NICE National Institute for Health and Care Excellence

Public slides

Sodium zirconium cyclosilicate for treating hyperkalaemia

1st appraisal committee meeting

3rd October 2018, 1st topic

Committee B

Chair: Amanda Adler

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

ERG: ScHARR

NICE technical team: Mary Hughes and Ross Dent

Company: AstraZeneca

Key issues: treatment and clinical effectiveness

- No comparative trial data on survival, long term outcomes and key proposed benefit of sodium zirconium cyclosilicate (SZC) – allowing optimum doses of cardio-renal protective blood pressure lowering drugs to be maintained
- Survival estimates in model based on estimates of complex relationship between serum potassium, use of blood pressure drugs and survival. Is this robust?

- What serum potassium concentration needs treatment as an emergency in hospital?
- At what potassium concentration would one treat ‘chronic’ hyperkalaemia?
- At what potassium concentration would SZC be started if used in a chronic setting?
- Will SZC avoid the need for a low potassium diet and change the management of drugs that raise potassium (i.e. RAASi) as company suggest?
- How long would maintenance treatment with SZC last?
- Is the placebo group of ZS-004 generalisable to people having current standard care after initial correction of hyperkalaemia?
  - In absence of trial data, is there observational evidence that a low potassium diet lowers the chance of having a subsequent hyperkalaemia event? Does low adherence to the diet affect this?

Hyperkalaemia - high blood levels of potassium

- **Hyperkalaemia:** K+ normal range 3.5 to 5.0 mmol/L. Definitions of normal to high vary. Company defines hyperkalaemia as >5.0 mmol/L and treatment at ≥5.5 mmol/L
- **Symptoms** include muscle weakness, muscle stiffness, fatigue, or no symptoms
- **Severe hyperkalaemia** can cause irregular heart beat, cardiac arrest and death
- **Risk factors for hyperkalaemia include**:
  - Diseases: Chronic kidney disease, adrenal disease
  - Medicines, including those used to treat high blood pressure, such as:
    - Renin-angiotensin aldosterone system inhibitors (**RAASi**) including angiotensin-converting enzyme (**ACE**) inhibitors, angiotensin II receptor blockers (**ARB**), direct renin inhibitors (e.g. aliskerin) and aldosterone-receptor antagonists (e.g. spironolactone). other potassium-sparing diuretics (e.g. amiloride)
    - beta-blockers (e.g. propranolol, metoprolol, atenolol – via inhibiting renin release)
  - Other medicines (heparin, NSAIDS, COX-2 inhibitors etc.)
  - Salt substitute (KCl)

Patient perspectives

- **Symptoms are dangerous and distressing**
  - “hyperkalaemia can make a person feel sick… and feel disorientated”
- **Current treatments are not adequate**
  - Extremely unpalatable and patients are looking forward to new treatment options
- **Dietary intervention not adequate, not always effective**
  - A low K+ 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”

Sodium zirconium cyclosilicate (SZC), Lokelma®

marketing authorisation does not define hyperkalaemia

Marketing authorisation	Indicated in adults for treating hyperkalaemia
Administration & dose	Administered as a 5g or 10g powder for oral suspension **Correction phase**: recommended starting dose 10g 3 times daily, max duration 72 hours **Maintenance phase**: recommended dose 5g once daily can be up titrated to 10g once daily or down titrated to 5g once every other day to maintain normal potassium levels
Mechanism of action	Non-absorbed, captures K+ in the GI lumen, thereby lowering serum K+ and increasing faecal K+ excretion
Proposed benefits (company)	• Sustained control of K+ levels without the need to adopt a restrictive low potassium diet • Management of underlying comorbid disease without need to alter cardio-renal protective agents (e.g. RAASi) • Well tolerated • Reduced risk of hospitalisation, morbidity and mortality

Decision problem: population and comparators

population in submission narrower than marketing authorisation

	NICE scope	Company
Population	Adults with ↑K^+	Adults with ↑K^+ and chronic kidney disease (CKD) (stage 3–5) or heart failure (CHF)
Comparator	Standard care. • low K^+ diet • with or without agents to reduce levels of K^+	Acute setting: insulin-glucose, calcium resonium as needed Chronic setting: no therapy
Rationale for difference from scope	All patients receive interventions to maintain serum K^+ e.g. dietary intervention and modifying medications, such as RAASi	

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

Decision problem: outcomes

No trial data for length or quality of life

	NICE scope	Company
Outcomes	• Serum K^+ level • Use of RAASi therapy • Mortality • Time to normalisation • Adverse effects of treatment • Health-related quality of life	• Serum K^+ • Time to normalisation • Adverse effects of treatment • Use of RAASi therapy *exploratory endpoint in trial, in model managing RAASi based on serum potassium, + assumption that can continue RAASi on SZC* • Mortality *Not an outcome in trials. Company: "would be confounded by underlying co-morbidities" In model use the estimated risk of death associated with serum K+ and stopping RAASi as surrogates* • Health-related quality of life *estimates from literature*
Rationale for difference from scope		

Abbreviations: RAASi, Renin-angiotensin-aldosterone system inhibitor

Treatment pathway

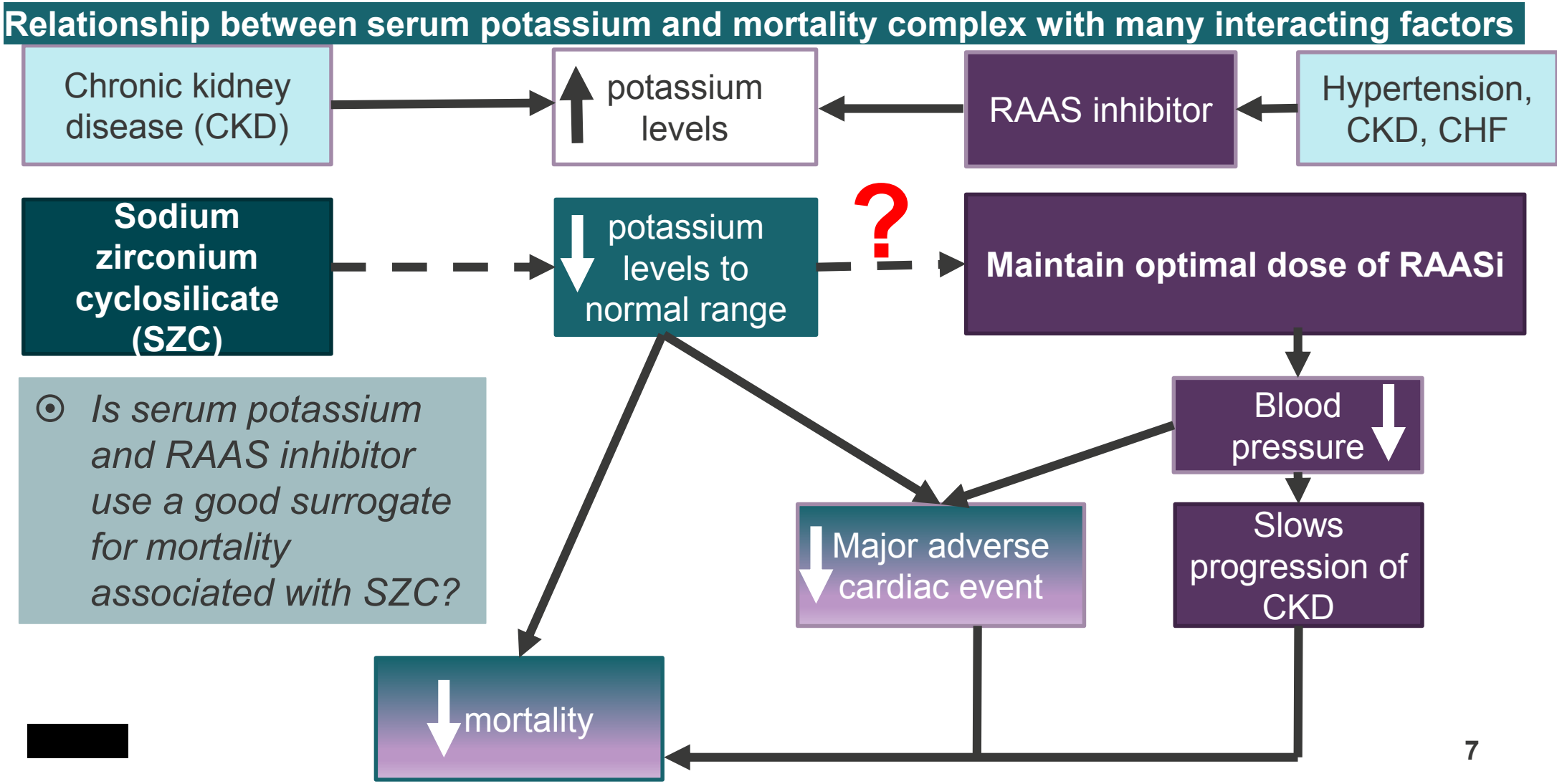
company: SZC will be used in acute + chronic setting

	Setting and K+ levels	Correction phase	Maintenance phase
Current	Acute ≥ 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	'Chronic' ≥ 5.5 mmol/L	**Stop or down-titrate drugs that raise K+** **Low K+ diet**	
Proposed	Can be used in acute or chronic	**Bind potassium and excrete** SZC 10g 3 x daily for up to 72 hours (+ insulin-glucose 1x dose in acute setting)	SZC 5 to 10g once daily or 5g every other day Company's suggested duration of treatment : Acute setting: 28 days Chronic setting: 52 weeks

- *How does the company define the acute treatment population – only people with confirmed life threatening hyperkalaemia?*
- *What are the indications for treating hyperkalaemia in an acute or chronic setting?*
- *Are the company's suggested K+ levels for treatment in each setting appropriate?*
- *Will SZC avoid the need for low potassium diet as company suggest?*
- *Will SZC change the management of drugs that raise potassium (i.e. RAASi)?*
- *How long is acute treatment with SZC? maintenance treatment with SZC?*

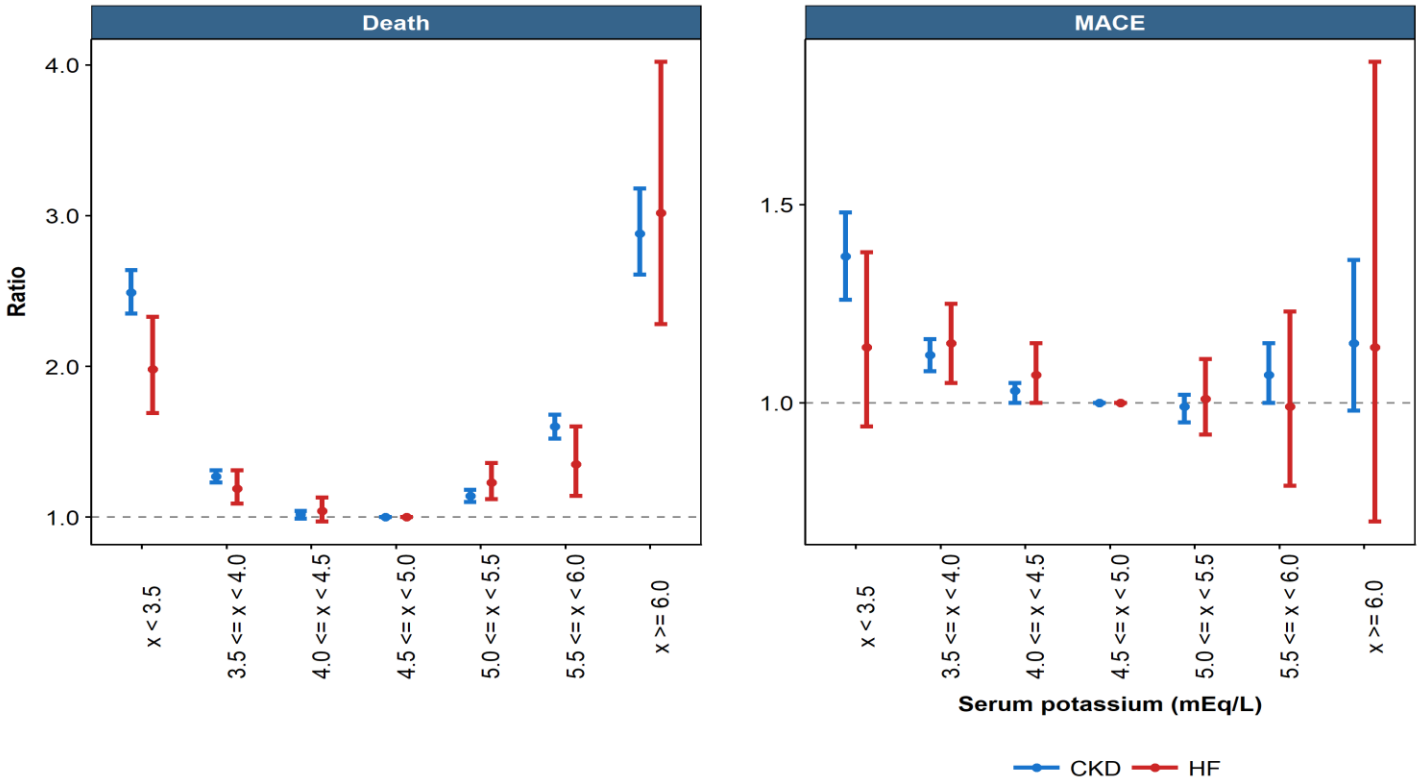
Relationship between potassium levels, RAAS inhibitor use and mortality

complex with many interacting factors



U-shaped association with serum K+ and major adverse cardiac events (MACE) and death

- UK Clinical Practice Research Datalink : incidence rate ratios for mortality and MACE by serum K+ in CKD (blue) and CHF (red)
- Reference for analysis K+ 4.5 to 4.9 mmol/l
- Normal serum K+ considered to be 3.5 to 5.0 mmol/l (n.b normal and study reference K+ differ)
- Elevated risk of death at values 3.5 to 3.9 mmol/l and ≥ 5.0 mmol/L
- Confounding likely – patients with high or low potassium at higher risk of death



⊙ *Is confounding possible? Is this observational association sufficient to prove that <u>lowering</u> chronically elevated serum K+ makes people live longer? Is there randomised evidence that lowering chronically elevated K+ with anything makes people live longer?*

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

Using renin-angiotensin-aldosterone system inhibitors (RAASi) in hyperkalaemia

People with CKD and/or CHF are offered RAASi which lower the risk of death, worsening renal function and major adverse cardiac events, but RAASi can raise K+

n.b. RAASi are stopped for reasons other than high K^+

Company submission: clinical advice on RAASi management	NICE CG 182: chronic kidney disease in adults: assessment + management
Chronic: serum K+ ≥5.5 mmol/L • Don't start RAASi if K+ ≥5.0 • 80% of people down titrate and 20% stop if K+ ≥5.5 to 5.9 mmol/L • Stop RAASi if ≥6.0 mmol/L **Acute:** serum K+ ≥6.0 • Stop RAASi	• Do not routinely offer a RAASi to people with CKD if pre-treatment serum K+ ≥5.0 mmol/L • Stop RAASi if serum K+ increases to ≥6.0 mmol/L

- *At what K+ levels do clinicians stop a RAASi? Down titrate?*
- *If so, do these differ for people with different comorbidities?*
- *Would people who stop RAASi switch to another blood pressure lowering treatment? Do all treatments offer same survival benefits?*

Association between RAASi and MACE/death

- Key study: Xie et al: taking RAASi lowers risk of cardiovascular events and death in people with chronic kidney disease
  - Systematic review and network meta-analysis evaluating RAASi (ACE and ARBs) compared with placebo and active controls
  - 119 trials, 64,768 patients with chronic kidney disease (any stage)
- Seattle heart failure model (SHFM) applies a lower risk of death in people with heart failure taking ACE or ARB inhibitors (types of RAASi)

Condition	Comparison	Risk of death	Source
Chronic kidney disease	On RAASi vs. placebo	0.870 (odds ratio)	Xie et al
Heart failure	On vs off ACE	0.770 (hazard ratio)	SHFM
Heart failure	On vs off ARB	0.850 (hazard ratio)	SHFM

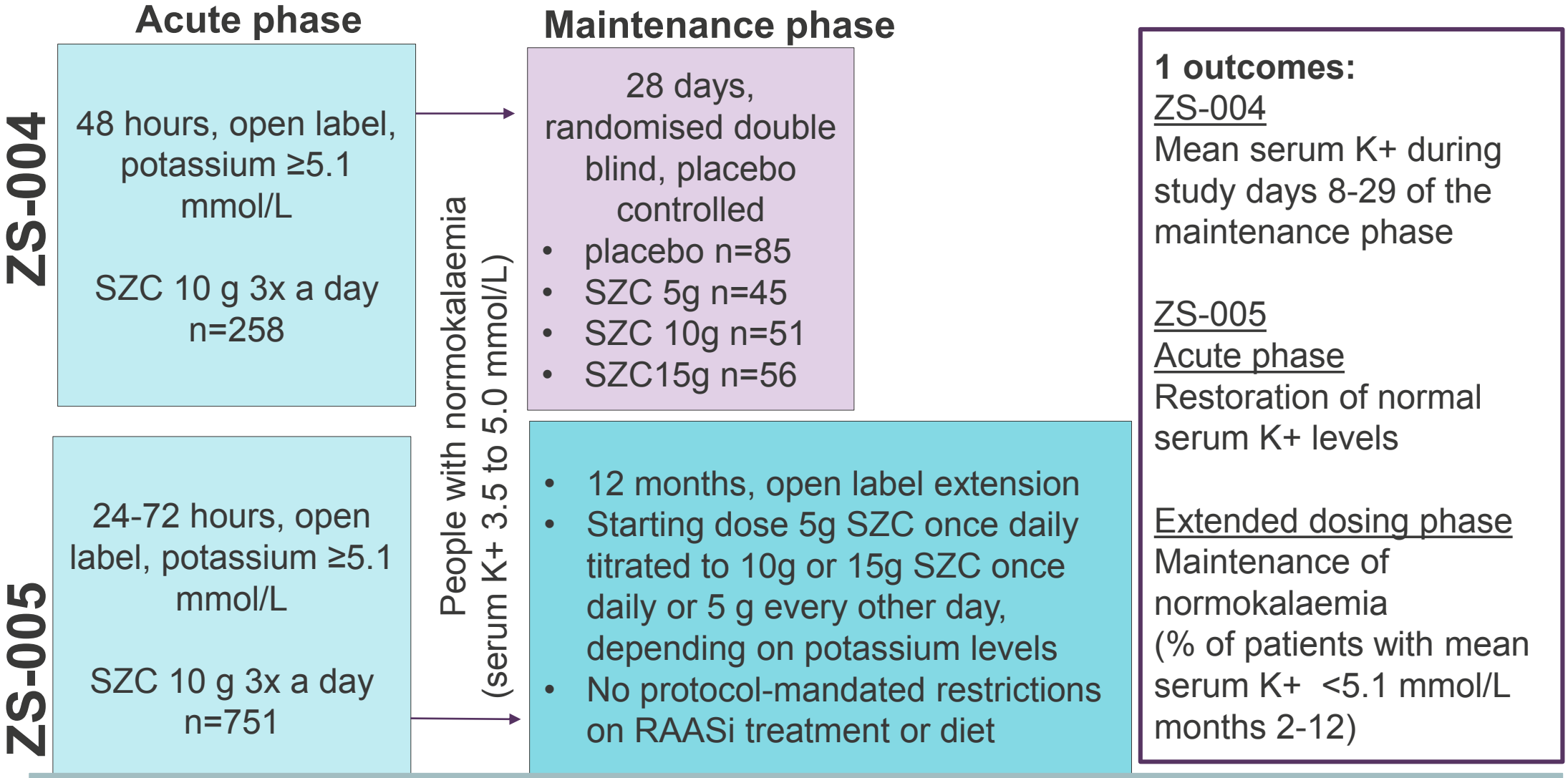
- *Is the Xie et al meta-analysis of people starting RAASi vs. placebo generalisable to people STOPPING RAASi?*
- *People stop RAASi for many reasons; is confounding by indication possible?*
- *Is placebo the relevant comparator or another antihypertensive (i.e. would another class of antihypertensive have similar benefit to RAASi)?*

Overview of key clinical relationships

Association between	Source	RCT	Use in model	Length of life	Quality of life
Higher serum K^+ and death	CKD: Luo et al. HF: Krogager et al. (ERG Aldahl et al.)	No (cohort studies)	• Risk by serum K^+ subgroup (0.5 mmol/L increments) • >5.0 or <4.5 = higher risk of death - risk increases as K^+ increases or decreases further	↓	N/A
Higher serum K^+ and CVD	CKD: Luo et al HF: above + clinical practice research datalink	No (cohort studies, Luo US study)	• Higher rate of major cardiac events by serum K^+ group as above	↓	↓
Being on RAASi and outcomes	Evans et al.	RCT of irebesartan (RAASi, ARB)	• Lower rate of progression of CKD to end stage renal disease (RAASi vs. no RAASi)	↑	↑
	Xie et al.	meta-analysis of RCTs	• Lower risk of death from chronic kidney disease • Lower rate of cardiovascular events	↑	↑
SZC and serum K+	ZS004 + ZS005	Maintenance phase of ZS004 only	• Lower serum K+ on SZC • Lower RAASi use based on trial serum K+ in standard care • Assumed no RAASi stopping on SZC	lower serum k+ and continued RAASi use increases length/quality life on SZC	

Clinical effectiveness evidence: trials used in model

Trials have limited comparative data and main outcomes are serum potassium levels: do not measure effect of SZC on cardiovascular outcomes, RAASi use or mortality



⊙ *Would clinicians consider a K+ of 5.1 mmol/l an emergency and treat it? Would clinicians continue to offer potassium lowering to people once they'd achieved normokalaemia?*

Availability of comparative data

No data for SZC vs standard care either direct or indirect

Evidence	Correction phase	Maintenance/extended phase
Intervention	• SZ-004 SZC for 48 hours • SZ-005 SZC for 24 to 72 hours	• SZ-004 SZC up to 28 days • SZ-005 SZC up to 52 weeks
Comparator	• No comparator in trials • Company did not present data for insulin-glucose because "these are administered earlier in the treatment pathway [than SZC] and have different mechanisms of action" • Company did not present data for calcium resonium because published evidence is not for dose used in UK	• Placebo (for up to 28 days) • No comparative data for days 29-365 • No comparative data presented for SZC vs. dietary modifications or SZC vs. reducing RAASi

- *Is the placebo group of ZS-004 generalisable to people who receive current standard care after initial correction of hyperkalaemia?*
- *(In absence of comparative data) is SZC expected to reduce serum K+ to a similar extent and in a similar timeframe to current treatments for correcting hyperkalaemia?*
- *Would clinicians abandon low K+ diets if a drug were available?*

Baseline characteristics in ZS-004 & ZS005

Characteristic	ZS-004 SZC 10 g (acute phase) (n=258)	ZS-005 Overall SZC group (n=751)
Age, mean (SD)	64.0 (12.7)	63.6 (13.03)
Male, n (%)	149 (57.8)	448 (59.7)
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. Majority of patients in ZS-005 were from the USA, Australia and South Africa. 10 people in ZS-005 from UK

ZS-005: restoring normal serum K+ acutely

majority of people had normal serum potassium after 2 day treatment

- Normal serum K+ defined as between 3.5 mmol/L and 5.0 mmol/L
- A primary outcome in ZS-005

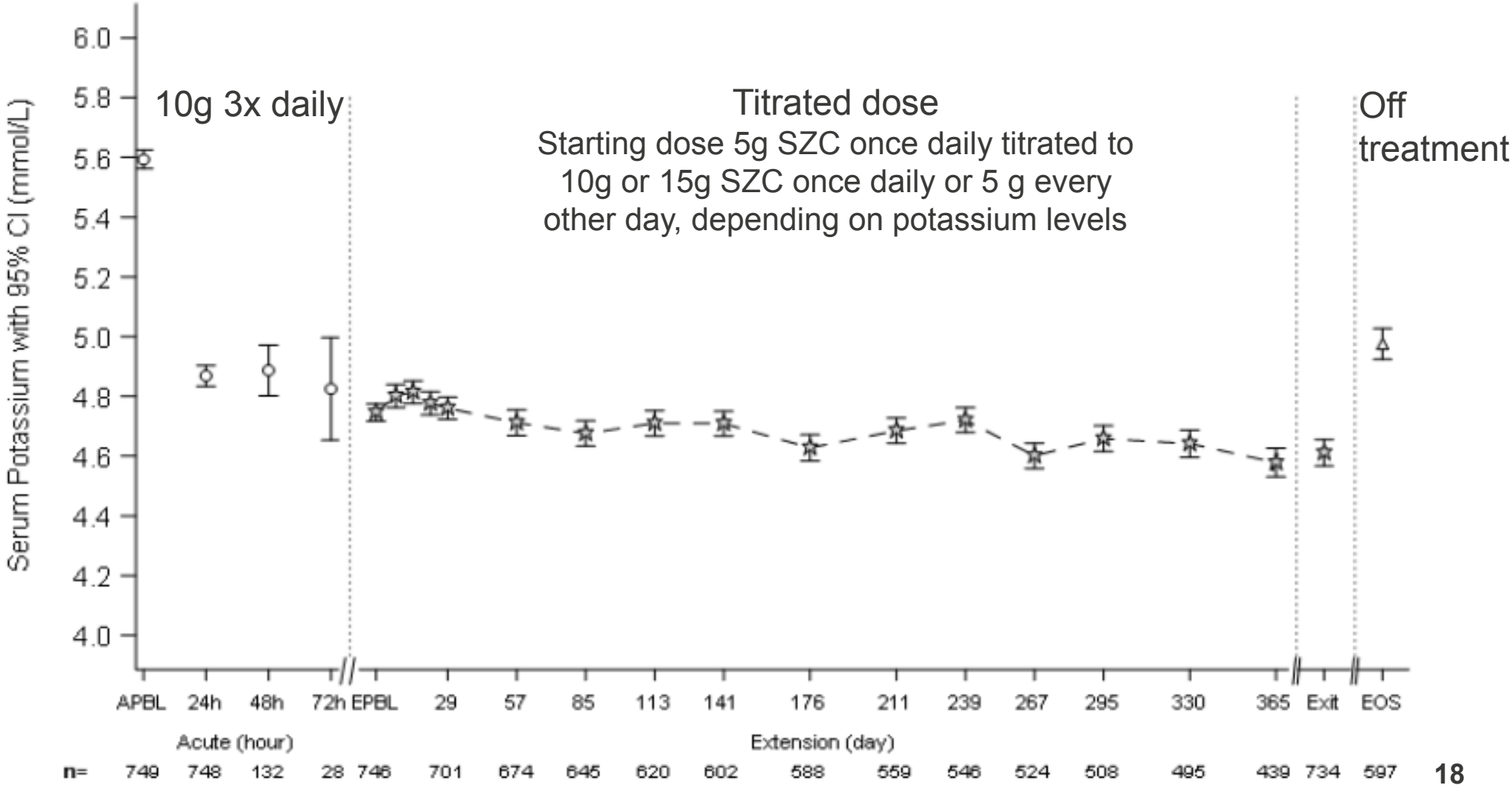
Acute phase ZS005	SZC 10 g 3 x daily (N=749)		
	Primary outcome definition of normal serum		
	Serum potassium 3.5–5.0 mmol/L inclusive		
	n/N	Proportion	95% CI
24 hours	494/748	0.66	0.63 to 0.69
48 hours	563/748	0.75	0.72 to 0.68
72 hours/last	583/748	0.78	0.75 to 0.81

- For comparison in ZS-004: proportion with normal serum potassium at:
  - 24 hrs: 66.1% (168/254)
  - 48 hrs: 88.0% (221/251)

This was a secondary outcome in that study

ZS-005 extended dosing phase: mean serum potassium over time

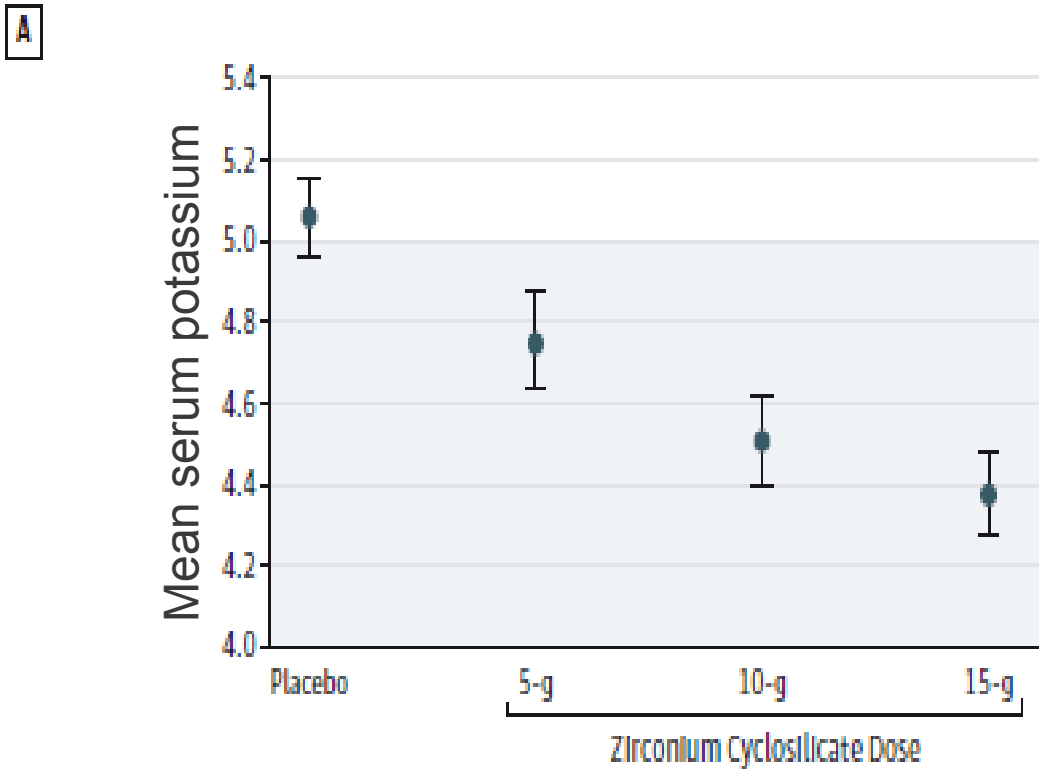
normal serum potassium maintained on SZC, increases when stop



ZS-004:mean serum potassium during maintenance phase study days 8-29

mean serum potassium statistically lower than placebo for each dose

Primary outcome ZS-004: mean serum potassium levels in randomised phase (days 8–29)



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

[redacted]

P ≤ 0.0001 for each dose, 15 g dose not in marketing authorisation

ZS-005 maintenance dosing phase: RAASi use

majority of people on RAASi continued taking same dose

Start of acute phase (n, %)		maintenance dosing phase (n, %)	
On RAASi	**********	Continued same dose	**********
		Increased dose	**********
		Decreased dose	**********
		Stopped	**********
Not on RAASi	**********	Started RAASi	**********

[redacted]

ERG overall conclusions on clinical effectiveness evidence

The clinical effectiveness evidence does not provide 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

[redacted]

Key issues: cost effectiveness

- Is the clinical evidence sufficient to populate a model?
- Should cost effectiveness be estimated separately for people with CHF and CKD?
- Is there evidence that SZC makes people live longer? Is there randomised evidence to show that lowering potassium in chronic hyperkalaemia extends survival?
- Acknowledging that people stop RAASi for reasons other than hyperkalaemia, are meta-analysis of trials of STARTING RAASi generalisable to people who STOP RAASi?
- If so, is the relevant comparator placebo or another antihypertensive?
- Are ERG estimates of 0.23 mmol/L or 0.1mmol/L higher serum K+ while taking RAASi appropriate?
- Company suggest that model overestimates treatment effect of standard care (because people in placebo arm of ZS004 had prior SZC) – if so, would a different trial design be better?
- Company and ERG have different preferred assumptions for: managing RAASi for people taking SZC, utility values for CKD health states, cost of managing RAASi and drug wastage. What does committee prefer?
- Is a 52 week time horizon in the acute setting appropriate?

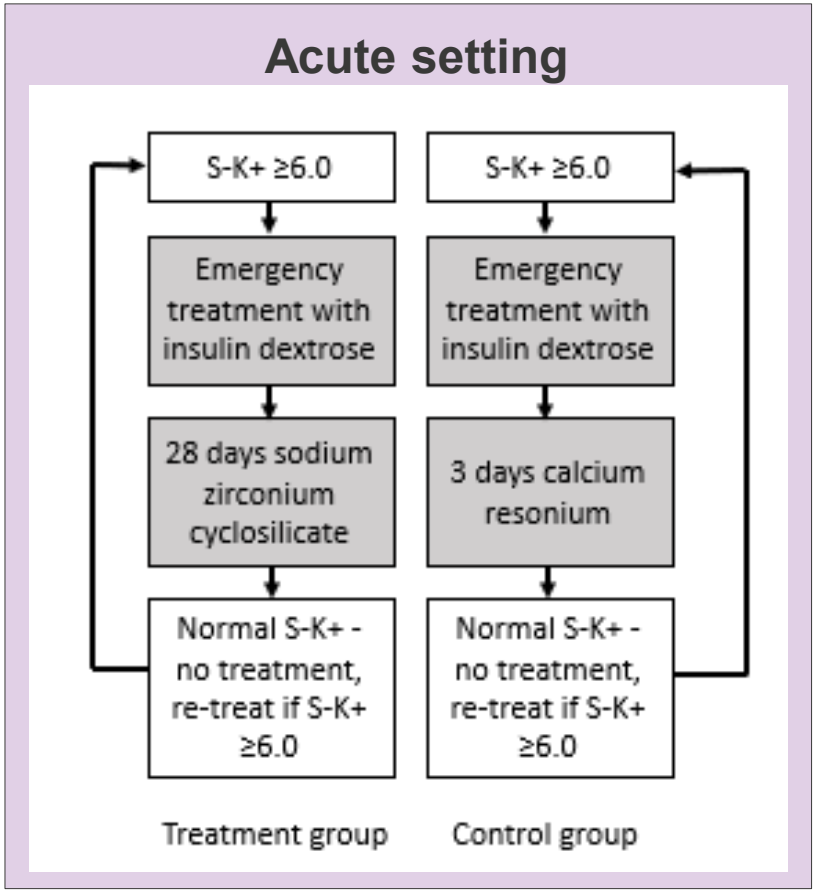
Company's modelling approach - overview

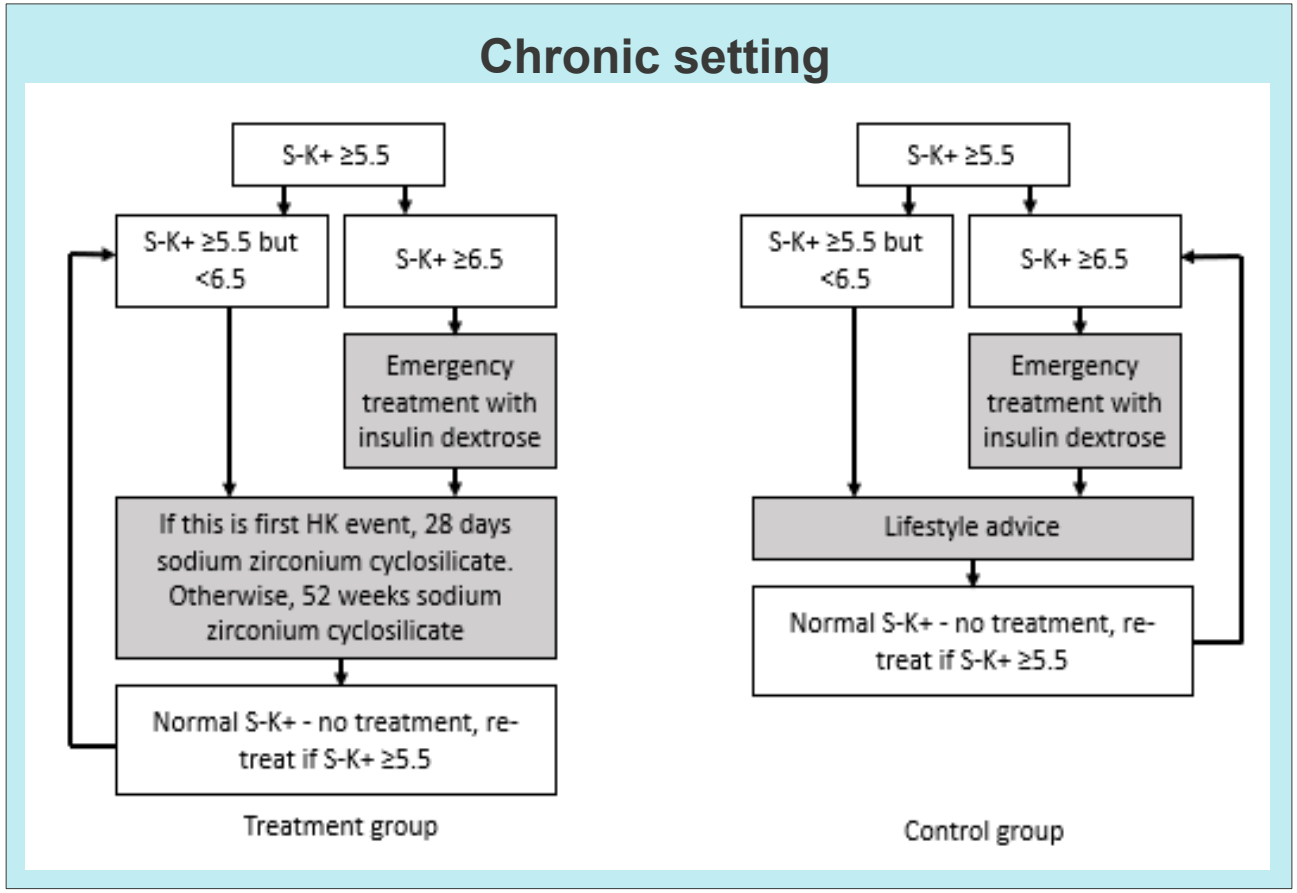
- Patient level simulation model. Rationale for this type of model:
  - clinical outcomes depend significantly on individual patient serum potassium levels
  - multiple co-existing and competing conditional risks of having an acute clinical event with hyperkalaemia
  - Markov approach would need unduly large number of health states
- Modelled population has either chronic kidney disease (pre-renal replacement therapy) or heart failure
- Acute setting hyperkalaemia (serum potassium ≥ 6.0 presenting in A&E) and chronic setting hyperkalaemia (serum potassium ≥ 5.5 presenting during routine follow up) modelled separately
  - treatment pathway and comparator (standard of care) differed in these scenarios
- Lifetime horizon used (80 years- maximum age in model 100 years). Max treatment duration (SZC or standard care) after initial correction of hyperkalaemia 28 days in acute setting, up to 1 year in chronic setting
- Cycle length in acute scenario (first 4 weeks) varies 1 day to 2 weeks, chronic management 28 days based on ZS-004 and ZS-005

[redacted]

Treatment pathway and comparators in model - acute and chronic setting scenarios

- Company presents cost effectiveness estimates for acute and chronic setting separately



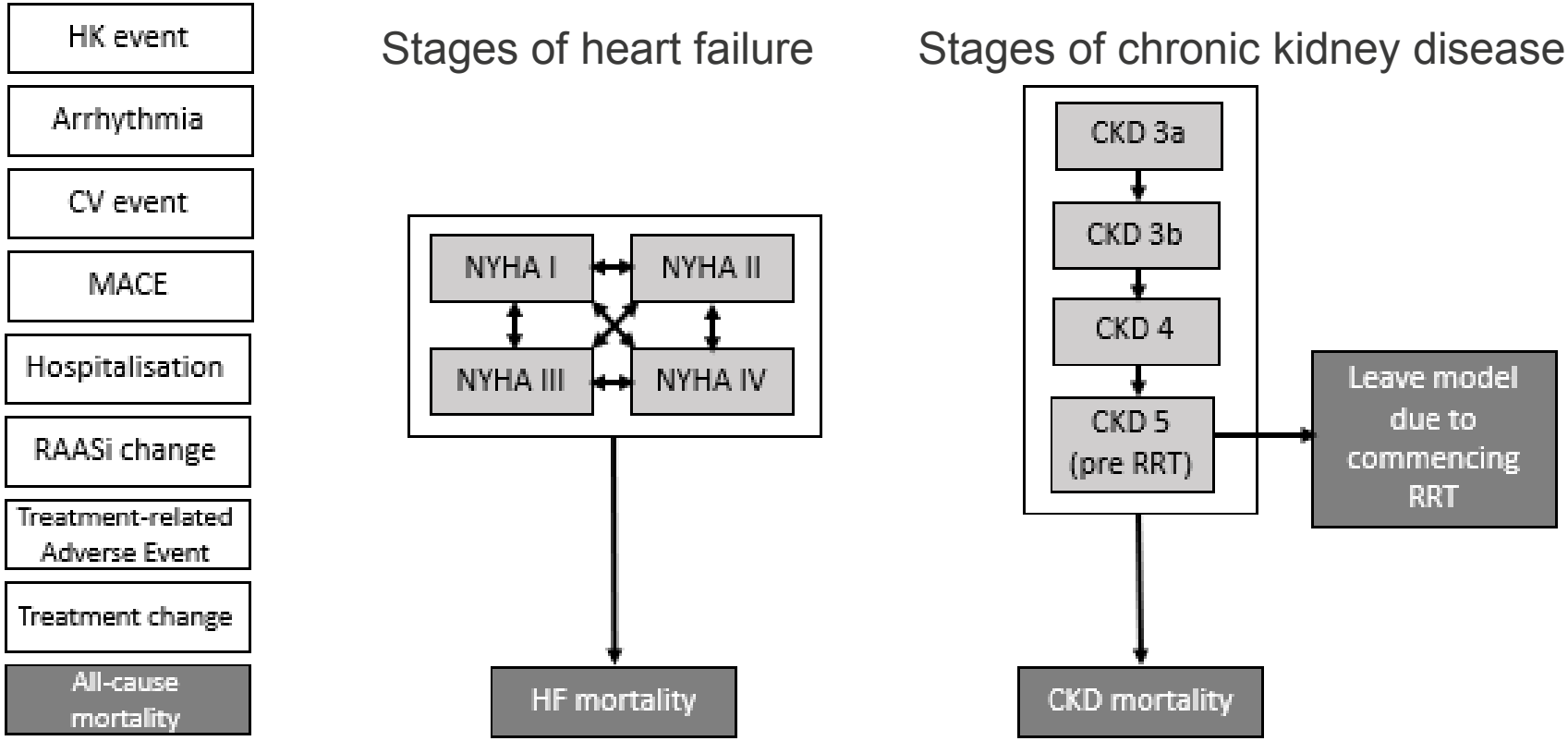


- Clinical advice to ERG: people with potassium >6.5 mmol/L and acutely unwell would be admitted for emergency treatment, but may have shorter hospital stay

⊙ *Would people treated in acute setting continue treatment in chronic setting? Should the cost effectiveness of SZC in chronic and acute setting be considered separately?*

Company's model structure

- Assumed that patients have heart failure or chronic kidney disease
- Takes into account disease progression of heart failure and chronic kidney disease
- Patients can experience non-fatal events (listed in white boxes)
- Patients exit model if die or are due to start renal replacement therapy (RRT)

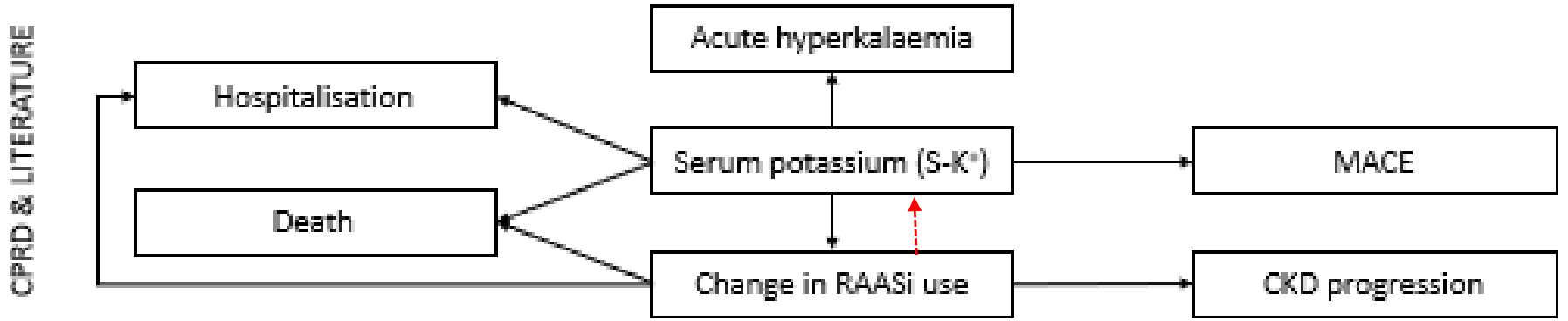


Abbreviations: HK, hyperkalaemia; CV, cardiovascular; MACE, Major Adverse Cardiac Event; RAASi, Renin Angiotensin Aldosterone System inhibitor; NYHA, New York Health Association; HF, heart failure; CKD chronic kidney disease; RRT, renal replacement therapy

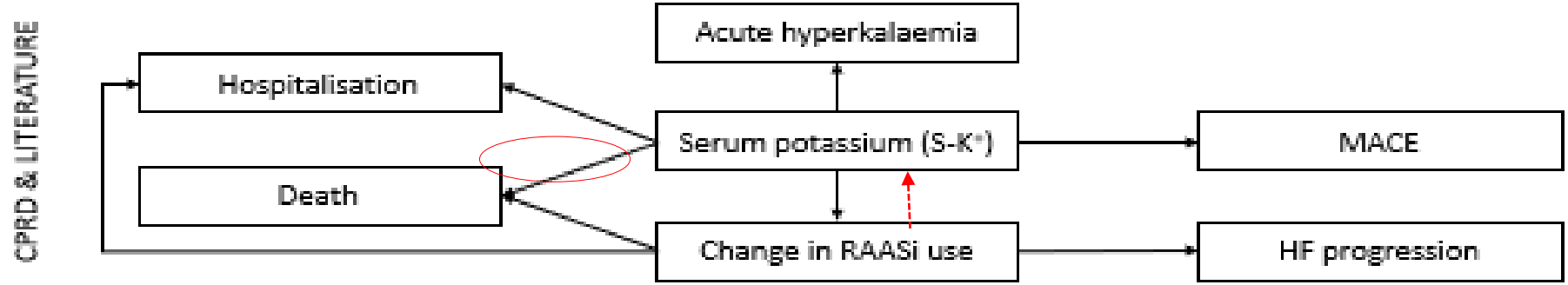
Serum potassium + changes in RAASi use are used to estimate clinical outcomes in model

- Risk equations for outcomes are based on data from literature
- Different risks of outcomes for people with chronic kidney disease and people with heart failure

People with Chronic Kidney Disease (CKD)



People with Heart Failure (HF)



ERG noted that the effect of change in RAASi use on serum potassium is not included in the model

ERG used different literature source for risk of death associated with serum potassium in people with heart failure

ERG's estimate of relationship between RAASi use and increased serum potassium

- ERG provide **2 estimates of the relationship between RAASi use and serum potassium**
  - **Increase of 0.23 mmol/L** based on increase associated with mineralocorticoid receptor antagonist (spironolactone) identified in a systematic review and meta analysis of RCTs in people with CKD n= 1581 (Ng et al., 2015). **This was the ERG's preferred estimate**
  - **Increase of 0.1 mmol/L** based on reported increases in serum potassium in clinical trials n=39 (Weir et al., 2010). These values were typically below 0.3 mmol/L for patients with CKD and between 0.1 and 0.3 mmol/L for patients with hyperkalaemia
- For both scenarios, the increase in serum potassium associated with sub-optimal RAASi use was 50% of with maximum RAASi use.
- Applied in model by decreasing serum potassium in people stopping RAASi

ERG alternative estimates for relationship between serum K+ and heart failure mortality

- Values for the risk of heart failure mortality based on people with hypertension. Clinical advice to the ERG was that this was not appropriate
- ERG alternative estimate of the relationship between serum K+ and heart failure mortality is based on 19,549 patients with chronic heart failure (Aldahl et al., 2017)
- In general the risk of mortality at serum potassium >5.1 mmol/L was **lower** in ERG estimates

S-K level	Company base case	ERG base case
<3.5	2.19	3.16
3.5 – 3.9	1.91	1.62
3.9 – 4.2	1.00	1.29
4.2 – 4.6	1.10	1.00
4.6 – 5.1	1.47	1.34
5.1 – 5.5	2.28	1.60
>5.5	6.60	3.31

⊙ *Are observational studies documenting an association between K+ and death sufficient to prove that LOWERING K+ makes people live longer?*

Modelled population

	Chronic kidney disease	Heart failure	Source
% modelled population	64%	36%	ZS005
(alternative estimated of CKD/HF split suggested by company for scenario analysis)	89%	11%	Horne et al 2017
Average age, years	64	65	ZS004/5
Sex, % female	37%	37%	
eGFR mL/min/1.73m^2	31.63	68.14	
Taking RAASi	36%	70%	ZS005
Baseline serum K+ acute setting*	≥ 6.0 mmol/L		Data from people meeting criteria in ZS004/5
Baseline serum K+ chronic setting*	≥ 5.5 mmol/L		

- *What is the evidence for the proportion of people with CKD and CHF? How do changing this proportions change cost effectiveness? Are RAASi more or less effective in each group?*
- *Should the cost effectiveness of people with CKD and CHF be considered separately?*

Clinical inputs: serum potassium levels

- Model simulates individual serum-potassium trajectories based on 1) mean serum potassium for average patient on SZC and standard care 2) variation in serum potassium over time in each modelled patient

mean serum potassium levels

- *No comparative data for correction phase: all people had SZC in trials. Does this overestimate treatment effect of standard care?*
- *ERG: reduction post 28 days modelling artefact? Company: reduction plausible, and scenario with no decrease after 28 days had minimal impact on cost effectiveness results*

Decision rules for discontinuing RAASi in the model (people receiving standard care)

Company base case: people receiving SZC do not stop RAASi in chronic setting

Serum potassium	RAASi use	Action	Rationale
≥ 6.0	On RAASi	Discontinue RAASi	Recommended in NICE clinical guideline 182
≥ 5.5 -6.0	On RAASi	20% patients discontinue RAASi 80% down-titrate	Clinical expert advice
any	Sub-max RAASi	Continue down titration	Assumption: more conservative than CG182, may reflect clinical practice better

People can return to max RAASi use in chronic setting; returns occur in 49.7% of eligible cycles based on a study of up-titration after stopping RAASi in people with CKD (Luo et al).

⊙ *company and ERG tested a scenario where people taking SZC who had serum potassium >6.0 mmol/L stopped RAASi for 12 weeks in chronic setting- does this reflect clinical practice*

[redacted]

Utility values: disease health states

- No health-related quality of life data collected in ZS-004/5 so utility values from literature
- Company and ERG prefer different sources of utility data for chronic kidney disease health states

Health state	Utility	Source	Type of data
NYHA I	0.855	Göhler et al (2009)	EQ-5D from eplerenone post-acute MI heart failure efficacy and survival study trial
NYHA II	0.771		
NYHA III	0.673		
NYHA IV	0.532		
CKD 3 a	0.870	Gorodetskaya et al (2005)	Time trade off survey of 205 people with CKD
CKD 3b	0.870		
CKD 4	0.850		
CKD 5 (pre-RRT)	0.850*		
ERG alternative estimates for chronic kidney disease (CKD) disease states			
CKD 3a	0.848	Gorodetskaya et al (2005)	HUI-3
CKD 3b	0.848		
CKD 4	0.696		
CKD 5 (pre-RRT)	0.684		
N.B. in response to its factual accuracy check of the ERG report the company introduced new data for CKD states based on EQ-5D (source: abstract only and unclear how identified ERG unable to validate). Values were 0.85, 0.85,0.81 and 0.74 for CKD 3a/b to 5 respectively			

⊙ *What are committee's preferred quality of life values for chronic kidney disease?*

Disutility values for adverse events

- Disutility values were applied for adverse events and hospitalisation. ERG did not comment on these values

Health state	No. cycles applied for	Utility	Source
Oedema	13 (1 year)	−0.0029	Sullivan et al.
Constipation	13 (1 year)	−0.0056	
Diarrhoea	13 (1 year)	−0.0008	
Nausea	13 (1 year)	−0.0037	Kristiansen et al.
Hypomagnesaemia	13 (1 year)	−0.0028	Nafees et al.
Anorexia	13 (1 year)	−0.0029	Sullivan et al.
Hypokalaemia	13 (1 year)	0.0000	Assumption – no study identified
Anaemia	13 (1 year)	−0.0015	Sullivan et al.
Urinary tract infection	13 (1 year)	−0.0004	Sullivan et al.
MACE event	1	−0.050	Palmer et al.
Hospitalisation	1	−0.024	Göhler et al.

⊙ *Is the assumption on disutility associated with hypokalaemia appropriate?*

[redacted]

Drug costs

- List price cost of sodium zirconium cyclosilicate currently confidential
- Company and ERG disagreed on drug wastage assumptions and the cost of changing RAASi dose

	Company assumption	ERG alternative assumption
SZC drug wastage	• SZC comes in packs of 3 sachets • Includes assumptions on wastage for first 28 days of treatment	Company wastage assumption + ERG costed 30 sachets for every 28 sachets prescribed in model
RAASi cost of changing dose	Max dose: £46 (CKD); £50 HF Suboptimal: £25 (CKD); £29 (HF) Cost of discontinuing: £481.48 Cost of up-titrating: £129.72 Cost of down-titration: £722.22	Assumed visit to change dose of RAASi treatment done as outpatient rather than 25% visits as inpatient Cost of discontinuing: £186.48 Cost of down-titration: £279.72

⊙ *What is committee's preferred assumptions on drug wastage and cost of changing RAASi treatment?*

[redacted]

Company deterministic base case results

- Company prefer combined CKD or HF population as base case (using estimates of proportion of people with hyperkalaemia with each underlying condition based on ZS005 trial population)
- Incremental cost effectiveness ratios lower in acute setting. Lower for heart failure than chronic kidney disease in chronic setting

Population	Incremental cost of SZC treatment	Incremental QALYs of SZC treatment	ICER (£/QALY)
Chronic Setting			
CKD or HF	£16,803	0.769	£21,849
CKD only	£14,623	0.577	£25,363
HF only	£9,722	0.726	£13,458
Acute setting			
CKD or HF	-£853	0.052	SZC dominates standard care (less costly, more effective)
CKD only	-£1027	0.037	
HF only	£393	0.053	£7,380

- ERG consider it inappropriate to combine these populations
- Probabilistic results similar, but ERG noted not all variables included in probabilistic sensitivity analysis

ERG exploratory base case summary

Scenario
Stop RAASi treatment for 12 weeks for patients taking SZC with serum potassium >6.0 mmol/L (*company assumption: RAASi treatment would not stop if taking SZC*)
RAASi treatment related to serum potassium levels (*company did not explicitly model this*) Stopping RAASi decreases serum potassium levels by: i) 0.23 mmol/L (ERG base case 1) (**ERG preferred**) ii) 0.1 mmol/L (ERG base case 2)
Different utility values for chronic kidney disease based on HUI-3 (*company used utility values based on time trade off survey*)
Alternative relationship between serum potassium levels and heart failure mortality (*company's based on people with hypertension, ERG's based on people with heart failure*)
Assume higher level of drug wastage associated with SZC treatment (*ERG assumed higher wastage after first month than company)*
Lower costs associated with RAASi dose changes (*company assumed some consultations to change RAASi dose done in an inpatient setting)*

[redacted]

ERG proposed a shorter time horizon (52 weeks) for acute setting base cases

- Company acute setting base case has a lifetime horizon, but does not model follow up in the chronic setting following multiple hyperkalaemia episodes
- ERG: people identified with hyperkalaemia in the acute setting would be followed up in the chronic setting following multiple episodes
- Suggest that using a short time horizon in acute setting (52 weeks), then assuming that the chronic setting cost effectiveness results apply to these people is valid
  - rationale: trial data is for people presenting in chronic setting only and modelling of acute setting patients based on a sample of people serum potassium >6.0 mmol/L at the start, but these concentrations decrease over time in the acute setting model and may reflect the characteristics of the chronic setting modelled population at the end of the 52 week time horizon

⊙ *What is the appropriate time horizon for the chronic and acute setting use of sodium zirconium cyclosilicate?*

[redacted]

ERG exploratory deterministic base case results

Scenario	Heart failure acute*	CKD acute*	Heart failure chronic	CKD chronic
Company base case (lifetime)	**£7,380**	SZC dominates	£13,458	£25,363
1) Stop RAASi if serum potassium ≥6.0 (both arms)	£10,263		£14,063	£27,056
2a) Increase in serum potassium with RAASi (0.23)	£51,652	£289,171	£19,012	£33,200
2b) As above but value (0.1)	£28,223	£2,627	£15,333	£28,851
3) HUI-3 utility values for CKD	-	SZC dominates	-	£30,537
4) Alternative risk between serum potassium and heart failure mortality	SZC dominates	-	£16,952	-
5) ERG assumptions on wastage	£12,098	SZC dominates	£14,329	£26,882
6) Lower costs for RAASi changes	£10,263		£14,301	£26,683
ERG base case 1 (assumption 2a)	**£100,093**	**£346,485**	£29,239	£46,936
ERG base case 2 (assumption 2b)	**£37,097**	**£28,760**	£23,296	£40,731
ERG combined population base case 1	£159,616		£37,983	

Incremental QALYs lower in ERG base case for acute and chronic settings (~50% lower in chronic setting; >95% lower in acute setting (note different time horizons)

ERG additional scenarios in response to company's factual accuracy check

Setting	Scenario	ICER around company base case		ICER around ERG base case 1	
Chronic		**Heart failure**	**Chronic kidney disease**	**Heart failure**	**Chronic kidney disease**
	Base case	£13,458	£25,363	£29,239	£46,936
	Company assumption: standard care has no treatment effect (n.b. ERG consider this optimistic and does not appear to be based on data)	£5,641	£4,532	£8,817	£15,877
	EQ-5D values for CKD identified by the company (n.b. ERG do not consider applying these to be valid)	Not applicable	£26,928	Not applicable	Not applied

- *Is it valid to assume that standard care has no treatment effect in chronic setting?*
- *Does applying this assumption cancel out bias in favour of SZC from excluding RAASi-potassium level association (in company base case)?*

[redacted]

Innovation: proposed benefits of sodium zirconium cyclosilicate (SZC)

Comments from the Royal College of Pathologists, Renal Association and company included:

- Company: represents a ‘step-change in the management of patients with HK’
- All agreed may allow people ‘to continue and optimise treatment on RAASi/MRA therapy’ although it was noted that the optimal management of RAASi in people with hyperkalaemia is not fully established
- Controls potassium levels ‘without the need to adopt a restrictive low-potassium diet’ (company). Renal Association suggested SZC would be used alongside diet restriction
- Renal Association and Royal College of Pathologists: may reduce unnecessary hospital admissions
- Company: ‘only potassium-binding agent with rapid onset of action (within 1 hour)’
- Renal Association: current potassium binding treatment with resonium is ineffective and poorly tolerated and has significant complications such as constipation, a major issue in chronic kidney disease.

[redacted]

End

Decision for part 2

Back up slides

- The following slides show the incremental costs and incremental QALYs for the ERG exploratory analyses. Total costs and QALYs are confidential and have not been shown

[redacted]

ERG exploratory deterministic base case results: CKD in acute setting

Scenario	Incremental life years	Incremental costs	Incremental QALYs	ICER
Company base case	**0.061**	**-£1,027**	**0.037**	SZC dominates
Company base case 52 weeks*	**0.002**	**-£256**	**0.002**	
1) Stop RAASi if serum potassium ≥ 6.0 both treatment arms	0.002	-£256	0.002	
2a) serum potassium decrease with stopping RAASi (0.23)	0.001	£195	0.001	£289,171
2b) As above but value (0.1)	0.001	£10	0.001	£2,627
3) HUI-3 utility values for CKD	0.002	-£256	0.001	SZC dominates
5) ERG assumptions on wastage	0.002	-£234	0.002	
6) Lower costs for RAASi changes	0.002	-£255	0.002	
ERG base case 1 (1, 2a, 3, 5 and 6)	**0.001**	**£204**	**0.001**	**£346,485**
ERG base case 2 (1, 2b, 3, 5 and 6)	**0.001**	**£25**	**0.001**	**£28,760**

[redacted] This is the company base case, but with a 52 week time horizon. In all of the acute setting analyses the ERG uses a 52 week time horizon

ERG exploratory deterministic base case results: heart failure in acute setting

Scenario	Incremental life years	Incremental costs	Incremental QALYs	ICER
Company base case lifetime	**0.103**	**£404**	**0.053**	**£7,380**
Company base case 52 weeks*	**0.016**	**£91**	**0.009**	**£10,263**
1) Stop RAASi if serum potassium ≥ 6.0 both treatment arms	0.016	£91	0.009	£10,263
2a) Increase in serum potassium with RAASi (0.23)	0.01	£289	0.005	£51,652
2b) As above but value (0.1)	0.013	£208	0.007	£28,223
4) Alternative risk between serum potassium and heart failure mortality	0.008	-£69	0.004	SZC dominates
5) ERG assumptions on wastage	0.016	£107	0.009	£12,098
6) Lower costs for RAASi changes	0.016	£91	0.009	£10,263
ERG base case 1 (1, 2a, 4, 5 and 6)	**0.004**	**£255**	**0.002**	**£100,093**
ERG base case 2 (1, 2b, 4, 5 and 6)	0.007	£130	0.003	£37,097

[redacted]

*This is the company base case, but with a 52 week time horizon
In all the acute setting analyses the ERG reduced the time horizon to 52 weeks

ERG exploratory deterministic base case results: CKD in chronic setting

Scenario	Incremental life years	Incremental costs	Incremental QALYs	ICER
Company base case	1.08	£14,624	0.576	£25,363
1) Stop RAASi if serum potassium ≥ 6.0 both treatment arms	1.01	£14,614	0.540	£27,056
2a) Increase in serum potassium with RAASi (0.23)	0.863	£15,045	0.453	£33,200
2b) As above but value (0.1)	0.978	£14,946	0.518	£28,851
3) HUI-3 utility values for CKD	1.08	£14,624	0.479	£30,537
5) ERG assumptions on wastage	1.08	£15,499	0.576	£26,882
6) Lower costs for RAASi changes	1.08	£15,289	0.576	£26,683
ERG base case 1 (1, 2a, 3, 5 and 6)	0.798	£16,299	0.347	£46,936
ERG base case 2 (1, 2b, 3, 5 and 6)	0.911	£16,266	0.400	£40,731

[redacted]

ERG exploratory deterministic base case results: heart failure in chronic setting

Scenario	Incremental life years	Incremental costs	Incremental QALYs	ICER
Company base case	**1.609**	£9,772	0.726	£13,458
1) Stop RAASi if serum potassium ≥ 6.0 both treatment arms	1.567	£9,943	0.707	£14,063
2a) Increase in serum potassium with RAASi (0.23)	1.096	£9,282	0.488	£19,012
2b) As above but value (0.1)	1.400	£9,626	0.628	£15,333
4) Alternative risk between serum potassium and heart failure mortality	1.666	£11,684	0.689	£16,952
5) ERG assumptions on wastage	1.609	£10,405	0.726	£14,329
6) Lower costs for RAASi changes	1.609	£10,384	0.726	£14,301
ERG base case 1 (1, 2a, 4, 5 and 6)	1.101	£13,112	0.449	£29,239
ERG base case 2 (1, 2b, 4, 5 and 6)	1.387	£13,284	0.570	£23,296

[redacted]

ERG additional scenarios around ERG exploratory base case

Setting	Scenario	Base case 1		Base case 2	
		HF	CKD	HF	CKD
Acute	**ERG Base case**	**£100,093**	**£346,485**	**£37,097**	**£28,760**
	Restart RAASi treatment allowed at 12 weeks (*company assume never restarted. Clinical advice to ERG if hyperkalaemia not life threatening RAASi could be restarted*)	£196,049	£140,264	£72,109	£44,566
Chronic	**ERG Base case**	**£29,239**	**£46,936**	**£23,296**	**£40,731**
	Lifetime SZC (*not max 12 months which was based on length of follow in trials. ERG clinical experts: life time SZC plausible if SZC efficacious)*	£30,668	£53,685	£25,026	£46,135
	Hospital stay independent of treatment (*not longer with standard care as assumed by company*)	£29,257	£46,965	£23,313	£40,761

[redacted]