics data to support variation of care in primary care setting
- Notes unmet need for people with persistent hyperkalaemia and S-K <6.0 mmol/L
- Suggested a cost-effective threshold of £30,000 per QALY for SZC vs. current SoC appropriate

Abbreviations: CKD, chronic kidney disease; QALY, quality-adjusted life year; RAASi, renin-angiotensin-aldosterone system inhibitor; RRT, renal replacement therapy; S-K, serum potassium; SoC, standard of care; SZC, sodium zirconium cyclosilicat

Stakeholder responses to Draft Guidance (1/2)

Submissions from AstraZeneca (company), NHS Renal and Cardiac CRG, UK Kidney Association, Renal Pharmacy Group, 1 clinical expert , 1 patient expert and 1 web comment)

Consultation comments – NHS Renal and Cardiac CRG:

- Not approving SZC for HF/CKD may lead to failure to up-titrate or premature RAASi discontinuation; worsening outcomes, with major QALY losses
- Prescribing SZC for 5.5–5.9 mmol/L enables RAASi/MRA continuation in primary care, reducing CKD progression and HF hospitalisations
- Prescribing SZC in this group supports 10-year plan: move care from hospital to community

Consultation comments – UK Kidney Association:

- Agree with recommendation given evidence limitations. Those with mild HK represent the highest frequency of HK; lowering S-K threshold (5.5 – 5.9 mmol/l) would have major impact on NHS services in primary and secondary care
- Limiting CKD treatment with SZC to 12 weeks risks hyperkalaemia rebound if RAASi continues

Consultation comments – Renal Pharmacy Group:

- Concerned that without SZC for S-K 5.5–6.0 mmol/L, clinicians may reduce or stop RAASi, potentially doubling mortality (see Epstein et al., 2015)
- ~10% of outpatients develop HK after starting RAASi therapy (Palmer & Clegg, 2017)
- Patients report difficulty following a low-potassium diet
- Waiting for S-K to reach >6 mmol/L drives costly hospital admissions; earlier SZC supports community care and reduces costs- also against 10-year plan to move care from hospital to community

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

Stakeholder responses to Draft Guidance (2/2)

Consultation comments – clinical expert:

- Recommendation not to treat HK at 5.5–5.9 mmol/L may create confusion + hesitancy in delivering optimal care
- Appraisal not considered that without SZC, people will need to visit GPs more frequently for S-K monitoring and are more likely to present to GP or hospital with worsening S-K and severe hHK

Consultation comments – patient expert:

- Evidence focusses on RAASi, but non-steroidal mineralocorticoid antagonists (like fineronone) also used to reduce risk of kidney decline
- Psychological impact of controlling potassium levels in this range not recognised; dietary control difficult and when [HK] caused by medicines [there is] great uncertainty. GPs have difficulty knowing how often to test patients in absence of clear symptoms.
- GPs [need] clear guidance on what advice to give patients [with S-K in this range e.g. 5.9]; unnecessary Emergency admissions and blood tests may happen in absence of guidance
- No mention of side effects from long term use of SZC

Consultation comments – web comment (manufacturer of patiromer):

- SmPC includes 3 additional RCTs (PRIORITIZE-HF, REALIZE-K, STABILIZE-CKD) for this population
- SmPC reports SZC may worsen pre-existing HF vs. placebo (very common ≥1/10) (n.b. from NICE team: this was observed in pooled analysis of above studies- noted most cases resolved without withdrawing SZC)
- Costs and consequences of HF worsening with SZC should be included in adverse event section of model

Are there likely to be benefits in terms of releasing capacity in primary or secondary care?

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; GP, general practitioner; HF, heart failure; HK, hyperkalaemia; RAASi, renin-angiotensin-aldosterone system inhibitor; RCT, randomised controlled trial; S-K, serum potassium; SmPC, Summary of Product Characteristics; SZC, sodium zirconium cyclosilicate

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Recap of issue ACM1

Key issue: Impact of SZC on RAAS inhibitor use (1/3)

ACM1:

- Company derived probability of down titrating or stopping RAASi by S-K level from the ZORA study re-analysis
- Company used a different rate per S-K level by treatment arm
- EAG: only baseline S-K used in re-analysis and no adjustment made for changes in S-K during follow up so does not support SZC affecting RAASi treatment independent of S-K levels

Committee at ACM1:

- Committee: acknowledged to some extent differences in probabilities of stopping/down titrating RAASi between 2 arms may be explained by clinician prescribing behaviour (less likely to change RAASi dose if on SZC), but not convinced by large difference as modelled
- Uncertainty in company's modelling of SZC's impact on RAASi use
- Requested evidence justifying differential stopping or down titration of RAASi treatment between 2 arms
- Requested an analysis of rates of stopping or down titrating RAASi treatment per time-unit spent in each S-K category, rather than per baseline S-K category (accounting for individuals switching categories over time)

Company response to DG:

- Not possible in ZORA reanalysis to estimate rates of stopping/ down titrating RAASi per time-unit spent in each S-K category

Abbreviations: HK, hyperkalaemia; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SoC, standard of care; SZC, sodium zirconium cyclosilicate

Key issue: Impact of SZC on RAAS inhibitor use (2/3)

Company response to DG (continued):

- RAASi down-titration/discontinuation rates differs in each S-K category by treatment arm for 2 main reasons:
  - S-K controlled by RAASi down-titration/discontinuation which is less predictable [than controlled by SZC]
  - Clinicians more likely to maintain RAASi dosages for people on SZC, as more confident people protected against HK
- Presented supportive data from CONTINUITY trial [open label European pragmatic trial capturing RAASi use for people attending hospital with S-K levels between >5.0 to ≤6.5 mmol/L but not currently receiving SZC])
- In CONTINUITY, at discharge, SZC group [redacted] to be prescribed RAASi vs those not on binder and [redacted] to be prescribed optimal dose* of RAASi therapy
- CONTINUITY study alleviates ZORA uncertainty; shows increased probability of people on SZC being prescribed RAASi therapy directly following a hyperkalaemic event verses SoC

EAG comments

- Company's description of the control of S-K as being "less predictable" for people receiving SoC unclear, and why this impacts RAASi use for people with same S-K
- Agree SoC patients more likely to have increased S-K and RAASi discontinuation vs SZC; but this supports SZC's effect via changing/ stabilising S-K, opposed to any independent effect
- Questions how well CONTINUITY data (people starting SZC at hospital) relates to people with persistent SZC
- Difference between RAASi use in CONTINUITY cohorts (SZC or no binder) smaller than ZORA cohorts
- Cautions comparison of RAASi use at discharge between CONTINUITY cohorts is descriptive only; significance of differences unclear; baseline patient characteristics not reported

*defined as ≥50% of guideline directed medical therapy dose: Abbreviations: HK, hyperkalaemia; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SoC, standard of care; SZC, sodium zirconium cyclosilicate

Key issue: Impact of SZC on RAAS inhibitor use (3/3)

EAG comments (continued)

- EAG disagreed with statement in draft guidance "EAG's approach did not account for changes in [S-K] over time" EAG model: probability of RAASi discontinuation/down-titration differs according to person's S-K in each model cycle (decreases if initiate SZC, increases if discontinue), effect of changes to S-K over time on RAASi use therefore accounted for
- Notes that company model assumes mean S-K remains constant after day 29 with SZC and day 4 on SOC Assuming constant S-K may underestimate SZC benefit if S-K rises under SoC but stabilises with SZC
- **EAG conclusion:** Company not shown robust evidence that SZC affects RAASi use independently of S-K.

- Proportions of people changing RAASi (95% CI) ZORA
- Mean modelled proportions stopping/down-titrating RAASi by S-K category
- Company use different rates in each arm
- EAG prefers same rate in each arm (provides 2 base case results with either the company's SZC or SOC rates applied to both arms)

	SZC [redacted]	no K+ binder [redacted]
Discontinued	[redacted]	[redacted]
Down titrated	[redacted]	[redacted]
Stabilised	[redacted]	[redacted]
Up titrated	[redacted]	[redacted]

S-K category (mmol/L)	SZC		SoC	
	stop	down-titrate	stop	down-titrate
<5.0	[redacted]	[redacted]	[redacted]	[redacted]
5.0–5.5	[redacted]	[redacted]	[redacted]	[redacted]
5.5–5.9	[redacted]	[redacted]	[redacted]	[redacted]
≥6.0	[redacted]	[redacted]	[redacted]	[redacted]

Do we have evidence to justify differential down titration of RAASi? If we assume the same rate of down titration for given serum potassium, do we base that on the downtitration rate for SZC?

Abbreviations: K+, potassium; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SoC, standard of care; SZC, sodium zirconium cyclosilicate

Key issue: Treatment duration with SZC (1/3)

Recap of issue ACM1

Committee at ACM1:

- Company original model assumes SZC treatment duration of 12 weeks (with restarting allowed if S-K ≥5.5 mmol/L); EAG prefer lifetime treatment
- Clinical experts: if S-K controlled by SZC, stopping it could lead to return in persistent hyperkalaemia
- Committee: assuming a lifelong treatment duration for SZC (subject to an annual stopping rate) is appropriate

Company response to DG:

- SZC duration varies in clinical practice, committee have not considered this
- Derived PES data covering all primary care prescriptions in England for past 6 years; most reflective for chronic hyperkalaemia (excludes acute secondary care cases)
- Data shows number of people 'Simply Active' (on treatment in that month) on SZC; includes those who started SZC in primary care ≥36 months before July 2025
- PES likely overestimates treatment duration for S-K ≥5.5–<6.0; data reflects more severe S-K ≥6.0 population currently reimbursed; many discontinue after secondary care discharge
- At end of analysis at 36 months [redacted] remained on treatment ([redacted] continuously treated, [redacted] restarted). Company note in PES population [redacted] reinitiated treatment, showing SZC is not often restarted after discontinuation in practice
- Area under the curve analysis results (see supplementary appendix) shows average % of time spent on treatment in first 3 years of company base case analysis is conservative regarding observed clinical practice using PES data ([redacted]% higher); EAG preferred base case almost triple ([redacted]% higher)

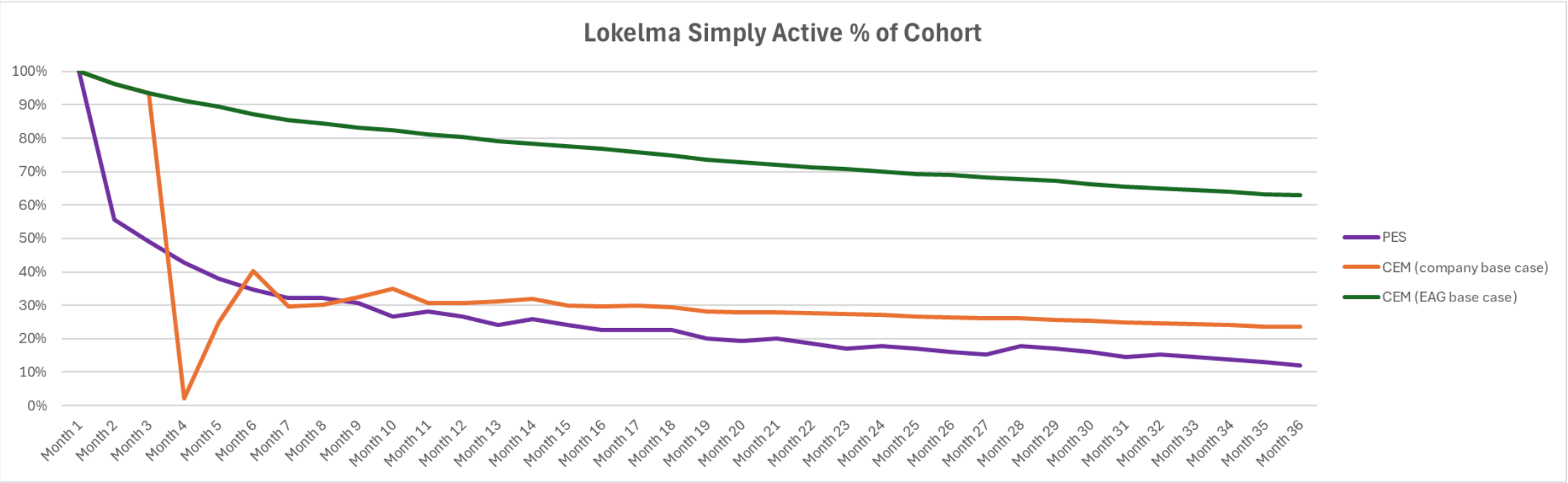
Abbreviations: PES, Prescribing Episode Statistics; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

Key issue: Treatment duration with SZC (2/3)

Company response to DG:

- Active treatment by month observed in PES over 36 months shows curves for PES data and company base case deviate: prior to month 4 (natural rate of treatment discontinuation, and month 4, (most discontinue treatment following the initial 3-month treatment cycle)
- People will then reinitiate treatment in company base case model; from month 6 both curves relatively consistent, gradually separating out to month 36
- EAG base case curve consistently higher, showing minimal change in practice over past 3 years

Proportion of Simply Active patients on SZC, 36 months



Abbreviations: PES, Prescribing Episode Statistics; SZC, sodium zirconium cyclosilicate

Key issue: Treatment duration with SZC (3/3)

EAG comments

- Company not explained why a 12-week SZC treatment duration better reflects patient heterogeneity than a lifetime treatment duration
- Company provided no information on S-K values at SZC initiation or discontinuation or reason for stopping
- Company appear to assume all people in PES dataset received SZC for persistent/chronic HK on basis that data is from primary care settings; substantial decrease in proportion remaining on treatment at month 2 ([redacted]) suggests large proportion may have received SZC for, or after, an acute HK event
- Unclear if dataset includes those treated for acute HK in secondary care + later prescribed SZC in primary care
- High rate of SZC discontinuation (and low rate of reinitiation) in PES data contrary to clinical advice that upon discontinuation of SZC, S-K will increase, and people may return to persistent HK
- Without further information confirming population in PES data received SZC for persistent HK only and explanation why so many discontinued SZC early on in follow-up, the EAG considers a lifetime treatment duration is more appropriate

- Is a fixed 12 week or lifetime treatment duration appropriate (subject to an annual stopping rate)?
- Would a stopping rule at 12 weeks (with re-starting if S-K ≥5.5 mmol/l) be clinically appropriate?

Abbreviations: HK, hyperkalaemia; PES, Prescribing Episode Statistics; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

Recap of issue ACM1

Key issue: Relationship between S-K and adverse outcomes (1/2)

ACM1:

- Company: Modelled rates of adverse outcomes based on SPARK for S-K and findings from a systematic review for RAASi dosage. If S-K assumed to have no direct impact on adverse outcomes, this has a small effect on company base case
- EAG: SPARK provided evidence for risk of adverse outcomes at 1 timepoint, preferred James et al. which showed relationship of time spent with different S-K on outcomes

Committee at ACM1:

- May be a relationship between S-K and adverse outcomes but unclear whether driven by S-K or RAASi down titration; adjusting for RAASi use in SPARK does not provide evidence that lowering S-K reduces risk of adverse outcomes independent of RAASi use
- Requested more evidence justifying relationship between S-K and adverse outcomes, independent of RAASi down titration

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

Recap of issue ACM1

Key issue: Relationship between S-K and adverse outcomes (2/2)

Company response to DG:

- Reiterated SPARK demonstrates independent association; assessment of strength of unmeasured confounders needed to reverse observed relationship show highly unlikely for any remaining confounder to overturn relationships
- James et al. (2021) study not well designed to answer decision problem; assesses long-term S–K variability and time spent in specific S–K cut-offs and re-confirms relationship between adverse outcomes and an elevated S-K (>5.0 mmol/L), showing U-shaped curve

EAG comments

- Company provided no new evidence
- Reiterated SPARK study does not show robust evidence of a correlation between persistent S-K and adverse outcomes, or how reducing S-K levels with a binder affects risk of adverse outcomes

Has sufficient evidence been provided to justify the link between S-K levels and risk of adverse outcomes, independent of RAASi use?

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

Key issue: SZC treatment in standard care arm

Recap of issue ACM1

Committee at ACM1:

- Company's original model: people on SoC do not have SZC even if S-K level is ≥6.0 mmol/L
- Committee preferred to assume people in SoC arm had SZC if S-K levels ≥6.0 mmol/litre; requested company update model including this; or scenario where maximum S-K level model capped at 6.0 mmol/litre

Company response to DG:

- Provided scenario in updated model: SoC arm patients initiated on treatment and retreated for 84-day cycle consistent with SZC arm), but with a threshold for treatment set at an S-K of 6.0 mmol/L, (rather than 5.5mmol/L)
  - ICER for mixed CKD & HF population decreases slightly

EAG comments

- Company did not provide information on how clinical benefit of SZC (decrease in S-K) was modelled for SoC when S-K ≥6.0 mmol/L
- In company model, upon initiation of SZC in SoC arm when S-K ≥6.0 mmol/L, S-K decreases to average S-K for those initially treated with SZC; EAG considers this assumption reasonable
- Change in ICER small given that [redacted] people on SoC experience S-K levels ≥6.0mmol/L
- Reiterated if average S-K levels are expected to rise over time, a substantially higher proportion of people may be eligible to receive SZC; scenarios exploring different S-K trajectories over time for SoC would be informative

Is the company's scenario (maximum S-K level model capped at 6.0 mmol/litre) appropriate?

Abbreviations: HF, heart failure; ICER, incremental cost-effectiveness ratio; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SoC, standard of care; SZC, sodium zirconium cyclosilicate

Recap of issue ACM1

Key issue: Chronic kidney disease health state costs

Committee at ACM1:

- Committee preferred costs for CKD stages 3a and 3b from Kent et al. (more up to date than EAGs estimate); but noted CKD stage 4 and 5 costs unsuitable as included cost of RRT
- Requested removal of RRT costs from Kent et al. (2015) estimates for CKD stage 4 and 5, or exploration of other suitable sources to populate health state costs for CKD that does not include RRT costs

Company response to DG:

- Costs recalculated excluding costs of dialysis and transplant, inflated to 2023 cost year → small decease in ICER
- Model conservatively includes mortality specific CKD costs within each health state, which disproportionately favours SoC due to its significantly higher mortality rates
- Kent et al costs used in original submission overestimated due to inclusion of dialysis and transplant costs, but as people having SZC spend longer in CKD stages 3a–5 (slower progression, lower mortality), this overestimate disproportionately affects SZC, making base-case costs conservative

EAG comments

- Company's updated approach is reasonable

	Kent et al. (original)	Kent et al. (dialysis and transplant costs removed)
CKD stage 3a	£1,354	£657
CKD stage 3b	£1,354	£657
CKD stage 4	£4,741	£733
CKD stage 5	£16,623	£1,014

Has sufficient evidence been provided to explore health state costs for CKD that does not include RRT costs?

Abbreviations: CKD, chronic kidney disease; ICER, incremental cost-effectiveness ratio; RRT, renal replacement therapy; SZC, sodium zirconium cyclosilicate

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Summary of base case assumptions post-consultation (1/2)

Green box- aligns with committee preference stated at 1st meeting; orange box committee preference unknown

Assumption	Company base case	EAG exploratory base case 1	EAG exploratory base case 2	Committee preference at ACM1
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**	**Uncertain-requested further evidence**
SZC treatment duration	12 weeks	Lifetime subject to annual stopping rate		Lifetime (same as EAG)
SZC treatment in standard care arm	No SZC even if S-K level is ≥6.0 mmol/L (company provided scenario around its base case with committee preference applied, EAG unable to run scenario around its base cases because of time/data limitations)			Assume people in SoC arm had SZC if S-K levels ≥6.0 mmol/litre (minimal ICER impact)
Risk of MACE, hospitalisations and mortality	Modelled using incidence rate ratio derived from SPARK study (scenarios excluding S-K dependent rates from SPARK provided)			Committee preference not determined; minimal ICER impact

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; MACE, major adverse cardiovascular event; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate

Summary of base case assumptions post consultation(2/2)

Green box- aligns with committee preference stated at 1st meeting; orange box committee preference unknown

Assumption	Company base case	EAG exploratory base case 1	EAG exploratory base case 2	Committee preference ACM1
RAASi model algorithm	At baseline, all people receiving optimal RAASi dose, and after discontinuation return to optimal dose			
CKD health state costs*	Provided scenarios is which Kent et al was used for CKD health state costs for stages 3a and 3b only- no RRT costs			Requested Kent et al. for CKD stages 3a and 3b only, no RRT cost
Probability of up-titration†	Luo 2016	ZORA study subgroup analysis		Committee preference not determined; minimal ICER impact
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 other issues slide for further details

Abbreviations: CKD, chronic kidney disease; EAG, External Assessment Group; RAASi, renin-angiotensin-aldosterone system inhibitor; RRT, renal replacement therapy

Other differences: company and EAG modelling assumptions

RECAP

Issue	Overview	Impact of EAG assumption on company base case
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 with Luo 2016 estimate so unclear whether this provides more robust estimates than ZORA study re analysis. → **prefers using ZORA study re-analysis treatment-specific estimates**	Increases ICER ~£1000
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 assumes **4 weeks** as consistent with clinical guidelines/current practice.	Decreases ICER ~£100

See supplementary appendix for impact of all EAG assumptions in mixed and separate populations

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; max, maximum; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SZC, sodium zirconium cyclosilicate; TA, technical appraisal

Company base case and deterministic scenarios around it.

Deterministic cost effectiveness results for mixed* CKD ([redacted]) and HF ([redacted]) population: SZC vs standard care

Scenario/EAG revisions	SZC		Standard care		Incremental		ICER (£/QALY)
	Cost	QALYs	Cost	QALYs	Cost	QALYs	
Company base case (deterministic)	£45,546	4.128	£40,234	3.703	£5,312	0.425	£12,495
Company base case (probabilistic)	£45,596	4.126	£40,321	3.703	£5,276	0.423	£12,417
***Company DG response scenario (s1):* maximum S-K level in the model capped at 6.0 mmol/litre**	£45,546	4.128	£41,673	3.815	£3,872	0.313	£12,355
***Company DG response scenario (s2):* Kent et al. (dialysis and transplant costs removed)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,097
Lifetime SZC treatment duration	£53,486	4.344	£40,234	3.703	£13,252	0.641	£20,689
Assume S-K has no effect on adverse outcomes	£47,808	4.343	£42,971	3.967	£4,837	0.375	£12,884

See supplementary appendix for company base case in separate populations (n.b. company DG response scenarios not provided in separate populations). * proportions are based on SPARK study

Abbreviations: CKD, chronic kidney disease; DG, draft guidance; HF, heart failure; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; S-K, serum potassium; S; scenario; SZC, sodium zirconium cyclosilicate

EAG base case results

see supplementary appendix for separate populations

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

CKD [redacted]%;HF [redacted]%

Scenario/EAG revisions	SZC		Standard care		Incremental		ICER (£/QALY)
	Cost	QALYs	Cost	QALYs	Cost	QALYs	
Company base case	£45,546	4.128	£40,234	3.703	£5,312	0.425	£12,495
Company base case + new CKD costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,097
EAG exploratory base case 1: • probability of down-tritrating/stopping RAASi uses SZC rates • + company assumption on CKD costs (from company scenario)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,475
EAG exploratory base case 2: • probability of down-titrating/stopping RAASi use SoC rates • + company assumption on CKD costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,895
Scenario around EAG base cases : assume S-K has no effect on adverse outcomes							
Applied to base case 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£36,758
Applied to base case 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£70,523

Abbreviations: 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; SoC, standard of care; SZC, sodium zirconium cyclosilicate

Other considerations

Abbreviations: CKD, chronic kidney disease; HF, heart failure; HK, hyperkalaemia; RAASi, renin-angiotensin-aldosterone system inhibitor; SGLT2, sodium-glucose cotransporter 2; SZC, sodium zirconium cyclosilicate

Equality issues:

- **Draft guidance:** The committee acknowledged there is an unmet need for people having dialysis in the emergency setting. But it noted that the current evaluation is for the treatment of persistent HK and not for HK in an emergency setting. So, it concluded that the exclusion of the dialysis population was not an equality issue that it could address.
- **Draft guidance consultation:**
- Exclusion of dialysis patients (with exception during pandemic) pertaining to the use of this effective technology could be perceived to be discriminatory
- Some areas of England can prescribe SZC in primary care, others cannot; not changing the level of potassium at which to prescribe SZC risks widening this inequality for use of RAASi for example
- Well known that CKD affects the poorest sectors of society and this inequality needs to be reduced

Uncaptured benefits:

- **Draft guidance:** potential for increased use of SGLT-2 inhibitors with SZC reducing adverse outcomes; people may have both CKD and HF, Model only allows separate modelling of these; disutility of a low potassium diet not included in standard care. Given the uncertainties in the evidence and modelling, the committee concluded that it was uncertain whether any of these potential benefits have been captured in the model

Are there any additional equality or uncaptured benefits to consider?

Committee decision making

Key issue	Questions for committee	Impact on ICER (ACM2)
Impact of SZC on RAAS inhibitor use	• Do we have evidence to justify differential down titration of RAASi? • If we assume the same rate of down titration for given S-K, do we base that on the downtitration rate for SZC?	large
Treatment duration with SZC	• Is a fixed 12 week or lifetime treatment duration appropriate (subject to an annual stopping rate)? • Would a stopping rule at 12 weeks (with re-starting if S-K ≥5.5 mmol/l) be clinically appropriate?	large
Relationship between S-K and adverse outcomes	• Has sufficient evidence been provided to justify the link between S-K levels and risk of adverse outcomes, independent of RAASi use?	Small (company base case), large (EAG base case)
SZC treatment in standard care arm	• Is the company's scenario (maximum S-K level model capped at 6.0 mmol/litre) appropriate?	Small
CKD health state costs	• Has sufficient evidence been provided to explore health state costs for CKD that does not include RRT costs	Small
Other considerations	• Are there any equality issues or uncaptured benefits to consider? • Are there likely to be benefits in terms of releasing capacity in primary or secondary care?	Unknown
Threshold	• What is the committee preferred ICER threshold - and why?	

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

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

Supplementary appendix

NICE National Institute for Health and Care Excellence

Review of TA599

RECAP

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

TA 599 appraisal history

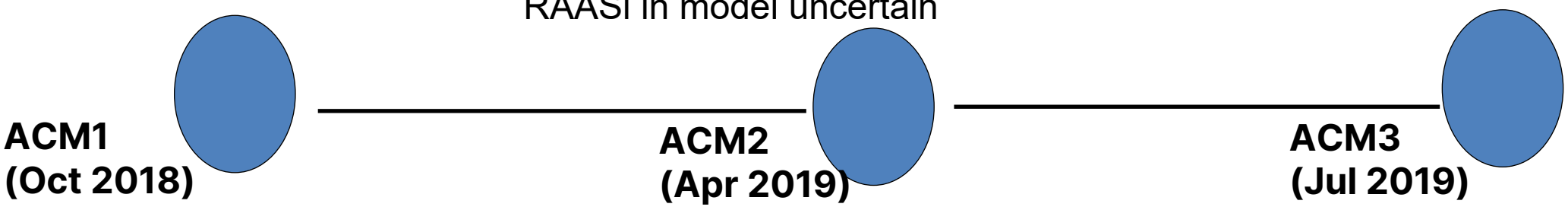
RECAP

- 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

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

- 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



❌ Not recommended

⚠ recommended in emergency setting only

✅ 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

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

Background:

RECAP

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

Evidence for SZC in people receiving haemodialysis

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 haemodialysis 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 haemodialysis 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 haemodialysis

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

SLRs and additional real-world evidence

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

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

Real-world studies

RECAP

	Spark study	Zora study re- analysis
Population	People aged ≥18 years with a recorded S-K measurement, a **diagnosis of HK**, 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

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, difference statistically significant

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

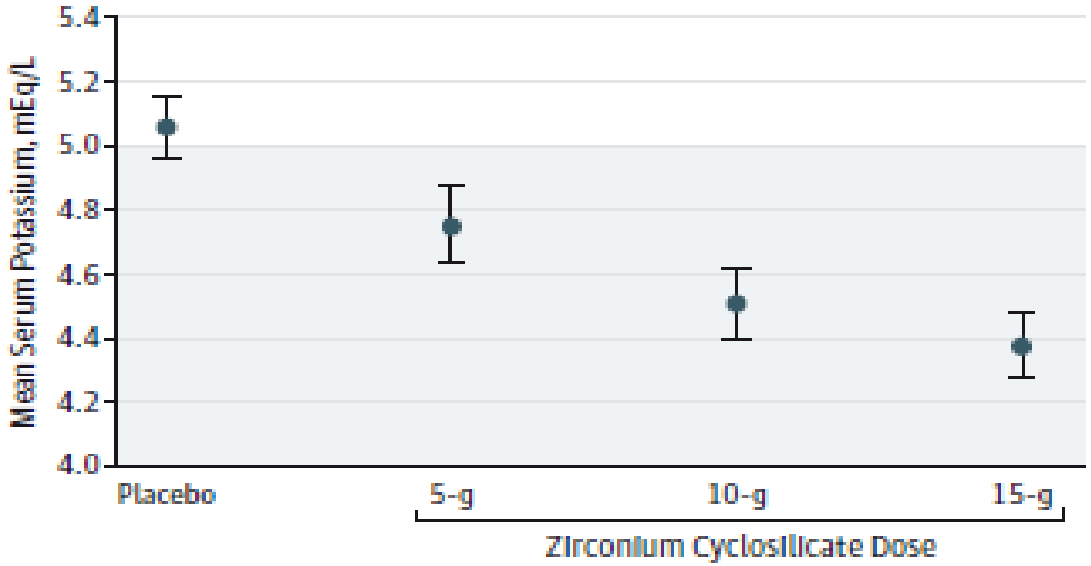
CI, confidence interval; CKD, chronic kidney disease; HF, heart failure; IRR, Incident rate ratio; MACE, major adverse cardiovascular event; S-K, serum potassium

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

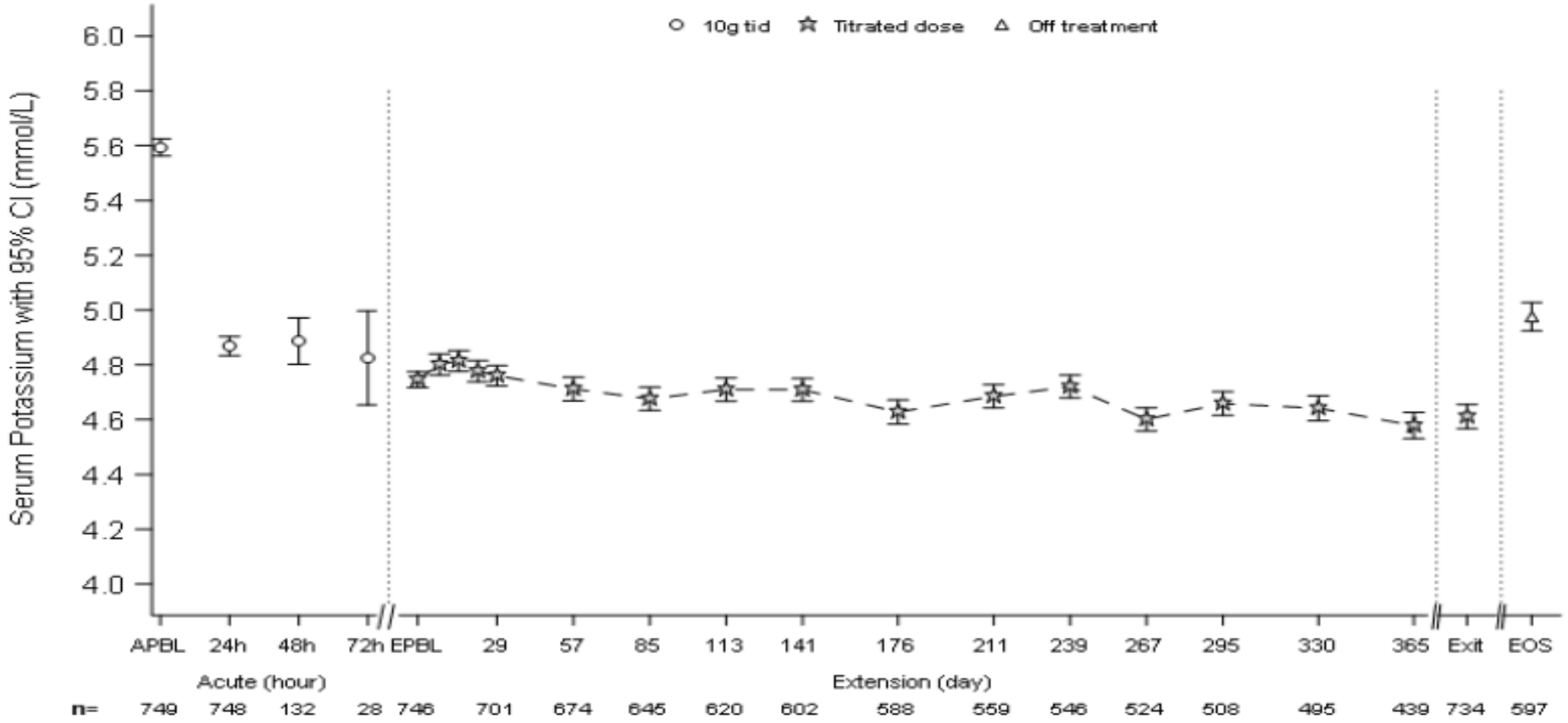
P<0.001 for all the SZC treatment groups

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

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

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

ZORA study re-analysis: key results

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

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

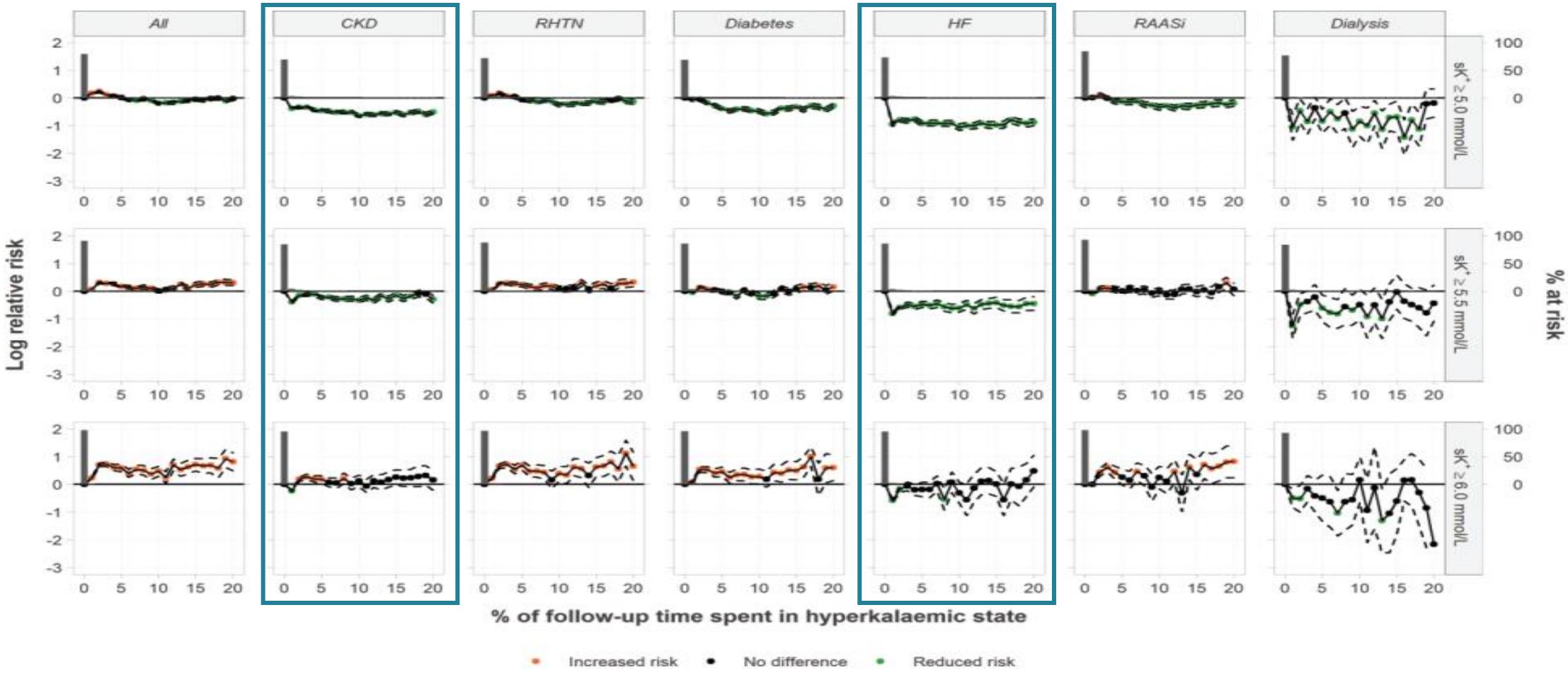
	SPARK study	James 2021
Design & objective	Retrospective cohort (CPRD Aurum+HES); investigates relationship between S–K and hospitalisation, MACE, and mortality, by S–K levels and eGFR	Retrospective cohort (CPRD GOLD+HES); explore impact of length of time spent in an HK state (S-K ≥5.0/5.5/6.0 mmol/L) 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.

RECAP

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



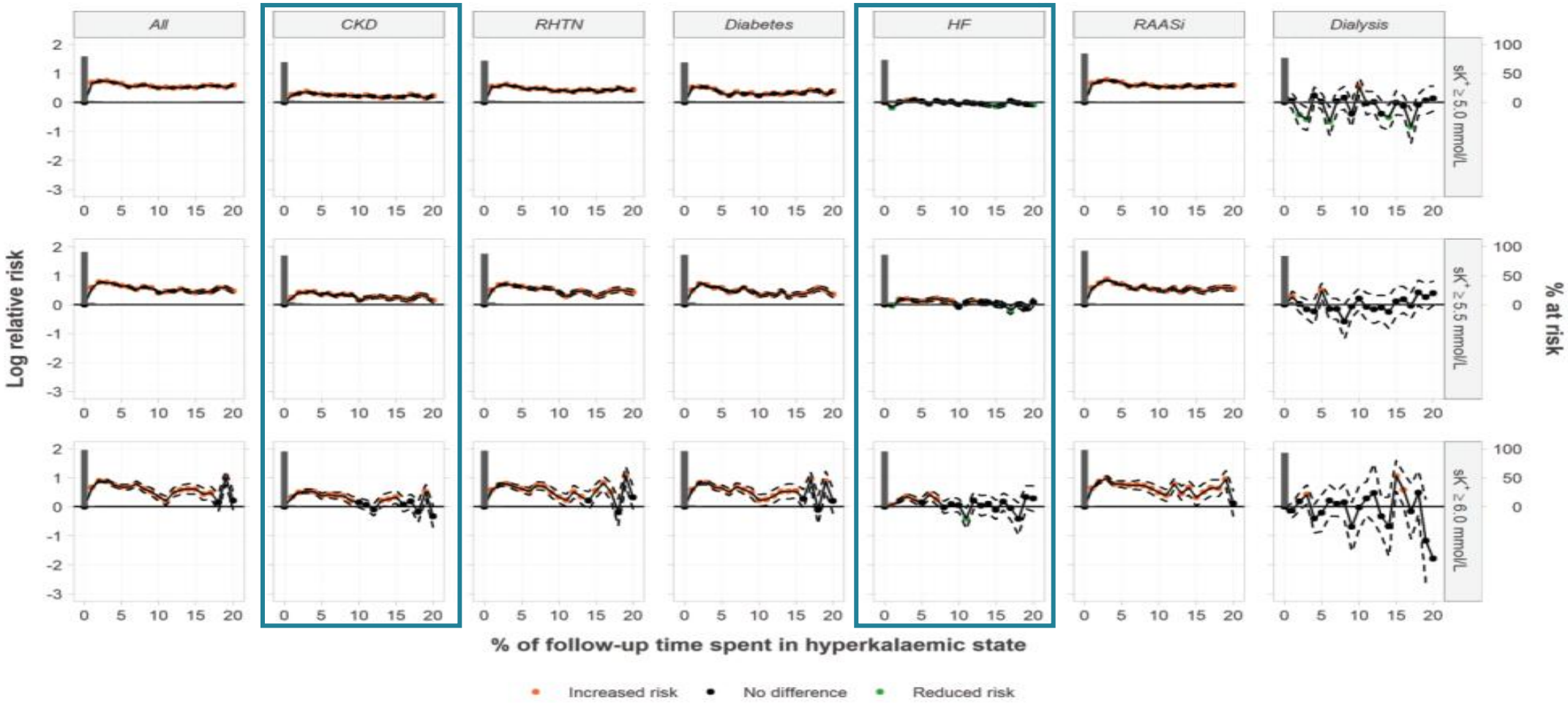
Lines represent the log relative risk, bars represent the number of patients ('000 000s') at risk for each time interval. Time is represented as % follow-up time spent in an HK state at the given sK+ threshold, in non-overlapping 1% windows, and is capped at 20%

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

RECAP

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]	[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]	[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

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

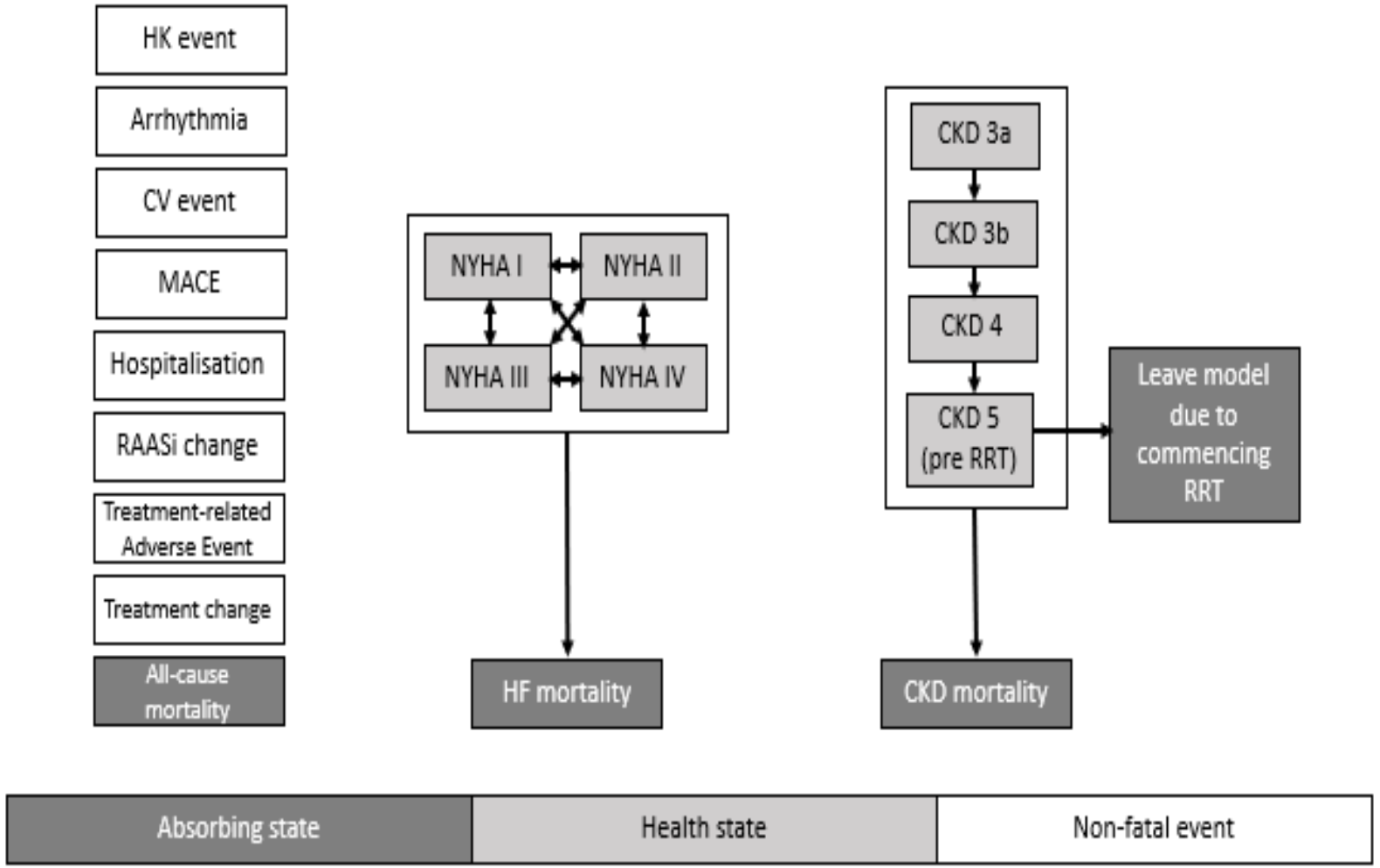
Company's model overview

The committee concluded that the model structure was acceptable for decision making

RECAP

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**

Abbreviations: 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

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

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

RECAP

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

Back to key issue

RECAP

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: 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

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

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

Key issue: Impact of SZC on RAAS inhibitor use

Company response to DG:

- Company identified the CONTINUITY study; captures RAASi use for people who attend hospital and have S-K levels between S-K >5.0 to ≤6.5 mmol/L but are not currently receiving SZC

CONTINUITY summary data	SZC (N=68)	SoC (N=69)
Number and percentage of patients without RAASI, n (%)	[redacted]	[redacted]
Number and percentage of patients with RAASI, n (%)	[redacted]	[redacted]
Number and percentage of patients on ACE/ARBs	[redacted]	[redacted]
Number and percentage of patients on MRAs	[redacted]	[redacted]
Number and percentage of patients on ACE/ARBs and MRAs	[redacted]	[redacted]
Percentage of patients with ≥50% GDMT of at least one RAASi therapy, n (%)	[redacted]	[redacted]

Back to Key issue: Impact of SZC on RAAS inhibitor use

Abbreviations: S-K, serum potassium; SZC, sodium zirconium cyclosilicate ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blockers; GDMT: guideline directed medical therapy; MRA: mineralocorticoid receptor antagonist; RAASi: Renin-angiotensin-aldosterone system inhibitor

Back to key issue

Key issue: Treatment duration with SZC

An area under the curve analysis: Average time spent on treatment

	Average time on treatment in first 36 months	Percentage increase vs PES statistics
PES statistics	[redacted]	-
Company base case	[redacted]	[redacted]
EAG preferred base case	[redacted]	[redacted]

Company base case results

Back to company base case results

RECAP

No updated company base case

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

Abbreviations: 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: mixed population

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**
Base case 1 with post consultation CKD costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£29,475**
Base case 2 with post consultation CKD costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£45,895**

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: CKD population

Back to EAG base case results

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**
Base case 1 with post consultation CKD costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£37,633**
Base case 2 with post consultation CKD costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£58,100**

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

EAG base case results: HF population

Deterministic results for HF population: SZC versus standard care

Back to EAG base case results

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 other issues slide for further details

Abbreviations: 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