NICE National Institute for Health and Care Excellence

Public

Sodium zirconium cyclosilicate (SZC) for treating hyperkalaemia

2nd appraisal committee meeting

26 March 2019

Committee B

Chair: Amanda Adler

Lead team: Mona Johnson, Chris O'Regan and Nigel Westwood

ERG: ScHARR

NICE technical team: Mary Hughes, Alan Lamb, Ross Dent

Company: AstraZeneca

Preview of key issues

1. Trials don’t show increased length of life or quality of life; company claims both
2. Positioning in clinical practice:
    1. outpatient setting
    2. emergency setting
3. Comparing SZC and standard care: ‘new’ trial 'ZS003’
4. SZC in emergency setting: new subgroup analyses
5. SZC in outpatient setting efficacy across co-morbidities
    - Yet, different treatment threshold by co-morbidity
6. Proportion of patients treated with SZC who resume RAASi: new analyses
7. Epidemiological relationship between serum K^+ and outcomes: new systematic literature review, company continue to include in model
8. Relationship between renin-angiotensin-aldosterone system inhibitor RAASi use and long term outcomes: new targeted literature review
9. New utility values for CKD
10. Updated company base case, new company scenario analyses, new ERG exploratory analyses

Hyperkalaemia - high blood levels of potassium

- Serum potassium (K^+) normal range 3.5 to 5.0 mmol/L
  definitions of normal to high vary; many have upper range of normal at 5.5 mmol/L
  - company defines hyperkalaemia as >5.0 mmol/L
- **Severe hyperkalaemia** can cause irregular heart beat, cardiac arrest and death
- **Risk factors for hyperkalaemia include**:
  - diseases: chronic kidney disease, heart failure
  - Medicines for high blood pressure and heart failure:
    - renin-angiotensin aldosterone system inhibitors (**RAASi**) including:
      - angiotensin-converting enzyme (**ACE**) inhibitors
      - angiotensin II receptor blockers (**ARB**)
      - direct renin inhibitors (e.g. aliskerin)
      - aldosterone-receptor antagonists (e.g. spironolactone)
    - other potassium-sparing diuretics
    - beta-blockers

[redacted]

Sodium zirconium cyclosilicate (SZC), Lokelma

marketing authorisation does not define hyperkalaemia; population is broad

Marketing authorisation	"For the treatment of hyperkalaemia"
Administration & dose	5 g or 10 g sachet - powder for oral suspension **Correction phase**: 10 g, 3 times daily, max duration 72 hours **Maintenance phase**: 5 g once daily can be up titrated to 10 g once daily or down titrated to 5 g once every other day to maintain normal potassium levels
Special warnings and precautions for use	• Monitor serum potassium (K^+) when clinically indicated, and after changes to medicines that affect serum K^+ (e.g. RAASi or diuretics) and after titrating SZC dose • Hypokalaemia – may require dose titration/discontinuation • May be opaque to X-rays • Risk of intestinal perforation currently unknown but has been reported with polymers that act in the GI tract

⊙ What is considered hyperkalaemia that requires treatment?
- Why would this differ, or not, by etiology?

Treatment pathway

Company: SZC will be used in emergency + outpatient setting

	Setting and K^+ levels	Correction phase	Maintenance phase
Current	Emergency ≥ 6.0 mmol/L	**Shift K^+ into cells** Insulin-glucose 2x doses then **Bind K^+ and excrete** Calcium resonium	**Low K^+ diet** **Manage drugs that raise K^+**
Current	Outpatient ≥ 5.5 mmol/L	**Stop or down-titrate drugs that raise K^+** **Low K^+ diet**	
Proposed	SZC	**Bind K^+ and excrete** SZC 10 g 3x daily for up to 72 hours After insulin-glucose 1x dose in emergency setting	SZC 5 to 10 g OD or 5 g every other day Company's suggested duration of treatment: Emergency setting: 28 days Outpatient setting: 52 weeks

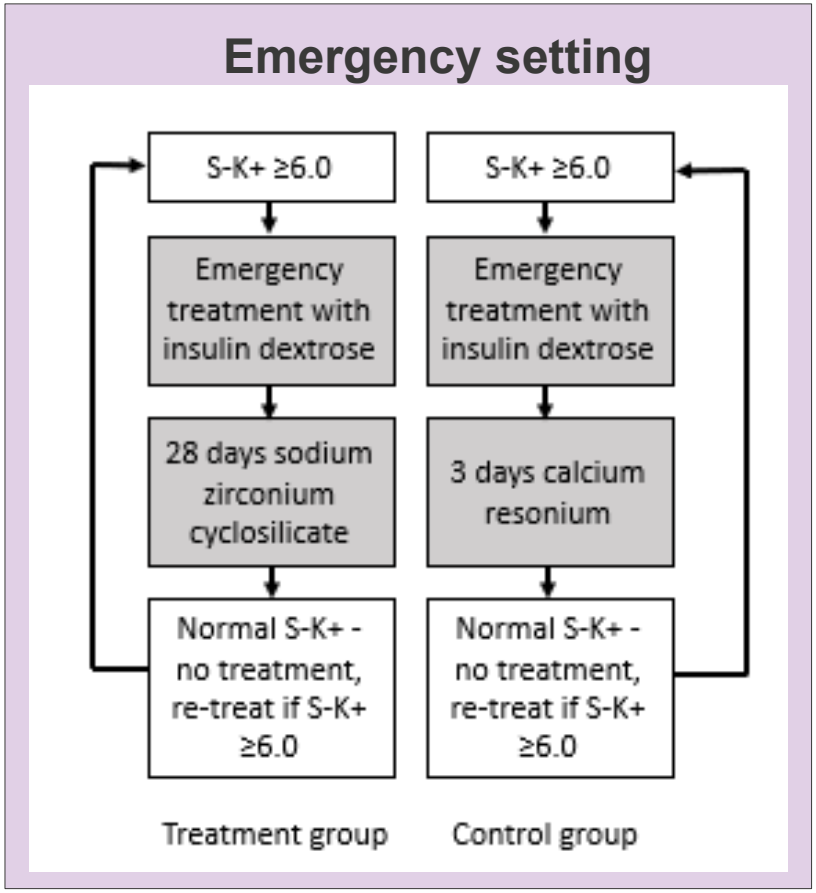
[redacted]

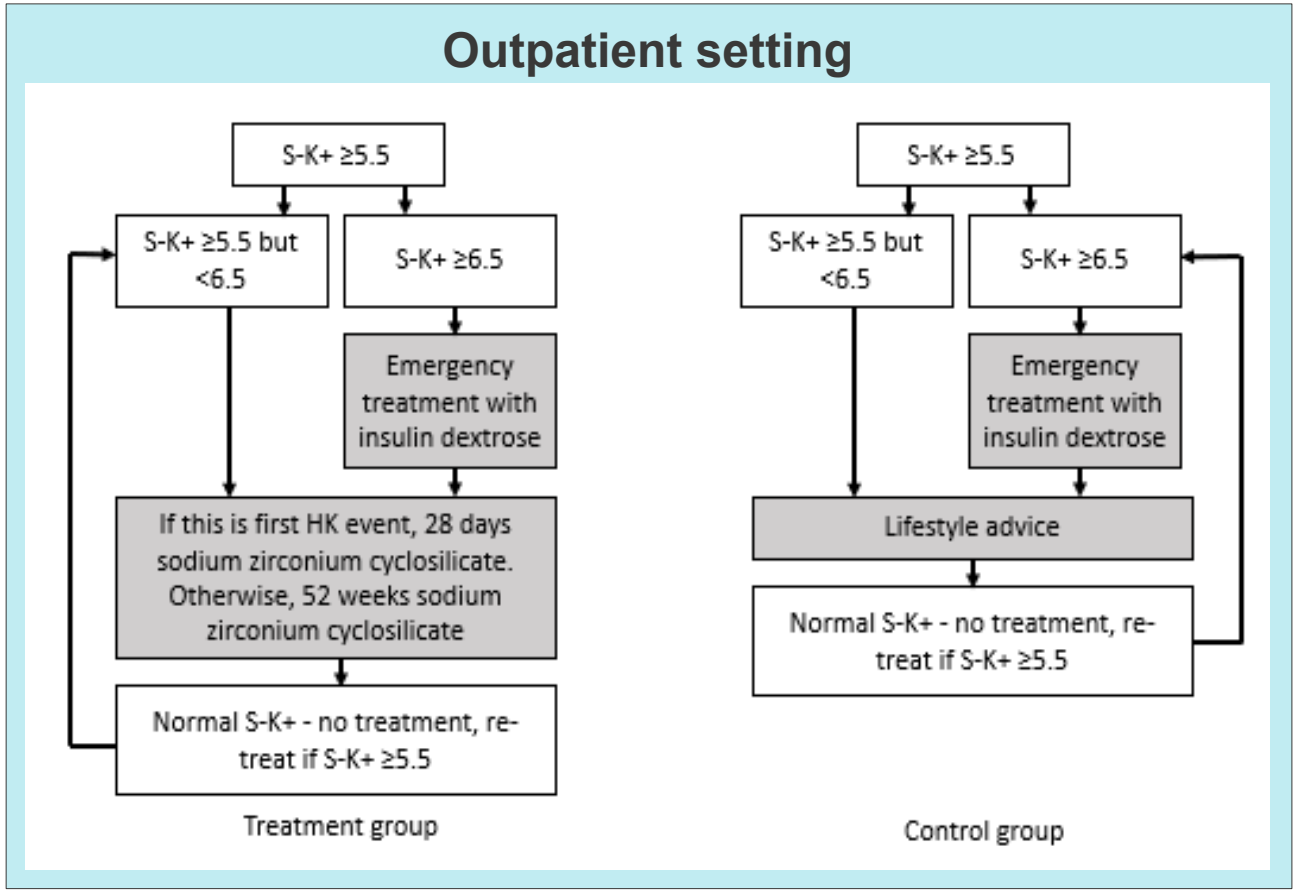
Decision problem: population and comparators

population in submission narrower than marketing authorisation

	NICE scope	Company	Comment
Population	Adults with ↑ K^+	Adults with ↑ K^+ and chronic kidney disease (stage 3–5) or heart failure	Company defined ↑ K^+ as ≥ 5.0 mmol/l in trials
Comparator	Standard care: • low K^+ diet • +/- agents to reduce K^+ levels	Emergency setting: calcium resonium (after insulin-glucose) repeat insulin-glucose Outpatient setting: None	Company did not present data for calcium resonium because published evidence is 'not for dose used in UK'
Outcomes	• Serum K^+ • Time to normalisation • Adverse effects of treatment • Use of RAASi therapy • Mortality • Health-related quality of life	• Serum K^+ • Time to normalisation • Adverse effects of treatment • Use of RAASi therapy • Mortality • Health-related quality of life	

Treatment pathway and comparators in model - emergency and outpatient setting scenarios





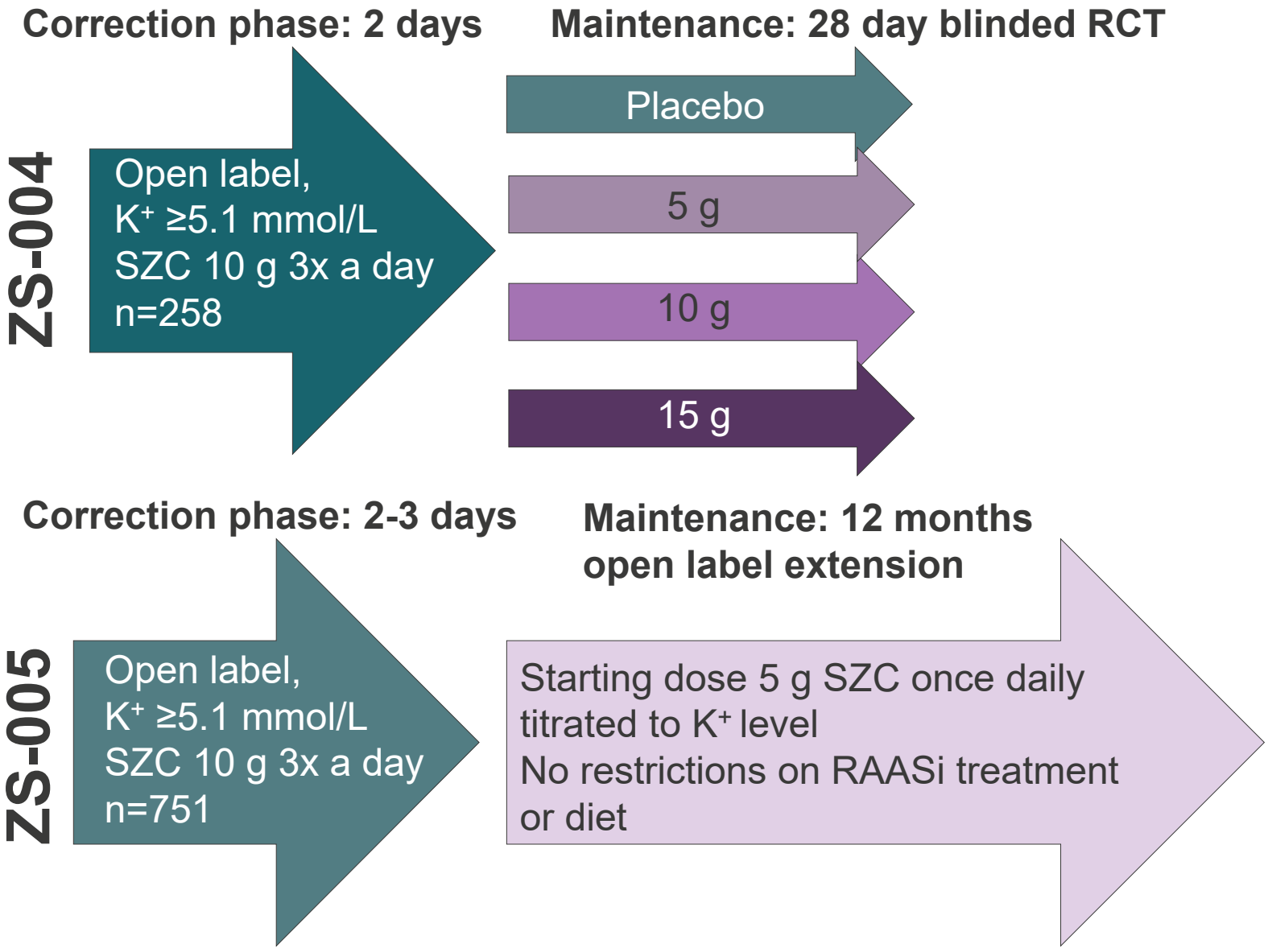
Time horizon in model: 52 weeks
Duration of SZC treatment: 28 days

Time horizon in model: Lifetime
Duration of SZC treatment: 52 weeks (or 28 days if first event)

[redacted]

2 trials ZS-004+ZS-005

Comparators: Correction phase: none. Maintenance phase: 1 trial for 28 days only



Maintenance phase of both trials included people with serum K^+ 3.5 to 5.0 mmol/L

1º outcomes:

ZS-004

Mean serum K^+ during study days 8-29 of the maintenance phase

ZS-005

Correction phase

Restoration of normal serum K^+ levels

Extended dosing phase

Maintenance of normokalaemia (% of patients with mean serum K^+ <5.1 mmol/L months 2-12)

Baseline characteristics in ZS-004 & ZS-005

Company proposed treating ≥ 5.5 mmol/l 1st meeting, ≥ 6.0 this meeting, but only for CKD

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

Trials excluded people on dialysis (although included CKD 5) and people with high arrhythmic risk

Results – not limited to population of interest

Achieving normokalaemia	Maintaining normokalaemia
ZS-004 (secondary outcome) • 24 hours: 66.1% • 48 hours: 88.0%	**ZS-004** K^+ higher in patients randomised to placebo
ZS-005 • 24 hours: 66% • 48 hours: 75% • 72 hours: 78%	**ZS-005** K^+ maintained

ERG overall conclusions on evidence for clinical effectiveness:
No direct evidence for:

- SZC as plausible alternative for dietary modification or versus any active comparator (no narrative or formal data synthesis in the systematic review to compare SZC versus anything)
- SZC efficacy or safety in acutely unwell patients

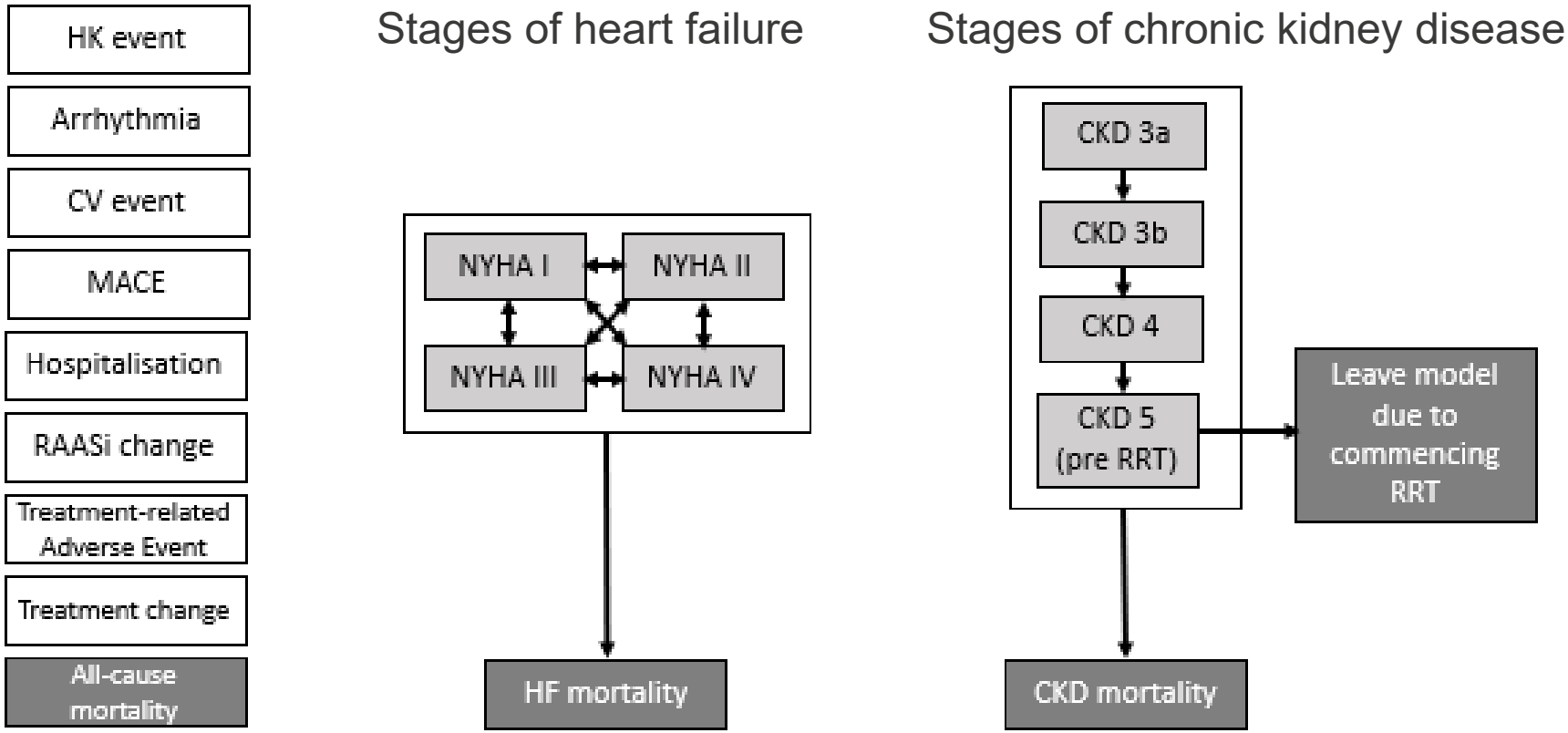
Evidence versus company's modelling

- Trials do not show that SZC improve length of life or quality of life
- Company proposes that drug improves both in its model
  - People with high K^+ die sooner than people with normal K^+
    - Source: epidemiological data
      - association is U-shaped
    - Affects: length of life
  - People with high K^+ more likely to have further CV events or be hospitalised
    - Source: epidemiological data
    - Affects: length of life, quality of life
  - People with hyperkalaemia more likely to stop RAASi and stopping RAASi shortens life and increases risk of progression of CKD/HF
    - Source: epidemiological data
      - N.b. *starting* RAASi based on RCTs
    - Affects: length of life, quality of life

Clinical: ACD conclusions and key uncertainties

Clinical need + practice	Managing emergency life-threatening hyperkalaemia differs from persistently raised non-life-threatening hyperkalaemia
	Lowering K^+ might allow continuing RAASi; unclear benefits in CKD 4; NICE for CKD stopping RAASi at K^+ 6.0 mmol/L
Population	Not everyone with serum K^+ >5.5 mmol/L (proposed by company) needs active treatment
	Trial include K^+ ≥ 5.0 mmol/L who would not be treated in NHS
	Trial excludes dialysis patients and emergency use
Comparator	SZC unlikely to replace a low-potassium diet Calcium resonium not well tolerated
Trial design	No comparator for correction period; no hard outcomes
Trial outcome	In maintenance phase SZC maintains K^+ No evidence that SZC prolongs survival
Corrective phase	Not relevant to how ↑ K^+ treated in NHS as an emergency
Maintenance phase	Company assumes people responding to SZC (serum K^+ 3.5-5.0 mmol) continue to have SZC; In NHS practice people with K^+ in normal range do not receive treatment

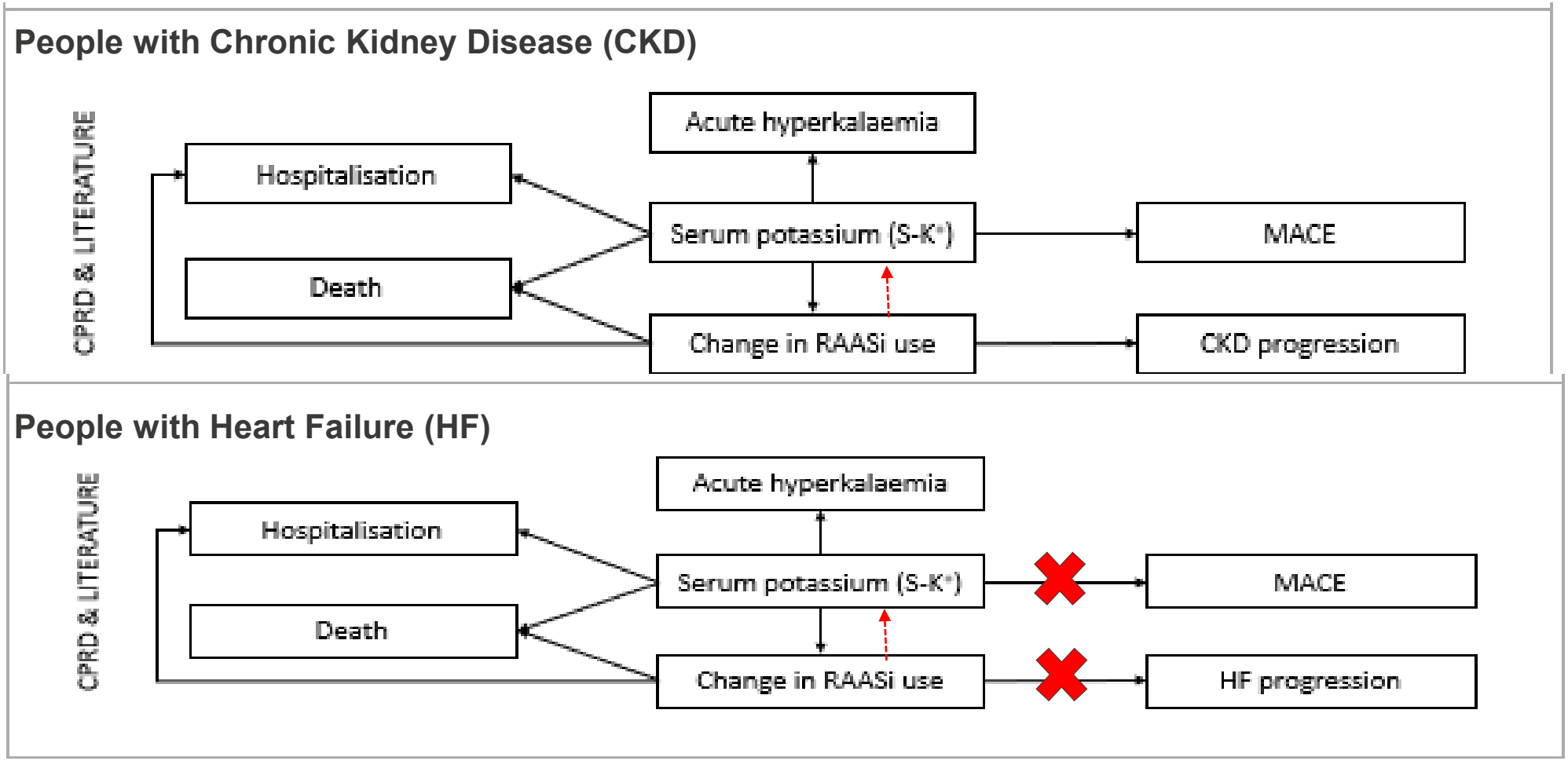
Company's model structure



Abbreviations: HK, hyperkalaemia; CV, cardiovascular; MACE, Major Adverse Cardiac Event; RAASi, Renin Angiotensin Aldosterone System inhibitor; NYHA, New York Health Association; HF, heart failure; CKD chronic kidney disease; RRT, renal replacement therapy

Company uses trial K^+ changes linked to observational data from literature for association between K^+ and outcomes, and association between changes in RAASi and outcomes

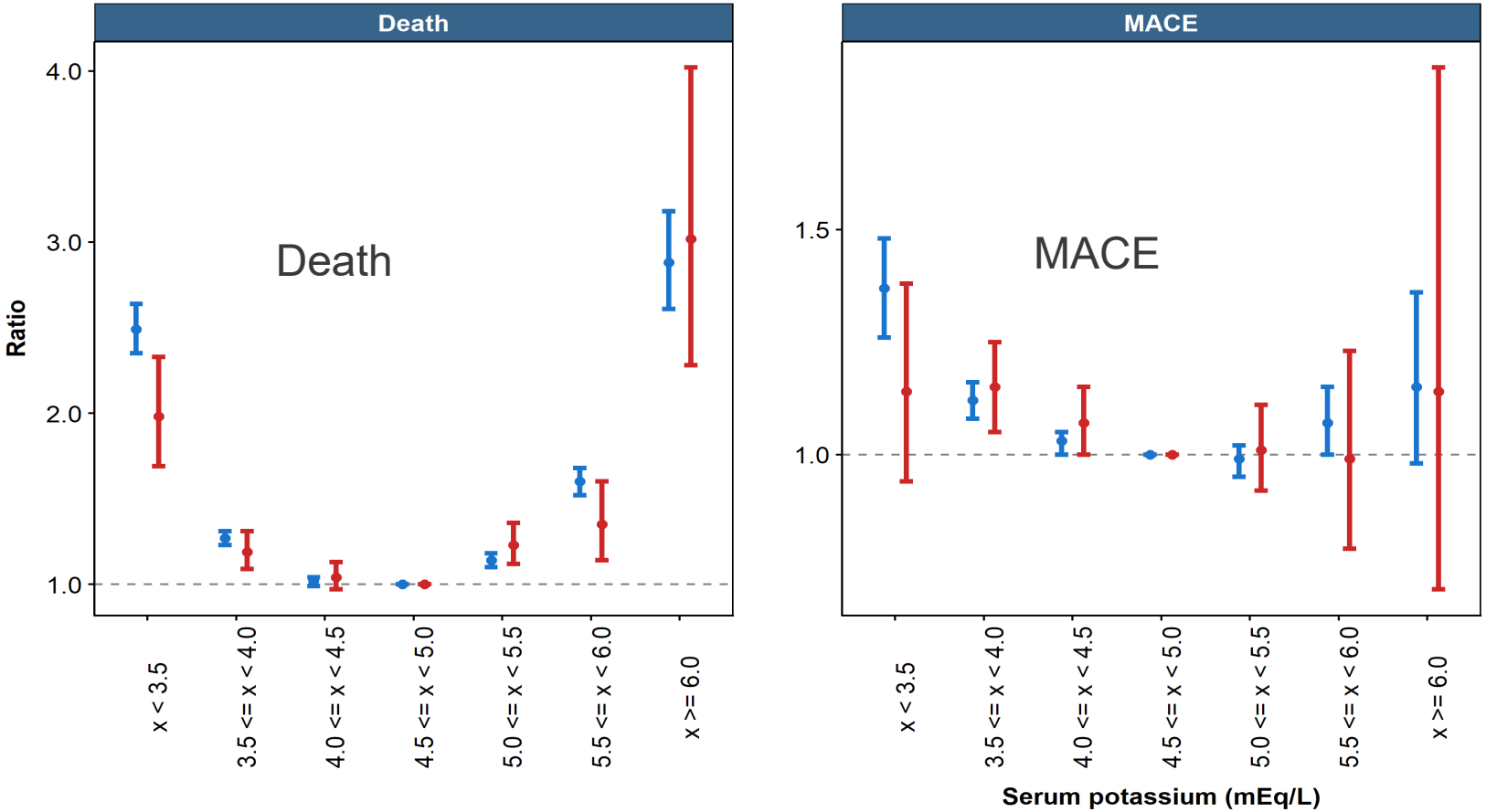
Relationships in model from original company submission



Note: Updated model also includes association between change in RAASi use and serum K^+ level (red arrows) and for people with HF removes the associations between serum K^+ and MACE and change in RAASi use and HF progression (red crosses)

Epidemiological association between K^+ + outcomes

- UK Clinical Practice Research Datalink: incidence rate ratios for mortality and MACE by K^+ in CKD (blue) and CHF (red)
- AstraZeneca funded
- Reference for analysis K^+ 4.5 to 4.9 mmol/l
- Elevated risk of death at values 3.5 to 3.9 mmol/l and ≥5.0 mmol/L



Reference: Qin et al. 2017, Qin et al. 2017, McEwan et al. 2017

Cost: ACD conclusions and key uncertainties

Model did not address problem	Did not reflect people actively treated in NHS
	No randomised data for starting vs. not starting SZC
Observational data - relationship between K^+ and death	No systematic review
	Residual confounding likely - ‘unmeasured or unknown’
	Observational association between K^+ and death does not necessarily mean that lowering K^+ prolongs life
	Lower K^+ (but within ‘normal range’) associated with increased risk of death
Observational data - relationship between stopping RAASi and death	Residual confounding likely
Interventional relationship between stopping RAASi and outcomes	Trials starting RAASi not necessarily generalisable to stopping treatment n.b. stopping RAASi improves K^+
Costs	Company excluded outpatient follow-up after hospital treatment for ↑ K^+
Model	Did not address stopping RAASi for other than ↑ K^+

Responses to ACD

Responses received from:

- Company (AstraZeneca)
- British Society for Heart Failure
- Pumping Marvellous
- Renal Association

Themes of comments from consultees:

- Need to consider subgroups separately (people with heart failure and chronic kidney disease)
- Distinct needs of people with heart failure and hyperkalaemia not addressed at 1st meeting
- For people with heart failure, benefits of treatment dependent on whether prognostic indication for RAASi
- When treatments with SZC should be started: managing episodes of hyperkalaemia vs. managing underlying condition to maintain RAASi use

[redacted]

Positioning of SZC in chronic setting

Consultation comments

Company

- CKD (**New**): K^+ threshold for treatment increased to ≥6.0 mmol/L from ≥5.5 mmol/L
- HF (**unchanged**): K^+ threshold for treatment ≥5.5 mmol/L
  - lower threshold for treating in heart failure
  - serum K^+ levels can rise faster in heart failure than chronic kidney disease

Renal Association

- Clinicians would use K^+ binders at serum K^+ >5.5 to prevent reaching >6 mmol/L

British Society for Heart Failure

- SZC might be of value for a narrow cohort of patients with HF and reduced ejection fraction (HFREF) with hyperkalaemia to facilitate using RAASi and prevent hyperkalaemia (serum K^+ >6.0 mmol/L)
  - RAASi are disease-modifying in HFREF

ERG: valid attempt by company to better represent NHS clinical practice

- Why 5.5 mmol/mol? What evidence exists for different thresholds of treatment by comorbidity?
- How are RAASi disease modifying in HFREF?
- Is there a group of people for whom there are particular benefits?

Comparative data: SZC vs standard care

ACD :

- Comparators in emergency setting: calcium resonium + managing RAASi; in outpatient setting, low potassium diet and decreasing or stopping RAASi
- Company provided no data for above in NHS
- No control group for correction phase in trial – not known what would have happened with standard care

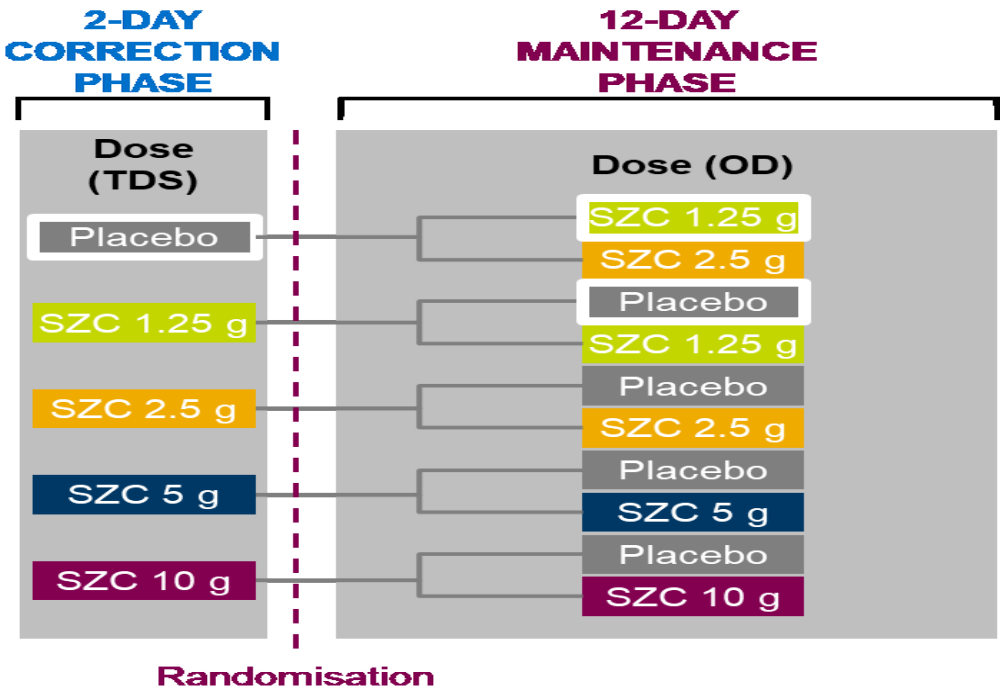
Company response:

- Few data on calcium resonium or low K^+ diet, non-compliance means they are limited as comparators
- **New: company presents an existing randomised trial** ZS003 it did not previously present for SZC vs. placebo in correction phase (next slide)
  - in original submission, company assumed effectiveness of SZC in correction phase equivalent to standard care (benefit from SZC modelled in maintenance phase only)

[redacted] Abbreviations: K^+, potassium; RAASi, renin-angiotensin-aldosterone system inhibitor

ZS003 reduction in serum K^+: correction phase

K^+ 5.0 to 6.5 mmol/L. Dose-ranging study



	Placebo (n=158)	SZC 5g (n=157)	SZC 10g (n=143)
Baseline K^+ (mmol/L)			
48h reduction, ITT pop.			
Adjusted 48h reduction, baseline K^+ ≥5.5,<6.0			
Adjusted 48h reduction, baseline K^+ ≥6.0			

Company adjusted values to match ZS004 baseline serum K^+: Used in model

Why did company only now include this trial?
Company: "not generalisable to UK clinical management of patients with hyperkalaemia and CKD or HF due to [~75%] having baseline serum K^+ below 5.5 mmol/L"

ERG comments:

- Questions whether placebo represents NHS standard care
- Baseline characteristics not generalisable to NHS
- K^+ levels not reported for subgroup of patients used to estimate comparative efficacy
- Only 1 i-STAT measurement of K^+ in trial reduces reliability of results
- In modelling, more appropriate to assume that decline in serum K^+ with placebo continues for 3rd day (a company scenario analysis)

Baseline characteristics in ZS-003, ZS-004 and ZS-005

Characteristic	ZS-003 Placebo (n=158)	ZS-004 SZC 10 g (correction phase) (n=258)	ZS-005 Overall SZC group (n=751)
Age, mean (SD)	65.6 (12.2)	64.0 (12.7)	63.6 (13.03)
Serum K^+ baseline in mmol/L, n (%)			
<5.5	117 (74.1)	119 (46.1)	287 (38.2)
5.5 to <6.0	Remaining 41 patients had serum K^+ 5.6 to 6.5	100 (38.8)	338 (45.0)
≥6.0		39 (15.1)	126 (16.8)
eGFR at baseline, n (%)			
<60 mL/min	120 (75.9)	179 (69.4)	552 (73.5)
≥ 60 mL/min	38 (24.1)	72 (27.9)	190 (25.3)
Comorbidities, n (%)			
Chronic kidney disease	9(60.8)	169 (65.5)	513 (58.3)
Heart failure	66 (41.8)	94 (36.4)	285 (37.9)
Diabetes mellitus	96 (60.8)	170 (65.9)	471 (62.7)
Use of RAASi medication, n (%)	101 (63.9)	180 (69.8)	383 (51.0)

Trials excluded people on dialysis (although included CKD 5) and people with high arrhythmic risk.

Positioning of SZC in emergency setting

Consultation comments:

ACD: [Committee] should consider SZC in emergency treatment setting . . . comparators were calcium resonium and management of RAASi

Company

- Unchanged from original submission: Serum K^+ ≥6.0
- Patients would be treated with insulin dextrose then SZC to maintain normal K^+ levels → prevent need for repeat insulin dextrose

British Society for Heart Failure

- Acute management primarily involves treatment such as calcium gluconate, insulin dextrose and calcium resonium. Novel potassium binders may
  - complement/add to current options, for example if calcium resonium was not tolerated
  - allow the patient to be managed safely at home → preventing hospitalisation

Renal Association

- [SZC] not intended for acute management of patients with K^+ >6.0

[redacted] Abbreviations: K^+, potassium; RAASi, renin-angiotensin-aldosterone system inhibitor

Company: subgroup from ZS004 that would be treated as emergency

ACD: submission not relevant to how hyperkalaemia is treated in the NHS as an emergency… because this population was not included in the trials

Company:

- Identified 8 patients with 'life threatening' hyperkalaemia (K^+ ≥6.5)
- [redacted] patients had K^+ <5.5 after 48 h
- Median time to normalisation (serum K^+ ≤5.0) in ITT group (baseline serum K^+ >5.1) was 2.2 h

ERG comments:

- Analysis based on small numbers → considerable uncertainty within results
- Comparative reduction associated with insulin dextrose unknown

Abbreviations: K^+, potassium; SD, standard deviation

Company: subgroup confidence intervals overlap

→ no difference in SZC treatment effect by co-morbid condition

ZS-004 maintenance phase: mean difference in serum K^+ on days 8–29 in SZC 10g vs placebo

ZS-005 maintenance phase: prop. patients with serum K^+ ≤5.1 on days 85–365 by comorbidity

ERG comments:

- Confidence intervals for CKD vs no CKD don't (or barely) overlap
- Suggests greater effect for people with CKD compared to without CKD
- Important because although separate cost effectiveness analyses for HF and CKD presented, these are based on **pooled efficacy data** for whole population

  → reduction in serum K+ for people with HF may be less than estimated by company

⊙ **Has committee seen evidence of interaction by subgroup?**

Company new data:

% of people with serum K^+ dropping below threshold for RAASi treatment

ACD: a key outcome would be the proportion whose serum K^+ dropped below 6.0 mmol/L

- **New** post-hoc analysis of data from ZS-004 and ZS-005 (not split by underlying condition)
- Majority of patients with serum K^+ above RAASi threshold drop below after SZC treatment

	Starting serum K^+ ≥5.5 (relevant to HF)		Starting serum K^+ ≥6.0 (relevant to CKD)	
	ZS004	ZS005	ZS004	ZS005
% with corrected levels after 2-3 days (defined as serum K^+ ≥4.0 and ≤5.5 or 6.0)	[redacted]			
% maintaining corrected levels after maintenance phase				

ERG: small numbers with serum K^+ >6.0 mmol/L → considerable uncertainty in results

⊙ How does the company use this in its modelling?

Abbreviations: K^+, potassium; RAASi, renin-angiotensin-aldosterone system inhibitor.

Stopping RAASi may be beneficial in CKD stage 4

NIHR/MRC funded trial – investigating effect of stopping RAASi on renal function

STOP-ACEi

STOP-ACEi is a national multi-centre randomised controlled trial of Angiotensin Converting Enzyme inhibitor (ACEi) / Angiotensin Receptor Blocker (ARB) withdrawal in advanced renal disease.

Trial details

Full Title: Multi-centre Randomised Controlled Trial of Angiotensin Converting Enzyme inhibitor (ACEi) / Angiotensin Receptor Blocker (ARB) withdrawal in advanced renal disease

Short Title: The STOP-ACEi Trial

Aim of the study: To test the hypothesis that stopping treatment with ACEi, ARB or a combination of both, compared with continuing on these treatments, improves or stabilises renal function in patients with progressive stage 4 or 5 Chronic Kidney Disease (CKD).

Study design: Open-label randomised controlled trial (RCT).

Relationship: serum K^+ and long term outcomes

ACD: trial results show SZC may lower serum K^+ but benefit to patients is unclear

- Company provided evidence from a single observational study showing an association between serum K+ levels and death but did not provide a systematic review of the evidence
- Causal relationships cannot be guaranteed by observational data
- The extent to which the company took confounding variables into account was unclear

Consultation comments:

Company:

- **New:** systematic review (see next slides)

Renal Association:

- "The many recurrent and unnecessary hospitalisations that are associated with hyperkalaemia in patients with CKD and/or heart failure … are associated with major cost, morbidity and mortality."

[redacted] Abbreviations: K^+, potassium; CKD, chronic kidney disease; HF, heart failure

Company: relationship between K^+ and outcomes – new systematic review for CKD, no meta-analysis

Mortality

[redacted] observational studies identified
Base case: **Luo**
[redacted] studies used in scenario analyses

MACE

[redacted] observational studies identified
Base case: **Luo**
Scenario: [redacted] study

Hospitalisation

[redacted] observational studies identified
Base case:

- All studies show U-shaped relationship" death, hospitalisation or MACE
- Uses Luo base case (**unchanged** from original base case). US-claims data base
- From Luo: 'Although efforts were taken to adjust for many plausible influential variables, confounding by unconsidered factors is possible'
- From Luo: 'Because this is an observational study, associations do not necessarily allow for causal interpretation.'
- Company scenario analyses: using other studies or adjusting risk ratio by ± 20%
- Company does not present scenario assuming no causal link between K^+ and outcomes

Company: relationship between serum K^+ and long term outcomes – new systematic review for HF

Mortality

[redacted] RCT and [redacted] observational studies identified
Base case: **Desai (RCT)**
[redacted] studies suitable for scenario analyses

MACE

No relevant studies identified
Base case: **CPRD data** modified by K^+ levels from **Luo**

Hospitalisation

[redacted] observational studies identified
Base case: estimated from **Desai** (RCT)

[redacted]

- U-shaped association
- Desai (**new**) and CPRD/Luo (**unchanged**) used in base case
- Company scenario analyses: using other studies or adjusting risk ratio by ± 20%

◉ Why did the company choose Desai?

Abbreviations: K^+, potassium; CPRD, clinical practice research datalink; HF, heart failure MACE, major adverse cardiovascular events

ERG: relationship between serum K^+ and outcomes

- Observational AZ-sponsored study in patients with HF (Nunez et al.) shows that patients who move from a hyperkaelaemia to normokalaemia have 'improved survival outcomes'
- From Nunez '..the question of causality arises as to whether risk associated with low or high potassium levels is the result of harm related to disruption of potassium homeostasis or rather the result of confounding factors associated with or having led to serum potassium changes.'
- Accompanying editorial highlights:
  - need to "be careful to assert a general causal relationship between hyperkalaemia and clinical outcomes across the entire spectrum of hyperkalaemia"
- Company 'RCT evidence exists for the relationship between S-K and outcomes in HF patients'
  - n.b. this appears to be an observational analysis of a trial
- Exploratory analysis: no causal link between serum K^+ and outcomes

⊙ Has the committee seen evidence to change committee's conclusion that the observational study used by company to support SZC extending life may have residual confounding?

⊙ If this association is 'causal', has the committee seen evidence robust evidence that lowering potassium improves survival?

Relationship: RAASi use and long term outcomes

Consultation comments

ACD: unclear whether benefits of starting a RAASi are same as the risks of stopping a RAASi to manage serum K^+ levels because patients may change to another antihypertensive drug.

Company

- Not always appropriate to switch from RAASi therapy to another anti-hypertensive or one with similar benefits.
- **New:** review (see next slides)

Renal Association

- [SCZ would] facilitate safer use of ACE-I and ARB, necessary treatments for patients with CKD and/or heart failure

Pumping Marvelous Foundation

- The value of SZC to people with heart failure is … managing their condition to ensure they maintain their triple therapy

Relationship: RAASi use and long term outcomes

New tageted review CKD

	Company response	Model
Effect on outcomes	• Identified 2 observational studies of impact of down-titrating/ stopping RAASi on outcomes: supported the results of Xie et al. NMA used in original submission • Effect of RAASi discontinuation on survival appears to be at least as large as the benefit of starting RAASi	Base case **unchanged:** Odds ratios (Xie) comparing RAASi to placebo **New** scenario analyses: • Odds ratios (Xie) comparing RAASi with other active antihypertensive • RAASi assumed to have no effect on outcomes
Effect on CKD progression	• Evidence that RAASi reduces proteinuria and that delayed disease progression is dose-dependent	

ERG comments:

- No trial evidence to show differential effect on RAASi treatment after using SZC,
- No evidence that using SZC does not impact on the effectiveness of RAASi
- Company approach and range of scenario analyses appropriate
- Given conclusions in ACD that alternative RAASi are available in event of hyperkalaemia, believes committee would prefer scenario comparing with other active antihypertensives rather than placebo

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

Relationship: RAASi use and long term outcomes

new targeted review HF

	Company response	Model
Effect on mortality/ CV events/ hospitalisation	• Identified 3 studies on the effect of RAASi down-titration or discontinuation on outcomes that support original company submission • Effect of RAASi discontinuation appears to be at least as large as RAASi initiation	Base case **unchanged** **New** scenario: • Odds ratios for hospitalisation from Xie • RAASi assumed to have no effect on outcomes
Effect on HF progression	• Meta analysis of aldosterone agonists from 14 RCTs showed improvements in ejection fraction and NYHA class	

ERG comments:

- No trial evidence to show differential effect on RAASi treatment due to SZC use, or evidence that using SZC does not impact on the effectiveness of RAASi
- Company approach and range of scenario analyses appropriate

⊙ For CKD does the committee prefer to use odds ratios compared to placebo or an alternative antihypertensive?

Abbreviations: K^+, potassium; RAASi, renin-angiotensin-aldosterone system inhibitor; HF, heart failure.

Company: new utility estimates for CKD

Company:

- Identified 2 studies with EQ-5D data for people with CKD and chose study based on patients in Europe in updated model (Erikksson et al, 2016)
- Replaces values used in the original company submission based on HUI-3 from Gorodetskaya et al.

ERG:

- Company used data for patients without anaemia only whereas majority of data were collected in patients with anaemia
- ERG have estimated alternative values assuming independence between anaemia and CKD stage and performing a weighted average due to a lack of granular data

CKD stage	Company	ERG
3a/b	0.85	0.80
4	0.81	0.74
5 (pre renal replacement therapy)	0.74	0.71

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

Company revised base case assumptions

Assumption	Original submission	Revised base case	Rationale for change
Threshold K^+ for treatment –outpatients	≥ 5.5 mmol/L regardless of underlying condition	• ≥6.0 mmol/L for CKD • ≥5.5 mmol/L for HF	Reflects NHS practice
Source of data for standard care in correction phase	ZS004/005	ZS003	Source of comparative data
Association K^+ with mortality/MACE: CKD	Luo et al	Luo et al	Unchanged
Association K^+ mortality/ hospitalisation: HF	Krogager et al, Luo et al	Desai et al	Relevant for HF population
Quality of life	Gorodetskaya et al	Eriksson et al	EQ-5D
RAASi effect on K^+	Not modelled	↓ by 0.115/0.23 mmol/L reduce/stop RAASi	As ERG assumption
Time horizon emergency setting	Life time	52 weeks	As ERG assumption
Costs of changing RAASi dose	Some dose changes happen as inpatient	Dose changes happen as outpatients	As ERG assumption
Stop RAASi on SZC	No stopping RAASi on SZC irrespective of K^+	Stop RAASi for 12 weeks if serum K^+ >6.0	As ERG assumption

Other ERG comments on modelling

Company assumes (based on clinical expert opinion):

- All patients with serum K^+ >6.0 mmol/L stop RAASi for 12 weeks
- For people with serum K^+ 5.5 to 6.0 mmol/L:
  - 20% on standard care stop RAASi, 80% downtitrate
  - All on SZC continue RAASi
- Restarting RAASi depends on whether on SZC or standard care
  - 100% on SZC restart RAASi in 12 weeks vs. 49.7% on standard care

ERG believes it is plausible that rates are equal in both arms → conducted exploratory analysis setting RAASi discontinuation/down titration and reinitiation equal across both arms

[redacted] Abbreviations: K+, potassium; RAASi, renin-angiotensin-aldosterone system inhibitor

Company: revised base case results

	Emergency setting					
	CKD			HF		
	Δ Costs (£)	Δ QALYs	ICER	Δ Costs (£)	Δ QALYs	ICER
Revised base case	-4,079	0.007	Dominates	-3,536	0.009	Dominates

		Outpatient setting					
Revised base case		8,249	0.71	11,644	14,860	0.82	18,158
Key scenario analysis around company revised base case							
Placebo rate of serum K^+ decline continues over 3 days		11,362	0.57	19,815	13,928	0.64	21,729
Xie RAASi vs. active control	**OR: mortality**	10,006	0.79	12,703	-	-	-
	OR: CV event	8,532	0.71	12,066	-	-	-
	OR: hospitalisation	-	-	-	14,937	0.82	18,253
RAASi: no effect on outcomes		7,054	0.63	11,173	12,575	0.50	25,208

Company:

- scenario analyses show results robust to range of assumptions
- SZC remains cost-effective in scenario assuming no effect of RAASi on clinical outcomes (i.e. the potential benefits of SZC in enabling RAASi-use are not translated to clinical benefits)

Abbreviations: K^+, potassium; RAASi, renin-angiotensin-aldosterone system inhibitor; OR, odds ratio

ERG exploratory analyses

	Outpatient setting					
	CKD			HF		
	Δ Costs (£)	Δ QALYs	ICER (£)	Δ Costs (£)	Δ QALYs	ICER (£)
Company revised base case	8,249	0.71	11,644	14,860	0.82	18,158
ERG exploratory analyses around company revised base case						
1) Rate of serum K^+ decline for placebo from ZS-003 continues over 3 days	11,362	0.573	19,815	13,928	0.641	21,729
2) Setting RAASi discontinuation and down-titration rates in SZC arm equal to standard care	1,397	0.443	3,155	12,293	0.634	19,385
3) OR for RAASi from Xie compared with active treatment	10,302	0.786	13,102	-	-	-
4) ERG utility values for CKD	8,249	0.654	12,605	-	-	-
5) Serum K^+: No effect on outcomes	3,369	0.088	38,287	11,732	0.106	111,035
ERG alternative base case combining 1 to 4	**5,282**	**0.307**	**17,179**	**11,531**	**0.475**	**24,291**

Emergency setting SZC dominates standard care in all ERG analyses

Summary of ERG conclusions

Cost effectiveness analyses in outpatient setting relatively unbiased but considerable uncertainty within the decision problem

- Further limitations in emergency setting as no trials have been done

Uncertainties that prohibit the ERG forming a definitive ICER include:

- No trial comparing SZC and **current standard care** in NHS in either correction phase OR maintenance phase for either emergency or outpatient setting
  - approach to populating model reasonable but relatively small numbers in some subgroups → considerable uncertainty
- No trial to demonstrate the impact of SZC on hard clinical endpoints
  - guidelines recognise that high serum K^+ levels should be reduced indicating that clinicians believe high levels of serum K^+ warrant intervention
- Data suggests a potentially better treatment effect of SZC for patients with CKD
  - this would result in worse treatment effects in the HF patients
- No evidence that SZC enables patients to initiate, re-initiate or increase RAASi therapy and maintain optimum serum K^+ levels

Abbreviations: K^+, potassium; RAASi, renin-angiotensin-aldosterone system inhibitor