NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Sodium zirconium cyclosilicate for treating hyperkalaemia [ID1293]

The following documents are made available to the consultees and commentators:

1. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - British Society for Hearth Failure
   - Pumping Marvellous
   - Renal Association

2. **Comments on the Appraisal Consultation Document received through the NICE website**

3. **Appendix of new evidence –** submitted by AstraZeneca

4. **Evidence Review Group critique of company response** – prepared by the School of Health and Related Research (ScHARR)
   - Critique of the company's response to the Appraisal Consultation Document
   - Addendum

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

NICE National Institute for Health and Care Excellence

Sodium zirconium cyclosilicate for treating hyperkalaemia [ID1293]

Consultation on the appraisal consultation document – deadline for comments 5pm on 19/11/2018 **email:** TACommB@nice.org.uk/NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Society for Heart Failure (BSH)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted], on behalf of British Society for Heart Failure Board

Comment number	Comments
	Insert each comment in a new row.

Please return to: **TACommB@nice.org.uk**/NICE DOCS

NICE National Institute for Health and Care Excellence

Sodium zirconium cyclosilicate for treating hyperkalaemia [ID1293]

Consultation on the appraisal consultation document – deadline for comments 5pm on 19/11/2018 **email:** TACommB@nice.org.uk/NICE DOCS

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	**Background and general comments:** Patients with heart failure and reduced ejection fraction (HFREF) derive major prognostic benefit from with angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), sacubitril/valsartan, beta blockers and mineralocorticoid receptor antagonists (MRAs) [data summarised in ESC guidelines, 1]. For many of these drugs, the benefit is additive. For example, the combination of sacubitril/valsartan, beta blocker and MRA results in a reduction of all-cause mortality with a hazard ratio of 0.37 against placebo [2]. Renin angiotensin aldosterone inhibitors (RAASi) may lead onto hyperkalaemia, in particular in patients with co-existent chronic kidney disease (CKD). In some instances this may result in clinicians stopping or reducing doses of one or more RAASi. The British Society for Heart Failure (BSH) feel that the management of hyperkalaemia during co-existent RAASi use should be directed according to the strength of indication for the RAASi. That is when the drugs have clear prognostic benefit (i.e. HFREF or post MI left ventricular systolic dysfunction or CKD with albuminuria) every effort should be made to ensure their continuation at highest possible dose. This is very different to when they are used to treat hypertension – here many other good alternatives exist and switching the drug to a different class seems very appropriate, if problems such as moderate or severe hyperkalaemia ensue. Similarly if a patient has heart failure with preserved ejection fraction (HFPEF) RAASi have not been shown to be of prognostic benefit. The BSH, Renal Association (RA) and Think Kidneys have published guidelines on the management of changes in renal function and potassium on initiation and up titration of RAASi in patients with heart failure [3]. 1. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). *Eur Heart J* 2016;**37:**2129-2200Burnett H, Earley A, Voors AA, Senni M, McMurray JJ, Deschaseaux C, Cope S. 2. Thirty years of evidence on the efficacy of drug treatments for chronic heart failure with reduced ejection fraction: a network meta-analysis. *Circ Heart Fail* 2017;10: pii: e003529 3. https://tinyurl.com/y7yrlk69
2	The NICE summary documents are confusing and mix multiple conditions like heart failure, CKD and hypertension and the acute and post-acute/chronic management of hyperkalaemia. It will be almost impossible to make one single recommendation for all of these things. As such the BSH agree that there should not be a very broad indications such as 'hyperkalaemia in adults' for these drugs. However, we feel that availability of novel drugs to lower potassium might be of clinical value in the management of a very select cohort patients with HFREF who develop hyperkalaemia in order to facilitate the use of life prolonging drugs (i.e. RAASi) and to prevent development of hyperkalaemia (e.g. potassium

Sodium zirconium cyclosilicate for treating hyperkalaemia [ID1293]

Consultation on the appraisal consultation document – deadline for comments 5pm on 19/11/2018 **email:** TACommB@nice.org.uk/NICE DOCS

	>6.0mmol/l). It is uncertain as to how many patients this might effect, but we feel the numbers will be very small. Some patients who develop hyperkalaemia will have other issues such as worsening renal function and/or hypotension, which themselves might limit continued prescribing of RAASi. In summary, by not approving these novel treatments in any clinical scenario patient care may suffer. A suggestion would be restricted use for high risk HFREF patients under secondary care teams (this would for example include compassionate use in advanced heart failure patients with multiple previous admissions who have needed to stop a RAASi due to isolated hyperkalaemia). The BSH feel unable to comment on potential use in patients with severe/end stage renal disease.
3	Throughout the document reference is made to the committee and clinical expert highlighting that most clinicians would only treat hyperkalaemia unless the value was 6 mmol/l or more. This is not correct and the BSH feel that this over simplifies the complexity of management of hyperkalaemia. The document mentions that in this case treatment would be as an emergency in secondary care with agents such as insulin/dextrose, calcium gluconate and calcium resonium. It does highlight that RAASi would be stopped or reduced. The BSH feel strongly that in routine clinical practice many clinicians do intervene or 'treat' at potassium values much lower than 6mmol/l. Whilst this may not involve prescription of additional therapy it is commonly a *reduction or cessation* of ongoing treatment with RAASi. For patients with HFREF, post MI left ventricular systolic dysfunction or CKD with albuminuria this has major adverse implications. 'Section titled: People would welcome an alternative to stopping RAASi'. The BSH agree with this statement but are concerned that the focus of the document is on patients with hypertension and is merely focusing on RAASi as anti-hypertensive agents. They are not just blood pressure lowering drugs - in HFREF, for example, they are disease modifying drugs. See below extract taken from page 7 below: ''The committee concluded that patients and clinicians were keen for new treatments that would allow them to continue to take RAAS inhibitors, but that the harms and benefits of stopping a RAAS inhibitor and **switching to an alternative blood pressure lowering treatment** would need to be taken into account.''
4	Whilst the BSH agrees that the acute management of severe hyperkalaemia primarily involves treatment such as calcium gluconate, insulin/dextrose and calcium resonium, there may be occasions when novel potassium binders compliment/add to current options. For example, if calcium resonium was not tolerated. Patients often require emergency admission when severe hyperkalaemia is diagnosed; the use of novel potassium binders may allow the patient to be managed safely at home preventing an unnecessary hospitalisation.
5	In summary, the BSH would like NICE to consider use of the new potassium binders for restricted use by secondary care clinicians involved in the management of patients with prognostic indication for RAASi. The BSH are concerned that the NICE evaluation only focuses on the acute presentations with very high potassium levels and fails to consider the downstream adverse effects on patients, associated healthcare costs and adverse outcomes if RAASi are withheld/reduced. The BSH feel unable to comment on potential use in patients with severe/end stage renal disease.
6	The BSH would also highlight that more research is needed, even in the shorter-term with soft heart failure outcomes (e.g. symptoms, QoL, BNP etc). If some use is approved, then the BSH would welcome the prospective collection of data relating to the practicality of use of these medications (e.g. drug interactions and adherence).

NICE National Institute for Health and Care Excellence

Sodium zirconium cyclosilicate for treating hyperkalaemia [ID1293]

Consultation on the appraisal consultation document – deadline for comments 5pm on 19/11/2018 **email:** TACommB@nice.org.uk/NICE DOCS

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Sodium zirconium cyclosilicate for treating hyperkalaemia [ID1293]

Consultation on the appraisal consultation document – deadline for comments 5pm on 19/11/2018 **email:** TACommB@nice.org.uk/NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	The Pumping Marvellous Foundation
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No links**
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

Please return to: **TACommB@nice.org.uk**/NICE DOCS

NICE National Institute for Health and Care Excellence

Sodium zirconium cyclosilicate for treating hyperkalaemia [ID1293]

Consultation on the appraisal consultation document – deadline for comments 5pm on 19/11/2018 **email:** TACommB@nice.org.uk/NICE DOCS

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	As the patient expert at the committee meeting, I can comment that the committee did not consider or listen to the conversation around why controlling and managing hyperkalaemia in patients with heart failure is important. I blame not only the committee for not having any representation from the clinical heart failure community but also the company for not pressing the case on the needs of the heart failure patient.
2	I am concerned that the meeting didn't take into account the needs of patients with heart failure where their needs are different from those without heart failure eg CKD patients.
3	I believe and witnessed the committee either miss the point of controlling and managing hyperkalaemia in heart failure where the focus was on CKD patients. Heart failure patients have additional needs. People with heart failure always have a need for their kidney function to be checked due to the evidence based triple therapy as indicated in the NICE Chronic Heart Failure Guidelines in Adults 2018. The core medication recommended by NICE includes ACE/ARB and MRA treatments which are considered to increase the likelihood of hyperkalaemia therefore the management of hyperkalaemia helps heart failure patients stay on prognostically significant cost-effective medication as recommended in the current NICE guidelines.
4	I know the committee missed the point as to the value of managing hyperkalaemia and its downstream effect on cost effective pharmacological management of heart failure. The committee was focussed on episodic management of hyperkalaemia in CKD specific patients.
5	My feeling was that the committee missed the point. The value of Sodium zirconium cyclosilicate to people with heart failure is not managing episodes, it is managing their condition to ensure they maintain their triple therapy through the rollercoaster of managing their prescribing levels. As indicated in the NICE Chronic Heart Failure Guidelines 2018 patients MDT's managing the prescribing regime with an aim to preventing patients being taken off life saving drugs.
6	Whether or not Sodium zirconium cyclosilicate has a prognostic value it would ensure people with heart failure maintain their triple therapy drugs if affected by hyperkalaemia which do have significant evidence around their prognostic value and cost effectiveness. This point clearly backups the argument that the committee didn't look or consider the value of Sodium zirconium cyclosilicate to people with heart failure.
7	It is clear that NICE didn't assess the cost effectiveness on treating heart failure patients with Sodium zirconium cyclosilicate as the downstream effects were not considered as mentioned already. A patient with heart failure could be said to be more cost effective to the system if managed with triple therapy than one who was not where there ACE/ARD and or MRA was stopped due to Hyperkalaemia.
8	Sodium zirconium cyclosilicate is innovative from the heart failure perspective as it enables people who depend on triple therapy as mentioned above to remain on optimal therapy thus having a prognostic benefit and better QOL. Anecdotally it is not diet that puts people with heart failure into a hyperkaliaemic situation it is the ADE/ARB/ARNI and MRA's they are prescribed.
9	It was a significant failure on behalf of NICE to not include representation from the British Society of Heart Failure or clinical expert with a sub specialty of Heart Failure. In my opinion this dramatically effected the clinical equipoise of the decision that has been made and potentially brings into question the credibility of that decision.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please return to: **TACommB@nice.org.uk**/NICE DOCS

NICE National Institute for Health and Care Excellence

Sodium zirconium cyclosilicate for treating hyperkalaemia [ID1293]

Consultation on the appraisal consultation document – deadline for comments 5pm on 19/11/2018 **email:** TACommB@nice.org.uk/NICE DOCS

- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Sodium zirconium cyclosilicate for treating hyperkalaemia [ID1293]

Consultation on the appraisal consultation document – deadline for comments 5pm on 19/11/2018 **email:** TACommB@nice.org.uk/NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[Renal Association]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**No new disclosures from last submission**] Was present as expert at NICE Meeting during review of drugs – therefore heard all comments during the open meeting
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

Please return to: **TACommB@nice.org.uk**/NICE DOCS

NICE National Institute for Health and Care Excellence

Sodium zirconium cyclosilicate for treating hyperkalaemia [ID1293]

Consultation on the appraisal consultation document – deadline for comments 5pm on 19/11/2018 **email:** TACommB@nice.org.uk/NICE DOCS

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that by not approving these novel treatments, at least with restrictions, this will limit optimal patient care and restrict clinicians from treating a cohort of patients with difficult to control potassium values, leading to premature dialysis, serious morbidity, unnecessary hospitalisation and possible mortality.
2	We feel that the new potassium binders have a role in facilitating safer use of renin angiotensin blockers (ie ACE inhibitors (ACE-I) or Angiotensin receptor blockers (ARB)) in some patients with CKD and/or cardiac failure. These agents are proven to be of definite clinical benefit in both conditions but can lead to hyperkalaemia; clinicians would choose to use potassium binders at [potassium] > 5.5 mmol/l to prevent [potassium] reaching 6 mmol/l and above . In both patient groups there are many occasions where renin angiotensin blockade has to be reduced or terminated due to hyperkalaemia, leading to increased patient risk.
3	We are concerned that there may have been some misunderstanding concerning the nature of patients suitable for treatment with the new potassium binders. These agents are not intended for acute management of patients with [potassium] > 6 mmol/l. However, they would provide treatment options, together with dietary restriction, that are currently not available after acute treatment of hyperkalaemia in order to prevent recurrent hyperkalaemia and to facilitate safer use of ACE-I and ARB, necessary treatments for patients with CKD and/or heart failure.
4	We feel that the NICE panel should recognise the importance of the many recurrent and unnecessary hospitalisations that are associated with hyperkalaemia in patients with CKD and/or heart failure. These are associated with major cost, morbidity and mortality. The new potassium binders appear to have the capacity to reduce this burden.
5	Calcium resonium has been available as a potassium binder for decades but most patients suffer gastrointestinal side effects; intestinal necrosis is a very serious but rare complication. We feel that NICE should recommend the use of the novel potassium binders as an alternative for calcium resonium therapy, which remains in guidelines.
6	In summary, we would like to see the NICE panel consider permitting use of the new potassium binders for restricted use and prescription by clinicians managing patients with CKD and/or heart failure in a secondary care setting. It is important that this therapeutic option gains real world experience in the UK such that clinicians can establish the use of these agents in a group of patients with multiple comorbidities and limited quality of life until further data becomes available to extend their use to other groups of patients.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or

Sodium zirconium cyclosilicate for treating hyperkalaemia [ID1293]

Consultation on the appraisal consultation document – deadline for comments 5pm on 19/11/2018 **email:** TACommB@nice.org.uk/NICE DOCS

the person could be identified.

- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	Consultant Nephrologist
Organisation	
Location	England
Conflict	Sponsored to travel to ASN meeting 2017 by Astra Zeneca
Notes	

Comments on individual sections of the ACD:

The consultation document has missed the main point about having potassium lowering agents, which is to allow continuation of RAAS inhibition in patients who have heart failure and hyperkalaemia, and will benefit from continuation of this therapy. This is not a narrow population as mentioned in 3.6 but likely to be the majority of cases who would be suitable for sodium zirconium cyclosilicate. General practitioners are likely to stop RAAS therapy when the potassium rises above 6mmol/l with subsequent inadequate treatment of heart failure. Whilst alternative antihypertensive medication may be used in patients with CKD, the benefits of RAAS inhibition specifically in heart failure are well established and alternatives have not shown similar benefit.

There are a small number of patients who have advanced stage G5 CKD, some on dialysis, who may also benefit by using sodium zirconium cyclosilcate. These are patients who have either had an intercurrent illness with hyperkalaemia, or established dialysis patients who have lost their vascular access. Many of these patients do not need to have urgent dialysis if the potassium level is safe (and fluid balance satisfactory). However, currently they may get admitted and have temporary vascular access for treatment of hyperkalaemia alone. Potassium lowering agents is may completely abrogate this need and avoid both temporary vascular access and admission. This is a likely to reduce risk to the patient and save money.

It is impossible to know whether sodium zirconium cyclosilicate alone prolongs survival as the aim is to lower hyperkalaemia in order to proceed to other therapy (restart RAAS inhibition) which has been established to prolong survival.

Name	[redacted]
Role	NHS Professional
Other role	Consultant Cardiologist - Professor of Cardiology (Hons)
Organisation	
Location	England
Conflict	
Notes	

Comments on individual sections of the ACD:

The comment on the effect of sodium zirconium on quality of life and life expectancy does not take into account that other drugs for the treatment of hyperkalaemia in use in the UK do not have any impact on either quality of life or survival
"In patients with cardiovascular disease K levels >5 mol/L are associated with

increased mortality. Most often patients presenting with hyperkalaemia receiving life saving medications like ACEi and MRAs have their therapies stopped. Despite being recommended for use, RAASi drugs are unfortunately seldom re-instated following an episode of hyperkalaemia at or after discharge even if a different clear precipitating cause of hyperkalaemia was detected and eliminated. The most common clinical scenario is that doses of RAASi are reduced, or they are simply discontinued; this is particularly true for MRAs. Although RAASi dose reduction or discontinuation may reduce the risk of reoccurrence of hyperkalaemia, discontinuation of RAASi is associated with an increased risk of worsening of the underlying cardiovascular condition and mortality.
"

"The statement:
""The clinical expert explained that people with normal serum potassium levels after hyperkalaemia has initially been corrected do not have maintenance treatment with a potassium-lowering drug in current clinical practice. This may be because potassium-binding treatments such as calcium resonium are poorly tolerated.""

supports the unmet medical need for a chronic K lowering therapy devoid of significant side effects"
"The committee statement:
""It was unclear whether the benefits of starting RAAS inhibitors on survival and lower progression of chronic kidney disease (that had been assessed in the network meta-analyses of trials) were the same as the risks of stopping RAAS inhibitors to manage serum potassium levels.""

is not supported by the evidence that suggest that stopping or using sub-optimal RAASi doses is associated with increased mortality in the general population of patients with cardiovascular disease, in patients with chronic kidney disease and in those with heart failure. Epstein M et al Am J Managed Care 2015; 21: s212-s220

However, the committee comment:
The committee concluded that the company had not proven that treatment with sodium zirconium cyclosilicate prolongs survival.
is fully endorsed "
"In its assessment on the risk/benefit of zirconium cyclosilicate, the committee may wish to consider the expert opinion of the Working Group on Pharmacotherapy of the European Society of Cardiology:
Rosano GMC, Tamargo J, Kjeldsen KP, Lainscak M, Agewall S, Anker SD, Ceconi C,
Coats AJS, Drexel H, Filippatos G, Kaski JC, Lund L, Niessner A, Ponikowski P, Savarese G, Schmidt TA, Seferovic P, Wassmann S, Walther T, Lewis BS. Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with renin angiotensin aldosterone system inhibitors: coordinated by the Working Group on Cardiovascular Pharmacotherapy of the European Society of Cardiology. Eur Heart J Cardiovasc Pharmacother. 2018 Jul 1;4(3):180-188. "

Name	[redacted]
Role	NHS Professional
Other role	Consultant Cardiologist - Professor of Cardiology (Hons)
Organisation	

Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Although Sodium zirconium cyclosilicate may not prolong life or improve quality of life directly, its use to lower serum potassium levels in a subgroup of patients with advanced CKD particularly those with diabetes and a high cardiovascular risk will allow the continued use of medications like ACE Inhibitors and ARBs which in turn have a strong evidence base for prolonging life.	

NICE National Institute for Health and Care Excellence

Sodium zirconium cyclosilicate for treating hyperkalaemia [ID1293]

Consultation on the appraisal consultation document – deadline for comments
5pm on 19/11/2018 **email:** TACommB@nice.org.uk/NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent	**AstraZeneca**
Disclosure	**None**
Name of commentator person completing form:	**Daniel Squirrell**

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Due to the technical nature of this response including tables, and figures, please see the response below.

Dear Appraisal Committee Members,

AstraZeneca welcomes the opportunity to comment on this Appraisal Consultation Document (ACD), and kindly ask the Committee to reconsider the recommendation published in the ACD.

To provide additional context to the response, AstraZeneca would like to outline the full extent of the unmet need of chronic kidney disease (CKD) and heart failure (HF) patients with hyperkalaemia (HK), to supplement the unmet need section in the ACD. A summary of the key uncertainties raised by the Committee and how each of these has been addressed can be found in the executive summary, and in Sections 1–6.

Hyperkalaemia is associated with an increased risk of major adverse cardiovascular events (MACE), hospitalisation and mortality, and can be a life-threatening condition

HK is associated with an increase in morbidity and mortality in patients with chronically elevated serum potassium (S-K), particularly when S-K increases ≥5.5 mmol/L; and can be immediately life-threatening due to the associated risks of conduction disease and cardiac arrhythmias.[1-10] The need to optimise treatment of HK in the emergency setting (i.e. in accident ann emergeny [A&E] / acute medical unit [AMU]) was recently highlighted in an NHS Improvement Patient Safety Alert.[11] Due to their underlying disease, patients with CKD or HF are at a higher risk of HK: approximately 40–50% of advanced CKD patients and 30% of HF patients have HK.[12,13] This risk is further increased due to Renin-Angiotensin-Aldosterone System inhibitors (RAASi) therapy, which is associated with elevated S-K levels (see below).[4,5,14-18]

In the chronic management setting, there is compelling evidence consisting of 27 interventional and observational studies, identified systematically, across several different comorbid populations and geographies on the association of high S-K with poor clinical outcomes (see Section 3). The wealth of evidence includes data from an RCT in HF patients[19] and a UK CPRD real-world study based on 191,964 CKD patients in the UK,[20] that demonstrate the association between HK and adverse clinical outcomes, including MACE, hospitalisation and mortality (see Section 3). This relationship has also been shown in the study by Nunez et al. 2018, which demonstrated that HK patients who *reduced* their S-K to the normal range had improved survival outcomes compared to HK patients who remained hyperkalaemic.[21]

RAASi therapy is an essential component of the management of patients with HF and CKD

The important cardio-renal protective role of RAASi therapy in the treatment of HF and CKD is described in clinical guidelines by NICE and the European Society of Cardiology (ESC), and consensus statements, by the ESC and Think Kidney, the Renal Association and the British Society for Heart Failure.[22-24] RAASi therapy is a cornerstone treatment for patients with HF or CKD due to the cardio-renal protective effects which delay disease progression, and reduce mortality, cardiovascular (CV) events, and hospitalisation (see Section 4).[23,25-29]

Current treatment options for HK are limited, and down-titration or discontinuation of RAASi therapy is common; meaning that patients lose the important cardio-renal protective effects

In the outpatient setting (i.e. those patients under the care of Cardiologists or Nephrologists), treatment options are limited, with guidelines recommending a combination of down-titration and/or discontinuation of RAASi therapy for the management of HK. In patients with advanced CKD, low-potassium diets are occasionally recommended (see NICE CG182), but patients typically have poor adherence and the diet is viewed as unhealthy (see Section 2.1.2).[30,31] In emergency admissions (i.e. patients treated in A&E or AMU), the Renal Association guidelines recommend that patients are treated when S-K ≥6.0 mmol/L with IV insulin-glucose ± salbutamol as temporising agents to normalise the S-K and to discontinue RAASi therapy.[32] However, insulin-dextrose are temporising agents to temporarily move potassium into the cells, and patients typically require repeat treatment.

Therefore, due to the lack of alternative treatment options to manage HK, Cardiologists and Nephrologists often do not have a choice but to down-titrate or discontinue RAASi therapy when

patients' S-K level elevate,[16,33-35] which means that patients forego the cardio-renal benefits of RAASi therapy (see Section 4).[36-39] In the UK, it is estimated that 50% of patients down-titrate their RAASi therapy following their first HK event.[40]

Furthermore, despite being recommended for use, RAASi therapy is unfortunately seldom re-instated following an episode of HK at or after discharge even if a clear precipitating cause of HK was detected and eliminated, which in turn may further exacerbate the loss of cardio-renal protection from RAASi therapy.[28,41] Clinical expert opinion survey,[42] published literature,[43-46] and submissions from professional organisations in advance of the first appraisal Committee meeting[47] unanimously consider HK to be a barrier to prescribing and optimising RAASi therapies in CKD and HF patients. This position was further supported by clinicians from across specialties during the consultation period.[30]

We have amended our positioning of SZC for CKD patients in the outpatient setting to better reflect NHS clinical practice. We ask for a recommendation of initiation of SZC treatment when patients with CKD have S-K ≥6.0 mmol rather than ≥5.5 (in the outpatient setting).

Expert opinion from clinicians across the UK and specialties (including A&E/AMU, Cardiology, Nephrology), support the adherence to published guidelines.[42] In particular, Nephrologists and Cardiologists indicate that HK management in patients with CKD and HF in the outpatient setting is currently initiated when S-K ≥6.0 mmol/L and S-K ≥5.5 mmol/L, respectively.

Given this, and the clinical advice received by the Committee, we have amended the positioning of SZC so that patients with CKD are treated when S-K increases ≥6.0 mmol/L rather than ≥5.5 mmol/L in the outpatient setting.[42]

SZC is a step change in HK therapy, providing a well-tolerated, rapid and sustained lowering of serum potassium, and enables simultaneous essential RAASi therapy in patients with CKD and HF. This has clinical value through associated reductions in the morbidity and mortality risks of chronic hyperkalaemia, whilst enabling the simultaneous cardio-renal protective effects of RAASi.

The need for a treatment option that avoids the need to down-titrate or discontinue RAASi therapy in CKD and HF patients is clearly recognised by clinicians, a consensus statement from the ESC and submissions from professional organisations in advance of the first appraisal Committee meeting,[28,47] all reinforcing the limitations associated with current treatment options (see above).[28,31,42] This need was further demonstrated by clinicians during the consultation period who highlighted that RAASi therapies are associated with long-term outcomes, and that patients can be excluded from optimising their RAASi therapy due to the risk of HK. It was also recognised that RAASi therapies are prescribed due to their proven cardio-renal protective effects, and not just the blood-pressure lowering properties. Therefore, it would not be appropriate to suggest switching from a RAASi therapy to another anti-hypertensive therapy.[30]

SZC is a potassium binder, which is viewed as a step-change in the management of HK; offering an alternative to down-titration/discontinuation of RAASi therapy whilst maintaining normokalaemia.[28,47] This allows patients to continue to accrue the cardio-renal benefits of RAASi therapy whilst reducing the risks associated with HK. Potassium lowering therapies, including SZC, is recommended by the ESC consensus statement in patients to allow continued RAASi therapy.[28]

The efficacy and safety of SZC was established in 3 pivotal clinical trials in patients with HK; ZS-003, ZS-004 and ZS-005.[i] The efficacy of SZC in correcting HK and maintaining normokalaemia has been shown, independently of the severity of HK:

Subgroup analyses from study ZS-004 and ZS-005 demonstrates that the majority ([redacted]%) of patients initiating SZC treatment at S-K ≥5.5 or ≥6.0 mmol/L respond to treatment, defined as S-K reductions

[i] Additional evidence was also provided by the ZS-002 placebo-controlled trials, and the ZS-004E open-label extension trial.

below the threshold at which treatment would be initiated in UK clinical practice. The majority of those who respond remain within clinically acceptable ranges with maintenance treatment, and few patients become hypokalaemic or fail to respond (see Section □).

AstraZeneca urges the Committee to consider the significant unmet need in CKD and HF patients with HK, and the clear benefits of SZC to these patients.

Your sincerely,

Market Access & Government Affairs Director

Executive summary

1 <u>Data at thresholds relevant to UK clinical practice demonstrates that SZC is highly efficacious and beneficial to patients with HF or CKD with HK (see Section)</u>

- AstraZeneca have amended the threshold for initiating treatment with SZC to ≥6.0 mmol/L in patients with CKD. Following engagement with the clinical community during the consultation period the threshold for initiating treatment in patients with HF remains at ≥5.5 mmol/L due to differences in the management of HK patients with different comorbidities (see Section 1.1). We believe that it is critical for the Committee to gain clinical input from Cardiologists at the next Committee meeting to understand the unmet need and clinical utility of SZC to patients with HF.
- In a sub-group of patients with baseline S-K >5.5 mmol/L, [redacted]% of patients achieved S-K ≥4.0, ≤5.5 mmol/L following 2-3 days of SZC correction therapy in ZS-004 and ZS-005, and [redacted]% of patients maintained a mean S-K level of ≥4.0, ≤5.5 mmol/L over the maintenance phases of ZS-004 and ZS-005.
- In the sub-group of patients with baseline S-K >6.0 mmol/L, [redacted]% of patients achieved S-K ≥4.0, ≤6.0 mmol/L following 2-3 days of SZC correction therapy in ZS-004 and ZS-005, and [redacted]% of patients maintained a mean S-K level of ≥4.0, ≤6.0 mmol/L over the maintenance phases of ZS-004 and ZS-005.
- The efficacy of SZC, as demonstrated in the clinical trial programme, was independent of patient's underlying comorbidity and therefore efficacy data of the pooled HF and CKD subgroups ≥5.5 and ≥6.0 mmol/L have been used in the revised base case to reflect UK practice.

2 <u>New methods have been used to estimate the comparative effectiveness of SZC vs standard care in the NHS, demonstrating value of SZC to UK practice (see Section 2)</u>

- To our knowledge, there is no evidence demonstrating the potassium-lowering effect of low-potassium diets, and this was supported by clinical engagement and published clinical opinion. Low-potassium diets are typically reserved for patients with stage ≥4 CKD and those on dialysis. In addition, any potassium-lowering effect in this subgroup of patients is likely to be short-lived due to poor adherence, and the negative impact on quality of life.
- To further understand the relationship between RAASi therapy and S-K, AstraZeneca conducted a targeted literature review.
    - One study reporting the effect of down-titration/discontinuation of RAASi therapy on S-K, indicated the S-K reduction to be of a smaller magnitude (-0.10 and -0.06 mmol/L for ACEi and ARB, respectively) than that recommended by the ERG (-0.11 to -0.23 mmol/L), which was based on evidence from patients who initiate therapy rather than from those who down-titrate or discontinue therapy.
- Placebo data from study ZS-003 was considered as an alternative source of evidence for the placebo arm in relevant patients by overcoming the limitation associated with the residual SZC effect in study ZS-004 placebo arm.
    - The S-K reduction in the placebo arm for patients with S-K ≥5.5, <6.0, and S-K ≥6.0 estimated to be [redacted] and [redacted] mmol/L, respectively.
    - A further reduction of 0.23 mmol/L were applied in the revised base case to account for the S-K lowering effect of RAASi discontinuation to model NHS standard care, as recommended by the ERG

3 <u>An SLR confirms the relationship between reducing S-K and preventing longer-term outcomes, such as mortality, MACE and hospitalisation (see Section 3)</u>

- AstraZeneca has conducted a systematic literature review (SLR) to identify published evidence on the association between S-K and longer-term outcomes, such as mortality, MACE, and hospitalisation, whilst adjusting for relevant confounders
- In patients with CKD, 9 studies were identified and deemed to be relevant to the submission for mortality, and 2 studies each identified for MACE and hospitalisation

- In patients with HF, one RCT study and a further 13 relevant observational studies were identified which reported the relationship between S-K and mortality. All studies highlighted that patients with HK had an increased risk of death when compared with those who had lower S-K levels.
    - In addition, 3 relevant studies were identified which reported the relationship between S-K and hospitalisation, and no data was identified reporting the relationship with MACE.
- Overall, a similar U shape 'curve' representing the relationship between S-K and each outcome is observed across all studies. Patients with a higher S-K were at a higher risk of death and hospitalisation than those patients with lower S-K values.
- The results of this SLR further support the relationship between S-K and outcomes, and address the Committee's concerns by demonstrating that we have identified all relevant evidence, whilst ensuring evidence used has been adjusted for relevant confounders. The relationship has been further tested through scenario analyses presented in Section 6.

4 <u>Additional evidence demonstrating the long-term cardio-renal protective effects of RAASi has been identified, and SZC is a cost-effective treatment option even when we conservatively assume no benefits of RAASi therapy (see Section 4)</u>

- Given the time constraints of the consultation period, it was not possible to conduct a full SLR, however, in an attempt to address the concerns raised by the Committee, AstraZeneca conducted a targeted literature review to understand the relationship between RAASi and outcomes.
- In summary, the studies identified address most of the Committee's concerns: the clinical benefits of reduced mortality, cardiovascular events, hospitalisation and rate of disease progression associated with RAASi therapy in CKD and HF patients are well recognised in the literature and emphasised in clinical guidelines and consensus statements, including those published by NICE, the European Society of Cardiology, and the British Society for Heart Failure, supporting the use of continuous and optimised RAASi therapy.[22-24,28]
- An SLR is underway to further address these concerns, but outputs of this will not be available in advance of responding to the ACD. In the absence of an SLR, we are providing scenario analyses in Section 6, where we conservatively assume that there are no benefits associated with RAASi therapy.

5 <u>Use of SZC in emergency admissions (see Section 5)</u>

- The Renal Association guidelines on the emergency management of HK in adults indicates that patients are treated with IV insulin-dextrose when S-K increases ≥6.0 mmol, and emergency treatment is initiated ≥6.5 mmol/L. Therefore, we position SZC as a treatment option following initial treatment with insulin-dextrose (i.e. after normalisation of S-K) to maintain normokalaemia which may prevent repeat treatment with IV insulin-dextrose in patients with S-K ≥6.0 mmol/L in this clinical setting.
- The need to improve treatment in this setting was highlighted recently in a Patient Safety Alert published by NHS Improvement, and the risks of death due to hypoglycaemia following treatment with insulin-dextrose was reported across NHS Trusts.[11,48]
- SCZ has a fast onset of action making it appropriate for use following initial treatment with insulin-dextrose in emergency admissions. The median time to normalisation to S-K <5.5 or S-K <6.0, levels relevant to UK clinical practice, is expected to be less than 2.2h
- In addition to patients with S-K ≥6.5 mmol/L, data from a subgroup of patients with S-K ≥6.5 mmol/L (n=8) is presented and demonstrates that all patients achieved S-K <5.5 and <6.0 mmol/L at the end of corrective treatment with SZC. Furthermore, the treatment effect in these patients is greater than that observed in patients with a lower baseline S-K ([redacted] mmol/L vs [redacted] and [redacted] mmol, respectively).

6 SZC is cost-effective vs standard of care in the outpatient setting and in emergency admissions

- We have revised the model to better reflect to UK clinical practice, in line with discussions in Sections 1-5.
- In the revised model, SZC is cost-effective compared to standard care in the outpatients setting in CKD and HF patients, with ICERs of £9,865 and £18,158, respectively
- In emergency admissions, SZC is dominant and associated with cost-savings and QALY gains compared to standard care.
- Scenario analyses show the model to be robust to a range of alternative assumptions and variations in model inputs. In the scenario which assumed no effect of RAASi on clinical outcomes (i.e. the benefits of SZC in enabling RAASi-use are not translated to clinical benefits), SZC remained cost-effective in the outpatient setting (ICERs: £9,124 and £25,207, respectively), and dominant in emergency admissions.

7 Summary

- Based on the above points and the technical information below, we ask the Committee to reconsider its decision and grant a recommendation for SZC in patients with HF and a S-K ≥5.5 mmol/L (outpatient setting) and in patients with CKD and a S-K ≥6.0 mmol/L (outpatient setting) and in emergency admissions when S-K ≥6.0 mmol/L (i.e. A&E or AMU) to ensure that clinicians and patients have access to a treatment that can address the current unmet medical need.

1 Key issue 1: Generalisability of clinical trials data

1.1 Relevant thresholds for treatment of hyperkalaemia in UK clinical practice and treatment before ECG changes

ACD Section 3.1: *'the clinical and patient experts explained that people do not automatically have treatment to lower serum potassium if it is more than 5.0 mmol/litre. The Committee and the clinical expert agreed they would not usually consider treating hyperkalaemia at serum potassium levels lower than 6.0 mmol/litre. (…..) The Committee understood that the decision to use potassium-lowering treatment would take into account the speed of onset of hyperkalaemia and changes on electrocardiogram, as well as serum potassium levels, because these show a patient's prognosis.'*

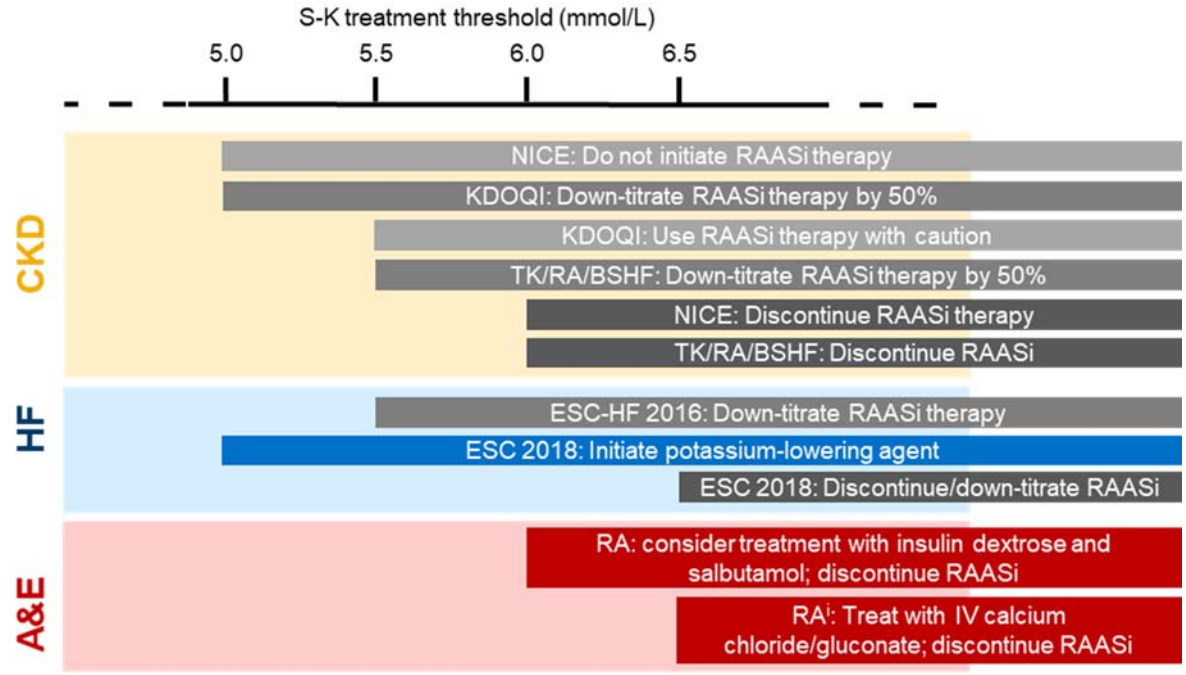
AstraZeneca agrees that patients with hyperkalaemia (HK) are not always treated when S-K levels are above 5.0 mmol/L. According to the input received from two Cardiologists, three Nephrologists and two A&E consultants and presented in the original submission,[42] the threshold to treat HK patients varies depending on the setting of care and was established to be 5.5 mmol/L and 6.0 mmol/L in the outpatient setting and emergency admissions, respectively. Whilst the S-K threshold for treatment in emergency admissions of 6.0 mmol/L concurs with NICE's conclusions as per the ACD, AstraZeneca note the discordance in the threshold for treatment in the outpatient setting.

To address NICE's concerns regarding the threshold for treatment, AstraZeneca engaged clinical experts further during the consultation process following the publication of the ACD.[30] During this consultation process it was indicated that the S-K threshold for treatment in the outpatient setting varies based on patients' underlying comorbidities. Specifically:

- In line with the recommendations published in the ACD, Nephrologists indicated that treatment of CKD patients in the outpatient setting would be initiated when S-K level is at least 6.0 mmol/L, which aligns with the Committee's conclusions from the ACD and input from the clinical expert Nephrologist attending the Committee meeting.
- In contrast, Cardiologists stated that treatment of HF patients in the outpatient setting would be initiated when S-K level is at least 5.5 mmol/L. We note that due to the lack of a clinical expert Cardiologist during the Committee meeting who would manage these patients, this important viewpoint may have not been fully considered during NICE's conclusions for when treatment of HK should be started in HF patients.

These treatment decision rules also align with international, national and local guidelines for the management of HK in the outpatient setting (see Figure 1).[22,23,49-51]

Figure 1. Summary of clinical guidelines for the management of HK in the outpatient setting (i.e. those treated by Cardiologists or Nephrologists during routine outpatient appointments) and in emergency admissions (i.e. A&E, AMU or inpatient)



[i]f patient is severely ill or has ECG changes, then treat at lower S-K

Abbreviation: A&E, accident and emergency; CKD, chronic kidney disease; ESC 2018; expert consensus by the Working Group on Cardiovascular Pharmacotherapy of the European Society of Cardiology; ESC-HF 2016, European Society of Cardiology – Heart Failure; HF, heart failure; KDOQI, Kidney Disease Outcomes Quality Initiative; NICE; National Institute for Clinical and Care Excellence Clinical Guidelines 182; RA, Renal Association; TK/RA/BSHF, Position statement from Think Kidney, the Renal Association and British Society for Heart Failure

Sources: ESC 2018,[28] ESC-HF,[23] KDOQI,[50] NICE,[22] RA,[51] TK/RA/BSHF[24]

The differences in S-K thresholds for initiating HK management, such as RAASi discontinuation, in CKD and HF patients can be explained by the underlying conditions and expected disease progression.

HK is common in patients with CKD, with the incidence increasing with disease severity. The risk of HK is further compounded by cardio-renal protective RAASi therapy, with studies reporting up to a 17-fold increase in HK in patients taking RAASi therapy.[16] In CKD, RAASi therapies have demonstrated significant benefits in reducing proteinuria and in slowing the progression of proteinuric CKD when compared with other anti-hypertensives having similar effects on blood pressure, regardless of aetiology,[52,53] with improved outcomes and delayed progression of disease being associated with maximal, and even supra-maximal, doses of ACE inhibitors.[54,55] Therefore down-titration or stopping RAASi therapy should be seen as a last resort.

In CKD patients, HK is universal and part of the expected disease progression, with the majority of patients experiencing mild to moderate HK on a chronic basis. The rise in S-K is often less quick in CKD patients and therefore may be less concerning compared to the often fast increase in S-K in HF patients. This, coupled with Nephrologists' experience in managing HK means they feel more confident in managing severe HK in CKD patients, and therefore may perceive a diminished risk associated with moderate S-K levels. As such, Nephrologists may not typically initiate treatment until S-K levels increase above 6.0 mmol/L.

In HF patients, HK may be associated with the disease and comorbidities but is more commonly seen in association with RAASi therapy. In the absence of other treatment options, Cardiologists routinely trade-off the cardio-protective benefits of RAASi in exchange for control of S-K levels. As such, cardiologists have a lower threshold for initiating treatment, and do not typically initiate management (RAASi down-titration or discontinuation) until S-K levels increase above 5.5 mmol/L.

Finally, whilst AstraZeneca agrees that changes to the electrocardiogram (ECG) can show a patient's prognosis, the presence of an ECG change constitutes a medical emergency and would therefore only guide the treatment of life-threatening HK in the emergency setting.[49,51,56-58] On the other hand, treatment of HK in the outpatients setting, would mainly be guided by S-K levels and clinical assessment of the patients.[22-24,50]

1.2 Outcomes in ZS-004 and ZS-005 relevant to UK clinical practice

ACD section 3.9: *'A key outcome for clinicians would be the proportion of people whose serum potassium levels dropped to below 6.0 mmol/litre, the level above which NICE recommends stopping RAAS inhibitors, but this was not an outcome in the trial.'*

AstraZeneca acknowledges NICE's request to understand the proportion of patients whose S-K level dropped below 6.0 mmol/L. Therefore, to better reflect outcomes relevant to UK clinical practice, post-hoc analyses of ZS-004 and ZS-005 trials were undertaken to evaluate the proportion of patients whose S-K dropped below:

a) 6.0 mmol/L among those with a baseline S-K >6.0 mmol/L in the corrective phase of the trials, more relevant to emergency admissions (i.e. patients treated in A&E/AMU) and CKD patients in the outpatient setting
b) 5.5 mmol/L among those with a baseline S-K >5.5 mmol/L in the corrective phase of the trials, more relevant to HF patients in the outpatient setting

The results from the sub-group analyses in Table 1 and Table 2 show that nearly all patients with baseline S-K >5.5 and >6.0 mmol/L respond to SZC treatment in the correction phase and reduce their S-K to ≤5.5 and ≤6.0 mmol/L, respectively. The majority of patients also maintain their S-K levels between ≥4.0, ≤5.5 and ≥4.0, ≤6.0 mmol/L, respectively. A small number of patients experienced S-K levels <4.0 mmol/L at the end of the correction phase and during the maintenance phase. In clinical practice, these patients would be identified through routine testing and their low S-K levels would be resolved through dose adjustment or discontinuation of SZC, as per the SPC.[59] Table 1. Distribution of patients by S-K level at the end of the correction phase and during the maintenance phase of ZS-004 and ZS-005, in patients with baseline S-K >6.0 mmol/L

Correction phase	**ZS-004 (N=26)**			**ZS-005 (N=89)**
Number of patients with S-K >6.0 mmol/L at the end of the correction phase (%)	[redacted]			[redacted]
Number of patients with S-K ≥4.0, ≤6.0 mmol/L at the end of the correction phase (%)	[redacted]			[redacted]
Number of patients with S-K <4.0 mmol/L at the end of the correction phase (%)	[redacted]			[redacted]
Maintenance phase	**ZS-004**			**ZS-005 (N=76)**
	Placebo (N=9)	**SZC 5 g OD (N=4)**	**SZC 10 g OD (N=8)**	
Number of patients with a mean S-K >6.0 mmol/L during the maintenance phase* (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients with S-K ≥4.0, ≤6.0 mmol/L at the end of the correction phase (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients with S-K <4.0 mmol/L at the end of the correction phase (%)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OD, once a day; S-K, serum potassium.
*ZS-004: Mean S-K value calculated based on S-K measurements on Day 8-29 of the maintenance phase; ZS-005: Mean S-K value calculated based on S-K measurements Day 85-365 in the maintenance phase

Table 2. Distribution of patients by S-K level at the end of the correction phase and during the maintenance phase of ZS-004 and ZS-005, in patients with baseline S-K >5.5 mmol/L

Correction phase†	**ZS-004 (N=114)**			**ZS-005 (N=360)**
Number of patients with S-K >5.5 mmol/L at the end of the correction phase (%)	[redacted]			[redacted]
Number of patients with S-K ≥4.0, ≤5.5 mmol/L at the end of the correction phase (%)	[redacted]			[redacted]
Number of patients with S-K <4.0 mmol/L at the end of the correction phase (%)	[redacted]			[redacted]
Maintenance phase‡	**ZS-004**			**ZS-005 (N=311)**
	Placebo (N=38)	**SZC 5 g OD (N=16)**	**SZC 10 g OD (N=23)**	
Number of patients with a mean S-K >5.5 mmol/L during the maintenance phase* (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients with S-K ≥4.0, ≤5.5 mmol/L at the end of the correction phase (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients with S-K <4.0 mmol/L at the end of the correction phase (%)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OD, once a day; S-K, serum potassium.
*ZS-004: Mean S-K value calculated based on S-K measurements on Day 8-29 of the maintenance phase; ZS-005: Mean S-K value calculated based on S-K measurements Day 85-365 in the maintenance phase
† Corrective phase = 10g SZC TDS for up to three days; ‡ Maintenance phase = 5 g OD with doses up titrated to 10 g OD or down-titrated to 5 g QoD to maintain normokalaemia.

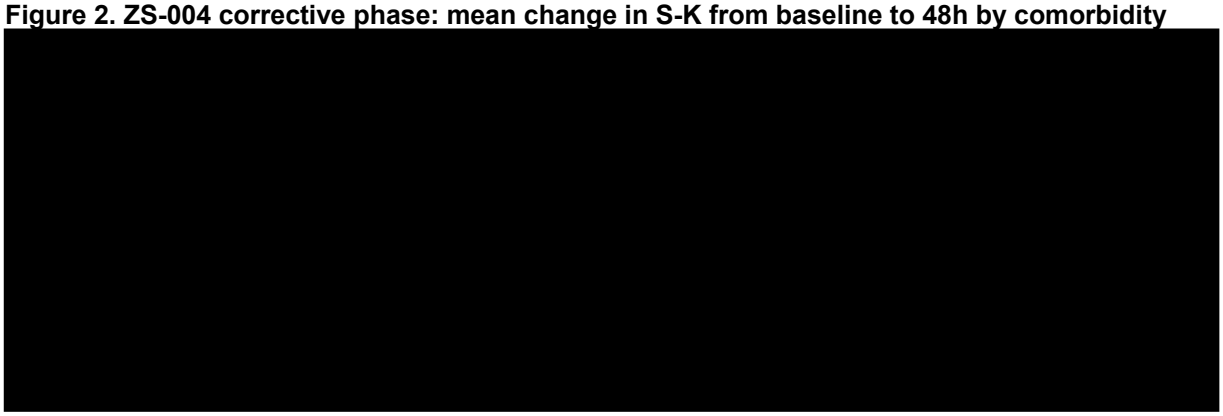
1.3 Response to treatment is independent of patient's underlying comorbidity

AstraZeneca has included subgroup analyses using definitions of comorbid conditions based on standardised Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQs) (narrow). The full details of these definitons are provided in Appendix D. These definitions provide a clinically relevant representation of patients with these comorbidities managed within the NHS.

The treatment responses in patients with and without CKD, or HF, are consistent in the overall study populations of ZS-004 and ZS-005 (Figure 2–Figure 6): the treatment effects are in the same direction for all sub-populations evaluated and none of the 95% confidence intervals substantially overlap with 0 (a difference of 0 versus placebo indicates no treatment effect).[60] All sub-group analyses (efficacy and safety) and patient numbers based on the MedDRA SMQ (narrow) definitions are presented in Appendix D. Based on these analyses, the pooled results for CKD and HF patients with baseline S-K ≥5.5 mmol/L and baseline S-K ≥6.0 mmol/L can be considered to be generalisable to the results observed when considering the response to treatment in patients with CKD or HF alone.

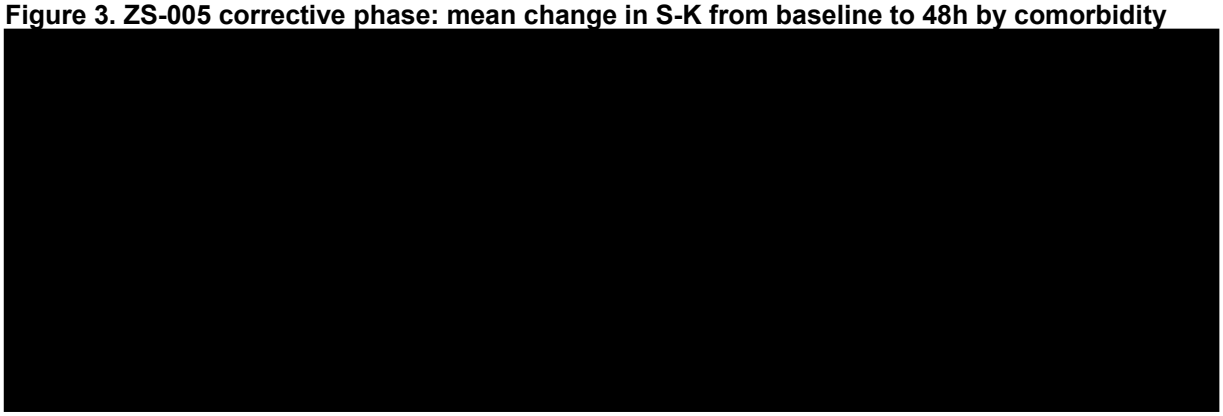
The response to treatment is independent of patients' underlying comorbidity (i.e. CKD or HF), justifying the use of pooled CKD and HF data to inform the clinical effectiveness analysis and cost-effectiveness analysis. This approach maximises the use of available clinical data and includes a larger number of patients in the analyses compared to analyses of CKD or HF patients in isolation.

Figure 2. ZS-004 corrective phase: mean change in S-K from baseline to 48h by comorbidity



Abbreviations: CI, confidence interval; SMQ, Standardised MedDRA Queries.

Figure 3. ZS-005 corrective phase: mean change in S-K from baseline to 48h by comorbidity



Abbreviations: CI, confidence interval; SMQ, Standardised MedDRA Queries.

Figure 4. ZS-004 maintenance phase: mean difference in S-K on days 8–29 in SZC 5 g OD versus placebo by comorbidity

Abbreviations: CI, confidence interval; SMQ, Standardised MedDRA Queries.

Figure 5. ZS-004 maintenance phase: mean difference in S-K on days 8–29 in SZC 10 g OD versus placebo by comorbidity

Abbreviations: CI, confidence interval; SMQ, Standardised MedDRA Queries.

Figure 6. ZS-005 maintenance phase: proportion of patients with S-K ≤5.1 on days 85–365 by comorbidity

Abbreviations: CI, confidence interval; SMQ, Standardised MedDRA Queries.

2 Key issue 2: Comparative data to inform the effect of standard care

ACD Section 3.7: *'[The Committee] concluded that the comparators were calcium resonium and management of RAAS inhibitors in the emergency setting, and management of RAAS inhibitors in the outpatient treatment setting.'*

ACD Section 3.8: *'The Committee concluded that the company had not provided any data for the clinical effectiveness of treatments currently used in the NHS to correct hyperkalaemia and maintain normal serum potassium levels in the outpatient setting (that is, a low-potassium diet and management of RAAS inhibitors).'*

ACD Section 3.9: *'There was no control group for the correction period of the trial. This meant that it was unknown whether the proportion of patients whose potassium returned to the normal range was similar to what is seen with standard care (see section 3.8).'*

2.1 Evidence base for clinical effectiveness of standard care

AstraZeneca acknowledge the Committee's conclusions for comparators listed in ACD Section 3.7 and 3.8. Whilst low potassium-diet was considered a comparator for SZC in the NICE scope and the original submission, if low potassium-diet was to be treated as background therapy for patients with or without SZC, there would be a very low risk of this influencing clinical effectiveness results for SZC versus relevant comparators in the UK. Low potassium diets are typically only recommended in the setting of end stage kidney disease for patients with identified HK,[61] with the challenges of strict adherence and that these diets are contrary to usual cardiovascular prevention dietary advice meaning there is a call for a more balanced and individualised approached to diet.[31] Furthermore, we agree that it is critical to explore the clinical effectiveness of SZC versus standard care i.e. stopping/reducing RAASi therapy (emergency and outpatient setting). Clinicians state that it is difficult to attribute an S-K lowering effect to low potassium diets, as patients are concurrently treated with many other interventions in CKD stage ≥4 (i.e. when low potassium diets are prescribed). Furthermore, any S-K lowering effect attributed to low potassium diets are likely to be short-term and limited due to poor compliance. In addition, clinicians highlighted the negative impact of low potassium diets on patients' quality of life which diminishes the overall benefits of low potassium diet.[30] As such, in the outpatient setting, low potassium diets can be considered as a background therapy for CKD patients with little influence expected on the results.

In the original company submission, data from the placebo arm of ZS-004 were used to inform the S-K trajectory of the standard care arm. We recognise the Committee's concerns that these data are not fully generalisable to standard care in clinical practice due to significant potassium-lowering effect of treatment with SZC in the correction phase of the trial, and due to the lack of explicit modelling of the effect of RAASi down-titration or discontinuation. However, as shown during AstraZeneca's response to the ERG report, the treatment effect of SZC in the placebo arm of ZS-004 would outweigh the effects of RAASi down-titration or discontinuation. Therefore, whilst we agree that the original company submission did not provide comparative clinical effectiveness data of SZC compared to standard care in the NHS, the placebo arm from study ZS-004 in the original submission included a significant residual effect of treatment with SZC which was greater than that expected from standard care. Therefore, clinical effectiveness evidence as generated by ZS-004 more than likely underestimates the benefits of treatment with SZC in UK clinical practice.

Nevertheless, to address NICE's concerns regarding the lack of comparative data to inform the effect of standard care, AstraZeneca has re-examined the published evidence base for relevant data to inform the clinical effectiveness of standard care. In the absence of relevant comparative clinical effectiveness data from ZS-004 and from published literature, and to ensure use of all available SZC clinical evidence to best address the Committee's concerns, AstraZeneca has proposed an analysis of data from the ZS-003 trial as an alternative source of clinical effectiveness data for standard care (see Section 2.2 for further information), with further adjustment by -0.23 mmol/L to conservatively account for the effect of RAASi discontinuation (see Section 2.1.1).

2.1.1 Evidence base for the effect of RAASi down-titration or discontinuation on S-K

Due to the time constrains for the ACD response, a targeted literature review approach was used in order to identify the most relevant studies on the effect of RAASi down-titration or discontinuation on S-K. This targeted literature review approach will be complemented with a systematic literature review of the evidence, however, outputs of this will not be available in advance of responding to the ACD.

The targeted literature review identified one study that reported the effect of RAASi down-titration or discontinuation on S-K levels. Ribeiro et al.[62] was a prospective observational cohort study of peritoneal dialysis patients, conducted in 122 Brazilian centres (n=636). Patients who discontinued ACEi and ARB had a -0.10 (SD: 0.6) mmol/L and -0.06 (0.46) mmol/L change in S-K, respectively (not statistically significant). This study was in dialysis patients rather than pre-dialysis patients, but the study provides evidence to show that RAASi down-titration and discontinuation are not associated with significant effects on S-K.

In the absence of more high-quality studies on the effect of RAASi down-titration or discontinuation on S-K, it is appropriate to consider the evidence available on the effect of RAASi initiation on S-K as proxy, to inform the clinical effectiveness analysis and cost-effectiveness modelling of the current decision problem.

As discussed in response to the ERG clarification questions, a previously conducted targeted searches identified a literature review of 39 clinical trials and meta-analyses on the effect or RAASi on S-K by Weir et al.[63] This publication showed RAASi therapy (ACEi, ARB, ARA and DRI) to be associated with small S-K increases in CKD and HF patients. In CKD patients, the S-K change associated with RAASi monotherapy versus no therapy, and RAASi dual therapy versus RAASi monotherapy range between 0.06 and 0.8 mmol/L, but are typically ≤0.5 mmol/L. Specifically, the meta-analysis by MacKinnon et al.[64] in patients with proteinuric renal disease (n=654), showed ACEi/ARB combination therapy resulted in a 0.11 (95% CI: 0.05–0.17) mmol/L increase in S-K compared to ACEi monotherapy. In HF patients, the increase in S-K associated with RAASi dual therapy compared to RAASi single therapy was smaller and ranged between 0.1 and 0.3 mmol/L.

The ERG use a targeted literature review approach to identify the meta-analysis of MRA by Ng et al.[65] in stages 1–5 CKD patients, including those on dialysis (n=1,581), which indicated that MRA therapy is associated with a 0.23 (95% CI: 0.13–0.33) mmol/L increase in S-K. The background therapy in the included studies varied: a proportion of studies allowed concomitant use of ACEi and/or ARB.

As MRAs prescribed less often in CKD patients in UK clinical practice when compared with ACEi/ARBs,[66] the results from MacKinnon et al. based on ACEi/ARB therapy (see above) is likely to be more generalisable to UK clinical practice compared to Ng et al. However, in order to address the Committee's concerns and ensure the effect of RAASi down-titration and discontinuation on S-K is fully taken into account, the 0.23 mmol/L value from Ng et al. is used in the revised cost-effectiveness model as a conservative estimate of the effect of RAASi discontinuation on S-K, in line with the ERG's assumptions. Similarly, as per the ERG's assumptions, a S-K reduction of 0.115 mmol/L (half of 0.23 mmol/L) is conservatively assumed in patients who down-titrate RAASi in the revised cost-effectiveness model (see Section 6).

2.1.2 Evidence base for effect of calcium resonium and low potassium diet

As explained in the response to the ERG clarification questions, the clinical systematic literature review (SLR) was updated to identify evidence on the effect of calcium resonium and low potassium diet on S-K in HK patients, but no additional RCT studies were identified. We re-examined the studies identified, including the non-RCT studies that were original excluded, but we were not able to identify any further evidence.

Published evidence on calcium resonium did not consider doses relevant to UK clinical practice.[67] The only somewhat relevant study on low potassium diets identified by the SLR, by Arnold et al., does not provide any informative evidence, due to protocol mandated differences in the use of SPS in the potassium restriction treatment and control arms. Furthermore, the patients randomised in the study

did not have elevated S-K values, and would not be routinely treated by low potassium diets in UK clinical practice.[68]

KEE engagement and published clinical opinion confirmed that there is very limited evidence available on the effect of calcium resonium or low potassium diet on lowering patients' S-K, relevant for this appraisal. In addition, calcium resonium is rarely used in UK clinical practice due to poor clinical efficacy, and is often discontinued due to gastrointestinal effects.[42] For low potassium diet, it is difficult to estimate based on clinical experience, as patients who are prescribed with low potassium diets are often also concurrently managed by a number of other interventions. Low potassium diets are usually only prescribed by nephrologists to stage ≥4 CKD patients in UK clinical practice. In contrast, low potassium diet is rarely prescribed by Cardiologists for HF patients, as RAASi down-titration or discontinuation is considered to be a more effective intervention in these patients.[30,31,42] Clinicians, also highlight the poor adherence to low potassium diets, and its negative impact on patients' quality of life.[30] Published clinical opinion highlights that many food items, such as fresh fruit and vegetables, legumes and grains, typically considered as essential components of a "heart healthy" diet, are not allowed on a low potassium diet. As such, low potassium diet is not only difficult to follow, limiting any potential effect it has on S-K, but it is also considered to contribute to the burden of cardiovascular disease.[30,31] KEEs and published clinical opinion calls for the use of potassium binding resins to control HK whilst allowing for a more heart-healthy diet.[30,31]

The impact of low potassium diet on patients' S-K levels are likely to be short-term and of limited magnitude given the poor adherence as indicated by clinical experts and as highlighted in the literature. The use of SZC in clinical practice may alleviate the burden of keeping to a highly restrictive low potassium diet, and in addition contribute to the consumption of a more heart-healthy diet.

2.2 ZS-003 placebo arm as an alternative source of evidence for standard care

Because of the lack of a common comparator in studies on the effect of RAASi on S-K and the SZC pivotal trial, it is not possible to conduct an indirect treatment comparison (ITC) in order to establish the relative clinical effectiveness of SZC compared to standard care (i.e. placebo treatment with RAASi down-titration or discontinuation).

In light of the limitations in the evidence base, data from the ZS-003 study was considered as an alternative source of evidence for the clinical effectiveness of standard care. The ZS-003 trial overcomes the limitation associated with the residual SZC effect in the ZS-004 trial design by including a placebo arm in the correction phase, and by including a placebo arm in the maintenance phase with a less significant SZC residual effect (1.25 g TDS correction therapy).

The ZS-003 study design, objectives and results are outlined in Appendix L and Appendix M of the original company submission. In short, ZS-003 was a phase 3, multicentre, prospective, randomised, double-blind, placebo-controlled, dose-ranging study. A total of 754 patients were randomised to receive SZC 1.25 g (n=154), SZC 2.5 g (n=141), SZC 5 g, (n=158), SZC 10 g (n=143) or placebo (n=158) TDS for 48 hours. Following the 48h correction phase, 447 patients were randomised to receive either placebo or the same dose as during the correction phase, but once daily. The patients who received placebo in the 48h correction phase were randomised to 1.25 g once daily or 2.5 g once daily (Figure 7).

Patient baseline characteristics in ZS-003 were comparable to ZS-004 and ZS-005, with the exception that patients in ZS-003 had a lower baseline S-K (see Document B and Appendix L of the company submission) with the majority of patients having a baseline S-K ≥5.1,<5.5 (Table 3). Because of the small patient numbers in the relevant trial arms, it was not feasible to use statistical methods to adjust the trial data to match the patient characteristics and baseline S-K levels to the sub-group of ZS-004 and ZS-005 relevant to UK clinical practice (S-K>5.5 mmol/L). Instead the clinical outcomes from ZS-003 were scaled according to the treatment effects size in ZS-004 by baseline S-K levels (Section 2.2.1), in order to adjust for the larger magnitude of treatment effect in patients with more severe HK and to adjust for any potential regression to the mean (Table 4 and Table 5).

2.2.1 S-K change from correction phase baseline in the placebo arm of ZS-003

The change in S-K from baseline for the correction phase placebo arm was -0.25 mmol/L for the ITT population in ZS-003. After scaling to adjust the placebo arm effect size based on the relative treatment effect size for patients with baseline S-K ≥5.5, <6.0, and S-K ≥6.0 the change in S-K from baseline was [redacted] and [redacted] mmol/L, respectively. The corresponding adjusted S-K changes from baseline for the SZC 10 g TDS treatment arm in ZS-003 were -1.11 and -1.39 mmol/L, respectively, which are comparable to the treatment effect in the S-K ≥5.5, <6.0 sub-group ([redacted] mmol/L), and S-K ≥6.0 sub-group ([redacted]_mmol/L) of ZS-004 (Table 4), providing confidence in the method used.

2.2.2 S-K change during maintenance phase in the placebo arm of ZS-003

Patients' S-K levels remain generally stable in the maintenance phase of ZS-003, with only a [redacted] and [redacted] change in S-K from maintenance phase baseline for patients on placebo TDS / 1.25 OD and SZC 1.25 g TDS / placebo and SZC 10 g TDS / 10 g OD, respectively, on day 12 of the maintenance phase (Table 7). Similarly, the 10 g OD arm of ZS-004 remained generally stable throughout the maintenance phase with small changes from the maintenance phase baseline (Table 7).

2.2.3 RAASi discontinuation in ZS-003

As in ZS-004, [redacted]% of patients in ZS-003 received RAASi therapy at baseline, with a similar proportion of patients receiving RAASi therapy at the start of the maintenance phase. In clinical practice, in patients with S-K ≥5.5 mmol/L, 80% are expected to down-titrate and 20% are expected to discontinue.[42] Accordingly, a further reduction in S-K is expected in patients treated by standard care, due to RAASi down-titration or discontinuation, compared to the placebo arm data from ZS-003.

As discussed above, a conservative assumption is made in this updated clinical effectiveness analysis and the revised cost-effectiveness model (see Section 6**Error! Reference source not found.**), to account for the effect of RAASi down-titration or discontinuation on S-K. In line with the ERG's assumptions, RAASi down-titration and discontinuation are assumed to be associated with an S-K change of -0.115 and -0.23 mmol/L, respectively (see Section 2.1.1)

2.3 Summary of clinical efficacy of standard care

In summary, the placebo arm data from ZS-003 indicates that patients with HK have a [redacted] to [redacted] reduction in S-K during the correction, dependent on the baseline S-K level, followed by generally stable levels of S-K. With the assumed 0.115 to 0.23 mmol/L reduction in S-K associated with RAASi down-titration or discontinuation, standard care is expected to be associated with a maximum reduction of [redacted] mmol/L ([redacted]_– 0.23 = [redacted] mmol/L).

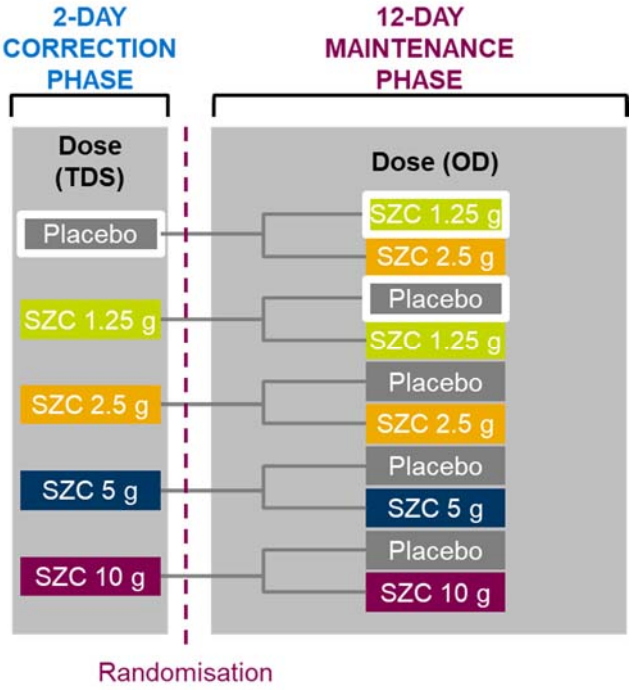
The S-K trajectories in the cost-effectiveness model have been revised to reflect the alternative clinical effectiveness data for standard care based on ZS-003 and based on the conservative interpretation of the literature on the effect of RAASi on S-K (see Section 2.1.1).

Table 3. ZS-003 correction phase baseline S-K distribution

	Placebo (n=158)	SZC 1.25 g TDS (n=154)	SZC 2.5 g TDS (n=141)	SZC 5 g TDS (n=157)	SZC 10 g TDS (n=143)
Baseline S-K ≥5.3, <5.5 (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline S-K ≥5.5 (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: S-K, serum potassium; SD, standard deviation; SZC, sodium zirconium cyclosilicate;TDS, three times a day
Source: ZS-003 CSR, Table 11-9 (page 87)

Figure 7. ZS-003 study design



Abbreviations: OD, once a day; SZC, sodium zirconium cyclosilicate; TDS, three times a day
White highlights: trial arms highlighted in white provide alternative standard care data

Table 4. ZS-004 open-label (10 g TDS) correction phase S-K changes by baseline S-K

Baseline S-K groups (mmol/L)	≥5.1, <5.5 (n=119)	≥5.5, <6.0 (n=100)	≥6.0 (n=39)
Mean baseline S-K (SD)	[redacted]	[redacted]	[redacted]
48h absolute reduction (SD)	[redacted]	[redacted]	[redacted]
Relative size of S-K reduction with respect to the baseline S-K ≥5.1, <5.5 group	[redacted]	[redacted]	[redacted]

Abbreviations: S-K, serum potassium; SD, standard deviation; TDS, three times a day
Source: ZS-004 CSR, Table 14.2.1.2.7–14.2.1.2.9

***statistically significant difference from baseline ≤ 0.0001 level, based on paired t-test [redacted]Table 5. ZS-003 correction phase S-K changes by treatment arm (ITT population)**

	Placebo (n=158)	SZC 1.25 g TDS (n=154)	SZC 2.5 g TDS (n=141)	SZC 5 g TDS (n=157)	SZC 10 g TDS (n=143)
Baseline[a] S-K (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48h absolute reduction, ITT population (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted 48h absolute reduction, for patients with baseline S-K ≥5.5,<6.0[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted 48h absolute reduction, for patients with baseline S-K ≥6.0[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ITT, intent to treat; S-K, serum potassium; SD, standard deviation; TDS, three times a day
Source: ZS-003 CSR, Table 11-9 (page 87)
* Statistically significant difference from placebo at the ≤ 0.001 level, based on unpaired t-test comparing ZS group indicated versus placebo
[a] Baseline was calculated by taking the mean of the screening time points (0h, 30 mins and 1h) averaged with the 0-hour time point on study Day 1; values used in the calculations were determined by the central laboratory.
[b] Adjusted by multiplying the 48h absolute reduction from the ITT population with the relative effect size ([redacted]) in the baseline S-K ≥5.5,<6.0 sub-population of ZS-004, relative to the baseline S-K ≥5.1,<5.5 sub-population of ZS-004 (see Table 4)
[c] Adjusted by multiplying the 48h absolute reduction from the ITT population with the relative effect size ([redacted]) in the baseline S-K ≥6.0 sub-population of ZS-004, relative to the baseline S-K ≥5.1,<5.5 sub-population of ZS-004 (see Table 4)

Table 6. ZS-003 maintenance phase S-K changes from maintenance phase baseline (only relevant doses are shown)

	Placebo TDS / 1.25 OD (n=0.46)	SZC 1.25 g TDS / placebo (n=41)	SZC 10 g TDS / placebo (n=61)	SZC 10 g TDS / 10 g OD (n=63)
Correction baseline S-K (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance baseline S-K (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance Day 1 absolute reduction (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance Day 2 absolute reduction (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance Day 3 absolute reduction (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance Day 6 absolute reduction (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance Day 12 absolute reduction (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: S-K, serum potassium; SD, standard deviation, TDS, three times a day; OD, once a day
Source: ZS-003 CSR, Table 11-15 and 11-16
* Statistically significant different from SZC 10 g TDS / placebo OD at the ≤0.001 level based on unpaired t-test

Table 7. ZS-004 maintenance phase S-K changes from maintenance phase by baseline S-K

Treatment arm	5 g OD			10 g OD		
Baseline S-K groups (mmol/L)	**≥5.1, <5.5 (n=23)**	**≥5.5, <6.0 (n=17)**	**≥6.0 (n=5)**	**≥5.1, <5.5 (n=18)**	**≥5.5, <6.0 (n=23)**	**≥6.0 (n=9)**
Correction baseline S-K (SD)						
Maintenance baseline S-K (SD)						
Maintenance Day 2 absolute reduction from maintenance baseline (SD)						
Maintenance Day 8 absolute reduction from maintenance baseline (SD)						
Maintenance Day 12 absolute reduction from maintenance baseline (SD)						
Maintenance Day 15 absolute reduction from maintenance baseline (SD)						
Maintenance Day 19 absolute reduction from maintenance baseline (SD)						
Maintenance Day 22 absolute reduction from maintenance baseline (SD)						
Maintenance Day 26 absolute reduction from maintenance baseline (SD)						
Maintenance Day 29 absolute reduction from maintenance baseline (SD)						

Abbreviations: S-K, serum potassium; SD, standard deviation, OD, once a day
Source: ZS-004 CSR Tables, Table 14.2.2.7.7–14.2.2.7.9

3 Key issue 3: Evidence on S-K and long-term outcomes

ACD Section 3.11: *'There was no comparative evidence from a randomised trial that lowering serum potassium in people with hyperkalaemia, prolonged survival. The company provided evidence from a single observational study showing an association between serum potassium levels and death, but did not provide a systematic review of the evidence. The Committee recognised that this observational data did not guarantee an independent association between high serum potassium levels and death, or provide evidence that lowering serum potassium extends life.'*

AstraZeneca acknowledge the Committee's concerns, and in order to address them, conducted a SLR including both randomised clinical trials and observational studies, to identify published evidence on the relationship between S-K and long-term outcomes (mortality, MACE and hospitalisation), which was subsequently used in the revised base case model to inform base case assumptions and scenario analyses for S-K and outcome (Section 6). The SLR methods are provided in Appendix A.

In total, [redacted] studies were identified of which [redacted] were prospective, [redacted] were retrospective, [redacted] were observational and [redacted] were randomised controlled trials (RCTs). Of the [redacted] RCTs, [redacted] was conducted in a population with hypertension,[69] and [redacted] in a population with HF.[70] An overview of the studies is presented in **Table 24** to **Error! Reference source not found.** of Appendix B. Covariates were reviewed to provide some confidence in the independent association between S-K and each of the outcome. The full SLR report is available in Appendix C.

Studies not conducted in North America or Europe ([redacted] and those conducted in patients with comorbidities other than CKD and HF ([redacted] were not considered relevant to this ACD issue and therefore are not discussed below.

3.1 Multiple large observational studies exist, confirming the relationship between S-K and outcomes in CKD patients

[redacted] potentially relevant observational studies were found that assessed the relationship between S-K and mortality in patients with CKD. [redacted] were not considered relevant to the decision problem and were subsequently excluded: [redacted] only included patients with dialysis; [redacted] examined the effect of hypokalaemia; [redacted] did not adjust the risk of death by eGFR as a potential confounder; [redacted] provided HRs for 'before ESRD' and 'after ESRD' at [redacted] only looked at CKD stage IV onwards and potentially included dialysis and RRT patients and in [redacted] the outcome of interest was composite sudden cardiac arrest and sudden cardiac death, rather than all-cause mortality.

In the [redacted] considered to be relevant to the decision problem, the cut-off time between S-K measurement and death event varied. [redacted] only included same day death [redacted] reported the relationship between S-K and mortality stratified by disease severity.

3.1.1 S-K and mortality

[redacted] was a retrospective observational analysis in CKD patients listed on the Clinical Practice Research Datalink (CPRD) in the UK. A total of [redacted] patients with a first record of CKD (stage 3a–5, pre-dialysis) between 2006 and 2015 were identified. In this study risk equations were developed and adjusted for significant covariates; directly addressing the concerns highlighted by the Committee. These risk equations were developed to assess the impact of S-K on mortality and adjusted for age, gender, time, S-K, history of diabetes, cancer, dementia, MACE, PVD and smoking, time-updated eGFR and RAASi, time-updated presence of HF, and prescription of diuretics, bronchodilators, insulin and statins ± 3 months from baseline. The risk equations in

[redacted] produced event probability estimates for six S-K categories, with S-K ≥4.5, <5.0 mmol/L set as the reference category. For S-K levels higher and lower than the reference category, the risk equations report a statistically significant increase in the risk of mortality for all S-K categories.

[redacted] in the USA) and [redacted]) were the only studies that provided incidence rate ratios (IRRs) and relative risk (RR) stratified by eGFR, which can be used as a surrogate for CKD stage. Both studies reported a U-shaped relationship between S-K and mortality for CKD patients regardless of disease severity.

[redacted], stratified by 4 eGFR categories: <30, 30-39, 40-49, and 50-59 mL/min/1.73m^2. All covariates that were imbalanced across the different S-K categories and either known or presumed to be associated with the outcomes studied were adjusted for. [redacted].

[redacted] provided IRRs for mortality in S-K ranges associated with 25%, 50%, 75% and 100% increase in risk compared to the reference S-K level (with the lowest risk) for 3 eGFR categories: ≥60, 30-60, <30 mL/min/1.73m^2. For each eGFR category, [redacted] reported an increased risk of mortality as S-K deviated from the reference category, demonstrating a U-shaped relationship. For the patients with 30 ≤ eGFR < 60 mL/min/1.73m^2, S-K of [redacted] was determined to have the lowest risk of mortality and so was selected as the reference category. A 50% increase in mortality risk was observed at a S-K level of [redacted] and a 100% increase in risk was identified at a S-K level of [redacted]. However, as the study by [redacted] was only represented as an abstract, it was unclear whether appropriate covariate adjustment was made.

Additionally, [redacted] reported risk ratios for S-K intervals covering hypo-, normo- and hyperkalaemia and all four observed a U-shaped relationship between S-K and mortality.

[redacted] patients without ESRD, investigated the effect that admission S-K level has on in-hospital mortality. Odds ratios (ORs) were produced for 7 S-K intervals, with 4.0 ≤ S-K < 4.5 mmol/L set as the reference category and were adjusted for age, sex, race, eGFR, principal diagnosis, Charlson comorbidity score, comorbidities and medications. For patients with HK, odds of in-hospital mortality increased from [redacted].

[redacted] retrospectively reviewed multiple US integrated health delivery networks to evaluate the association between all-cause mortality and potassium. Data from over [redacted], was used to perform a cubic spline regression analysis and generate IRRs that were adjusted for age, gender, hypertension, cardiovascular disease, acute myocardial infarction, CKD stages 3–5, HF, diabetes, RAASi, and diuretic prescriptions, along with multiple interactions (both age and gender with each comorbidity and RAASi, RAASi with CKD and with HF, and HF with CKD. With respect to the reference category of 4.5 ≤ S-K < 5mmol/L, the risk of death strictly increased to a IRR of [redacted].

[redacted] performed a retrospective analysis on the association between potassium and mortality. [redacted] with eGFR < 60 ml/min/1.73m^2 and S-K measurements, on the

Electronic Health Record-based CKD registry at Cleveland Clinic between 2005 and 2009 were identified and used to produce adjusted HRs. A U-shaped relationship was reported for S-K all-cause mortality with S-K ≥ 5.5 mmol/L linked to a [redacted].

[redacted] assessed over one million patients with varying kidney function and found that the risk relationship between potassium levels and adverse outcomes was U-shaped, with the lowest risk at S-K of [redacted] Compared with a reference of 4.2 mmol/L, the adjusted hazard ratio for all-cause mortality was [redacted] showing increased survival for normalised S-K.

The remaining [redacted] both reported an increased risk of mortality for patients with HK. Compared to non-HK patients, [redacted] documented that the risk of mortality more than [redacted] for patients with S-K > 5.5 mmol/L. [redacted] reported that the risk increased as HK severity increased (S[redacted] when compared to non-HK patients).

3.1.2 S-K and MACE

For the relationship between S-K and MACE, [redacted] were the only relevant studies identified in the systematic review[redacted] produced risk equations similar to those for the S-K and mortality relationship and the risk of MACE was adjusted for age, gender, time, S-K, baseline cholesterol, history of diabetes, rheumatologic disease, MACE, chronic pulmonary disease and smoking, time-updated eGFR, and prescription of CCBs, insulin and beta blockers ± 3 months from baseline were the significant covariates implemented in the risk equations. The risk equations produced event probability estimates for six S-K categories, with S-K ≥4.5, <5.0 mmol/L set as the reference category. Where there was insufficient evidence to support a deviation in risk from the reference category (i.e. there was no statistically significant difference from unity at the 5% level), the coefficient was assumed to be zero.

In the study by [redacted] the covariates adjusted for were: age, sex, race/ethnicity, diabetes, congestive heart failure, coronary artery disease, cerebrovascular disease, beta-blocker use, RAAS blocker use, no dihydropyridine calcium channel blocker use, thiazide diuretic use, loop diuretic use, and eGFR. IRRs were again presented for 7 S-K intervals of equal length across 4 eGFR levels and showed a U-shaped relationship for each eGFR level. The IRR for patients with S-K ≥ 6.0 mmol/L ranged from [redacted] highlighting increased risk of MACE for patients with more severe HK.

3.1.3 S-K and hospitalisation

[redacted] relevant studies were identified assessing the relationship between S-K and hospitalisation in CKD patients. [redacted] focusing on patients with hypokalaemia was excluded as it was not conducted in the relevant population. [redacted] concentrating on antihypertensive medications was not deemed appropriate as the analysis was not adjusted for medication usage.

Of the remaining [redacted] studies, the [redacted] reported IRRs for 7 different S-K intervals, whereas the study by [redacted] only specified risk ratios for 1 S-K intervals. [redacted]. reported a broadly U-shaped relationship between S-K and hospitalisation with patients with more severe HK (S-K ≥ 6.0 mmol/L) having an IRR of between [redacted] depending on eGFR level. Similarly, [redacted] reported that patients with HK have a [redacted] increased risk of mortality compared to non-HK patients.[5]

3.1.4 S-K and outcome summary

Overall, a similar U shaped 'curve' representing the relationship between S-K and each outcome was observed across all the studies (**Error! Reference source not found.**). Patients with a higher S-K were at a higher risk of death, MACE and hospitalisation than those patients with lower S-K values. (Table 24,

Table **25** and **Error! Reference source not found.** in Appendix B) Relative measures of risk ranging from [redacted] when compared to normokalaemic patients for death, MACE and hospitalisation respectively.

Figure 8: Relationship between S-K and outcomes in CKD patients sourced from the literature

[redacted]

Abbreviations: CKD, chronic kidney disease; HR, hazard ratio; IRR, incidence rate ratio; RR; risk ratio; S-K, serum potassium
Results reported as an x-year probability/incidence have been converted to a relative risk, using the lowest risk category as a reference

3.2 RCT evidence exists for the relationship between S-K and outcomes in HF patients and is supported by observational data

Of the [redacted] reporting on the relationship between S-K and mortality in HF patients, [redacted] were excluded: [redacted] did not assess hyperkalaemic patients and [redacted] did not state the S-K level for which the HRs were reported. Of the remaining [redacted] studies, [redacted] were observational studies[redacted]

3.2.1 S-K and mortality

[redacted] reported on the relationships between both S-K and mortality and S-K and hospitalisation. In the study, [redacted] patients from the Americas and [redacted] patients from Russia and Georgia with HF defined as NYHA class II-IV were included and HRs for 6 S-K intervals were stated for each outcome. The HRs were adjusted for region, age, gender, race, baseline GFR, baseline potassium, and baseline pharmacologic treatment (renin-angiotensin-aldosterone antagonists, beta blockade and loop diuretics) as well as for spironolactone. For the relationship between S-K and both outcomes, a U-shaped relationship was reported. This relationship was corroborated by all of the observational studies reporting rate ratios for patients with hypo-, normo- and hyperkalaemia.[redacted]

[redacted] was a retrospective analysis of the Danish National Population Register. A total of [redacted] patients were diagnosed with HF during hospital admission or in an ambulatory outpatient setting between 1994 and 2012. HRs, adjusting for age, sex, acute myocardial infarction, chronic obstructive pulmonary disease, diabetes, ICD, relevant concomitant pharmacotherapy (beta-blockers, mineralocorticoid receptor antagonists, thiazides, digoxin and potassium supplements) and a high serum creatinine level, were derived for 90-day mortality. The HRs were presented for 8 different S-K intervals between [redacted]/L of varying width and showed a statistically significant U-shaped relationship.

[redacted], as described in Section **Error! Reference source not found.**, also assessed [redacted] patients with HF and generated adjusted IRRs in a similar manner to those

produced for CKD patients. This study showed that moving from hypo- or hyperkalaemia to normokalaemia reduced the risk of death, with IRRs decreasing [redacted].

[redacted] evaluated [redacted] patients over the age of 75 from the RICA Spanish Heart Failure Registry. Whilst the population is not directly comparable to UK clinical practice, this study reported a U-shaped relationship between S-K and mortality. Both the 1-year probability and risk of death reduced for patients with a S-K level between 3.5 - 5.5 compared to those with a S-K level outside of the range.

[redacted] was a retrospective cohort study assessing [redacted] consecutive patients from 2004 through 2013. Odds ratios (ORs) for 5 S-K intervals were reported and showed a U-shaped relationship between S-K and mortality. However, the study was only reported as an abstract and did not specify which covariates were adjusted for.

[redacted] patients on the Danish national registries that were treated with loop diuretics after their first myocardial infarction episode and with a S-K measurement available within three months. HRs were produced for 7 S-K intervals and were adjusted by age, sex, biologically relevant comorbidities (e.g. stroke) and medication, including RAAS inhibitors. Again, a statistically significant U-shaped relationship was observed. Compared to the reference category of 3.9 – 4.2mmol/L, the study reported an increase in mortality risk for patients with S-K < 3.5mmol/L ([redacted]) as well as for patients with S-K > 5.5 mmol/L ([redacted]).

[redacted] investigated how a change in S-K affected the risk of mortality on a continuous scale, rather than by potassium intervals. The study was of prospective design, evaluating [redacted] patients with HF and a U-shape relationship between S-K and all-cause mortality was identified. [redacted] were reported for hypo-, normo-, and hyperkalaemia respectively and patients were independently found to have improved survival outcomes when their S-K was normalised (p-value = 0.001).

[redacted] patients with a serum sodium and potassium measurement available from the same day within 90 days of a loop diuretic prescription. Patients were sourced from the Danish national registries between 2000 and 2012 and HRs were presented for 5 S-K intervals, with the highest risk of death observed for patients with S-K < 3.5mmol/L and S-K > 5.0mmol/L. The HRs were adjusted for a range of covariates covering patient characteristics, comorbidities and concomitant pharmacotherapies such as RAASi.

Additionally, the [redacted] all highlighted that patients with HK have a higher risk of death compared to patients with lower S-K levels.

The remaining [redacted] observational studies reporting the relationship between S-K and mortality in HF patients can be found in Appendix B. These studies did not present granular results and were therefore not deemed appropriate to inform the relationship of interest.

3.2.2 S-K and MACE

No relevant studies were identified in the SLR that reported on the relationship between S-K and the composite endpoint of MACE in patients with HF.

3.2.3 S-K and hospitalisation

[redacted] observational studies assessed the relationship between S-K and hospitalisation in HF patients. [redacted] of these studies were excluded as they were not relevant to the decision problem: [redacted] only examined the effect of hypokalaemia and [redacted] study only assessed patients over the age of 75[redacted]

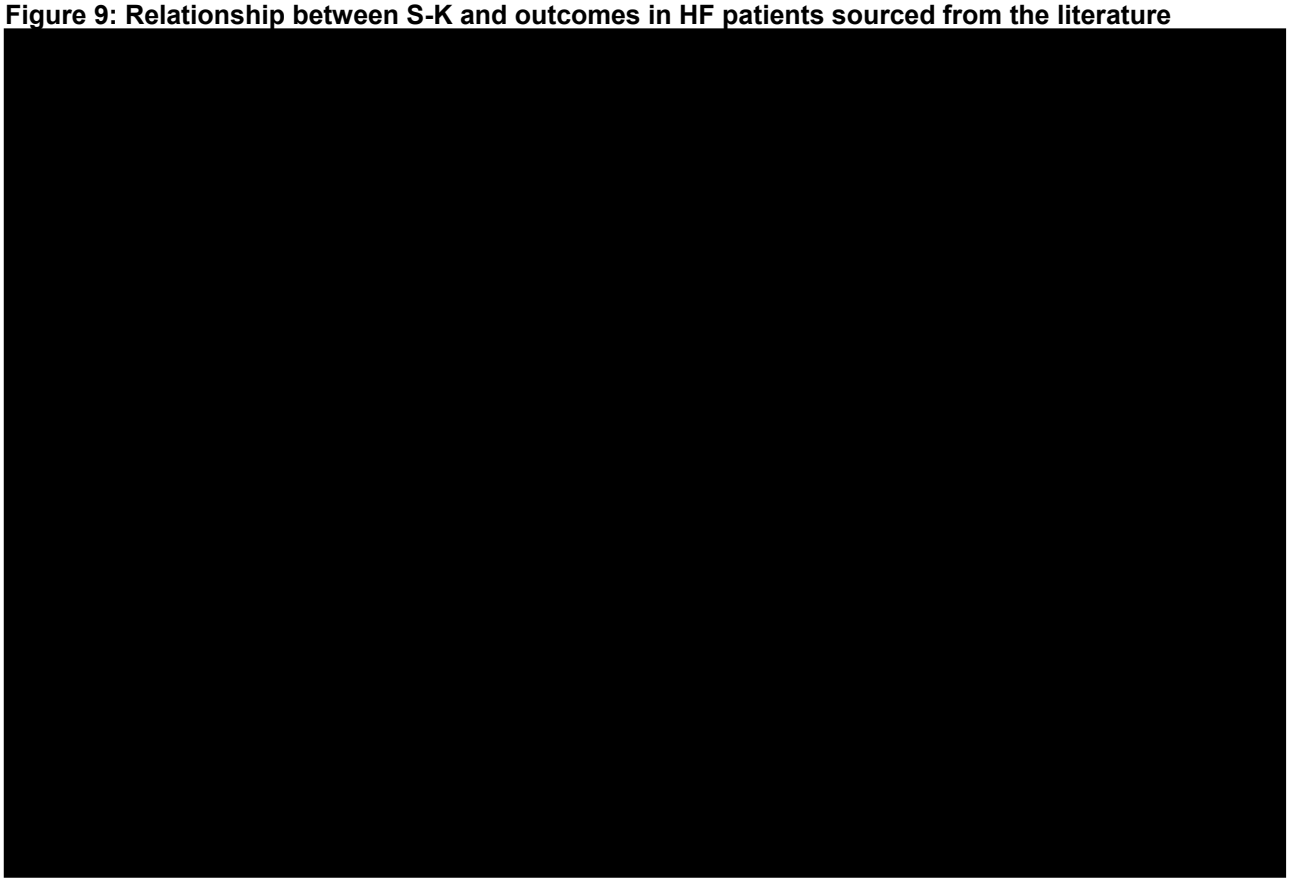
Of the remaining three studies, [redacted] showed a non-significant but slight decrease in hospitalisation risk for patients with mild HK ([redacted]), [redacted] reported that there was a [redacted] increase in death for patients with S-K > 5.5 compared to normokalaemic patients and [redacted] showed that the risk of

hospitalisation increased for patients as HK severity increased (S-K > 5mmol/L [redacted] when compared to non-HK patients).

3.2.4 S-K and outcome summary

Overall, a similar U-shaped 'curve' representing the relationship between S-K and each outcome was observed across all the studies. Patients with a higher S-K were at a higher risk of death and hospitalisation than those patients with lower S-K values. Relative measures of risk ranged from [redacted] when compared to normokalaemic patients for death, MACE and hospitalisation respectively (Figure 9).

Figure 9: Relationship between S-K and outcomes in HF patients sourced from the literature



Abbreviations: HF, heart failure; HR, hazard ratio; IRR, incidence rate ratio; OR, odds ratio; RR; risk ratio; S-K, serum potassium
Results reported as an x-year probability/incidence have been converted to a relative risk, using the lowest risk category as a reference

4 Key issue 4: Evidence on RAASi and long-term outcomes

ACD Section 3.4: '*The Committee concluded that factors affecting the harms and benefits of stopping RAAS inhibitors because of hyperkalaemia compared with using another antihypertensive (for people with high blood pressure) or with standard care (for people who would not normally be offered another blood pressure lowering drug) were affected by the: underlying condition, type of RAAS inhibitor, dose of RAAS inhibitor, number of RAAS inhibitors, reason for stopping RAAS inhibitor.'*

ACD: Section 3.11: '*It was unclear whether the benefits of starting RAAS inhibitors on survival and lower progression of chronic kidney disease (that had been assessed in the network meta-analyses of trials) were the same as the risks of stopping RAAS inhibitors to manage serum potassium levels. This was because patients may change to another antihypertensive drug.'*

AstraZeneca understand the concerns raised by the Committee and recognise the need for a thorough review of the literature in order to summarise the evidence base available on the relationship between RAASi and long-term outcomes (death, hospitalisation and MACE), as well the effect of RAASi on disease progression in CKD and HF patients. Due to the time constrains for the ACD response, a targeted literature review approach was used. We plan to complement the targeted literature review approach with a thorough systematic literature review of the evidence, however, outputs of this will not be available in advance of responding to the ACD.

4.1 Meta-analyses provide evidence on the relationship between RAASi and clinical outcomes in CKD patients

The targeted literature review identified 2 studies that reported the effect of RAASi down-titration or discontinuation on clinical outcomes.

Bennett et al. was a retrospective observational study based on the UK CPRD database. Patients with non-dialysis stage ≥3 CKD (n=144,388) or HF (n=23,541) were included in the analysis. The analysis showed that the 5-year mortality risk in CKD patients who discontinued RAASi increased by a factor of 2.3 compared to patients who received ongoing therapy.[121]

Epstein et al. was a retrospective observational study, based on a US electronic health records database, in patients with stage 3-4 CKD, HF and/or diabetes (n=250,108). CKD patients who discontinued RAASi therapy experienced higher rates of cardiorenal outcomes and mortality (54.4%) compared to patients on sub-maximum doses (47.4%, $p<0.05$) or maximum doses (42.6%, $p<0.05$), indicating clinical outcomes to be dose-dependent, although there was limited reporting on adjustment for covariates. The results also indicated that patients on sub-maximum dose or who discontinued RAASi therapy died twice as frequently as patients on maximum dose, irrespective of comorbidity status or patient age.[84]

In addition to the identification of the two retrospective studies described above, the targeted literature review also confirmed the systematic review and network meta-analyses by Xie et al. used in the original company submission to be the most appropriate source of evidence. Other meta-analyses encountered in the targeted literature review were based on observational studies only,[122] in dialysis patients,[123,124] exclusively in studies of MRA (not commonly used in CKD patients in UK clinical practice),[125,126] or included patients with early stage CKD (stage ≥2),[127] and therefore not relevant for the current decision problem.

As previously described, Xie et al. was a systematic review (studies published before November 2014) and Bayesian network meta-analysis of ACEi and ARB in CKD patients (n=64,768). The network meta-analysis showed ACEi and ARB to significantly reduce the odds of major CV events (OR: 0.82 and 0.76, respectively; 95% CrI: 0.71–0.92 and 0.62–0.89, respectively), compared to placebo. There was a numerical, but not statistically significant, difference in the odds of all-cause mortality with ACEi and ARB (OR: 0.87 and 0.99, respectively; 95% CrI: 0.74–1.01 and 0.78–1.21; respectively).

Xie et al. also evaluated the effect of ACEi and ARB versus active control treatments, defined as active antihypertensive drugs other than ACEi and ARB. There was a numerical, but not statistically significant, difference in the odds of CV events with ACEi and ARB (OR: 0.94 and 0.86, respectively; 95% CrI: 0.75–1.12 and 0.70–1.03; respectively) when compared to active control. The odds of all-cause mortality was significantly reduced with ACEi (OR: 0.72; 95% CrI: 0.53–0.92) compared to active control. There was also a numerical reduction in odds of all-cause mortality with ARB (OR: 0.81, 95% CrI: 0.61–1.03) compared to active control, close to statistical significance. Overall, compared to ARB, ACEi were consistently associated with lower probabilities of events evaluated.[128]

The results of this targeted literature review showed the clinical benefits of RAASi in CKD patients to mirror the risks associated with RAASi discontinuation. Furthermore, based on the evidence reviewed, the effect size of RAASi discontinuation on survival appears to be at least as large as the survival benefits of RAASi initiation, although the effect sizes are from different studies and therefore not directly comparable. Given the availability of more robust evidence on the benefits of RAASi initiation compared to the paucity of data on the effect of RAASi down-titration or discontinuation, it is appropriate to use data on RAASi initiation as proxy to model the effect of RAASi down-titration or discontinuation. This approach was taken in the original company submission and is also used in the revised base case model (see Section 6). The majority of CKD and HF patients in clinical practice are already treated with other antihypertensive therapies, and as such RAASi discontinuation is not accompanied by the initiation of another antihypertensive drug (see Section 4.3). Therefore, the effect size of RAASi compared to placebo has been used in the revised base case. However, in order to address the Committee's concerns that some patients may change from RAASi therapy to another antihypertensive drug, the odds ratios from the comparison of ACEi and ARB versus active controls, are applied in a scenario analysis.

4.2 Meta-analyses provide evidence on the relationship between RAASi and clinical outcomes in HF patients

The targeted literature identified 3 primary studies on the effect of RAASi down-titration or discontinuation on mortality, hospitalisation and CV outcomes, as described below.

Bennett et al. was a retrospective observational study based on the UK CPRD database. Patients with non-dialysis stage ≥3 CKD (n=144,388) or HF (n=23,541) were included in the analysis. The analysis showed that the 5-year mortality risk in HF patients who discontinue RAASi increased by a factor of 3.3 compared to patients who receive ongoing therapy.[121]

Epstein et al. was a retrospective observational study, based on a US electronic health records database, in patients with stage 3-4 CKD, HF and/or diabetes (n=250,108). HF patients who discontinued RAASi therapy experienced higher rates of cardiorenal outcomes and mortality (59.8%) compared to patients on sub-maximum doses (52.3%, $p<0.05$) or maximum doses (42.6%, $p<0.05$), indicating clinical outcomes to be dose-dependent, although there was limited reporting on adjustment for covariates. The results also indicated that patients on sub-maximum dose or who discontinued RAASi therapy died twice as frequently as patients on maximum dose, irrespective of comorbidity status or patient age.[84]

Gilstrap et al., was a retrospective observational study in patients hospitalised for HFrEF in the US (n=16,052). A multivariate Cox proportional hazards model adjusted for demographics, past medical history, vital signs, laboratory values, HF characteristics, inpatient procedures and hospital characteristics was used to determine the relationship between ACEi/ARB and outcomes. The adjusted HRs for 30-day, 90-day and 1-year mortality rates for patients who discontinued RAASi versus those who continued RAASi were 1.92 (95% CI: 1.32–2.81), 1.68 (95% CI: 1.31–2.15) and 1.35 (95% CI: 1.13–1.61), respectively, showing RAASi discontinuation to be associated with worse survival. The 30-day readmission rates were also significantly higher for patients who discontinued RAASi compared to those who continued RAASi (HR: 1.40; 95% CI: 1.16–1.71), whilst the 90-day and 1-year readmission rates were numerically higher (HR: 1.18, 1.07, respectively; 95% CI: 0.98–1.41, 0.82–1.25, respectively).[129]

The targeted literature review also identified 2 meta-analyses evaluating the clinical benefits of ACEi, ARB and MRA in HF patients, as described below, which were not previously included in the original company submission. Additionally, one meta-analysis evaluating the effect of ACEi and MRA by patients' NYHA class was identified.[130] Other meta-analyses encountered through the targeted literature review were based on observational cohort studies,[131] or in dialysis patients,[132] and therefore not relevant to the current decision problem. No meta-analysis of RAASi therapy in HF reported MACE as an outcome were identified.

Xie et al. was a network meta-analysis that utilised both direct and indirect evidence to compare the relative efficacy of all available RAASi therapies with each other and with placebo. The network meta-analysis was informed by 21 double-blinded RCTs in patients with HFrEF or left ventricular dysfunction (n=69,229). Compared to placebo, ACEi (OR: 0.80; 95% CrI: 0.71–0.89), ARB (OR: 0.86; 95% CrI: 0.75–0.97) and ARA (OR: 0.74; 95% CrI: 0.62–0.86) all significantly reduced the odds of all-cause death. Similarly, odds for HF hospitalisation were lower for patients treated with ACEi (OR: 0.69; 95% CrI: 0.61–0.77), ARB (OR: 0.71; 95% CrI: 0.63–0.81) and ARA (OR: 0.70, 95% CrI: 0.57–0.82).[133] A sensitivity analysis conducted based on 9 RCTs (n=30,878) with a high background use of ACEi and/or ARB evaluate the effect of adding an ARB or ARA to background therapy. The addition of ARA to background therapy was associated with a significant reduction in the odds of all-cause mortality and HF hospitalisation (OR: 0.73 and 0.67, respectively; 95% CrI: 0.51–0.95 and 0.47–0.87, respectively). The addition of ARB to background ACEi was associated with a numerical reduction in the odds of HF hospitalisation (OR: 0.85; 95% CrI: 0.64–1.17), but there was a limited effect on the odds for all-cause mortality (OR: 1.01; 95% CrI: 0.73–1.51).[133]

Thomsen et al. conducted pair-wise meta-analyses to compare ACEi, ARB and MRA against placebo in patients with HFrEF, based on 47 RCTs from references used by the ESC and ACCF/AHA guidelines, and 38 additional studies identified through an SLR. The results from Thomsen et al. align with those from Xie et al., showing ACEi, ARB and ARAs to significantly reduce the risk of mortality (RR: 0.86, 0.84 and 0.82, respectively; 95% CI: 0.81–0.91, 0.72–0.97 and 0.76–0.88, respectively) and HF hospitalisation (RR: 0.71, 0.69 and 0.78, respectively; 95% CI: 0.65–0.77, 0.59–0.79 and 0.66–0.93, respectively).[134]

Miller et al.[130] was a systematic literature review and meta-analysis with the primary objective to evaluate the effect of NYHA class on the efficacy of HF interventions, including ACEi (4 RCTs, n=7,100) and MRA (3 RCTs, n=4,838) in HF patients with left ventricular ejection fraction <45%. The pooled relative mortality risk for NYHA class I/II versus II/IV were similar for ACEi (RR: 0.90 and 0.88, respectively; 95% CI: 0.81–0.99 and 0.78–1.00, respectively) and for MRA (RR: 0.79 and 0.75, respectively; 95% CI: 0.66–0.95 and 0.73–0.86, respectively), showing that the relative risk reductions associated with ACEi and MRA were not dependent on patients' NYHA class.[130]

The relationship between ACEi and hospitalisation in the original company submission was informed by Flather et al.,[135] a systematic overview of individual patient data from 5 large RCTs in patients with HF or left ventricular dysfunction (n=12,763). The use of ACEi was associated with reduced odds of death and HF hospitalisation (OR: 0.80 and 0.67, respectively; 95% CI: 0.74–0.87 and 0.61–0.74, respectively). There was a trend towards greater reduction in risk of death or HF hospitalisation in patients with lower ejection fractions, but the benefit of ACEi was apparent over the range of ejection fractions examined.

Published RCT evidence demonstrates the clinical benefits of RAASi to vary with RAASi dose.[136] In the ATLAS study, patients in the low-dose group had a numerically higher risk of death (8%, p=0.128) and a statistically significant higher risk of hospitalisation (12%, p=0.002) compared to patients in the high-dose group.[136]

In summary, the targeted literature review identified several primary studies (Bennett et al., Epstein et al. and Gilstrap et al.) that patients who discontinued RAASi have worse outcomes in terms of mortality and HF hospitalisation compared to patients who continued on RAASi.[84,121,129] Similarly to the effect of RAASi in CKD patients (Section 4.1), the effect size of RAASi discontinuation appears to be at least as large as the effect size of RAASi initiation,[130,133-135] although these effect sizes are from different studies and therefore not directly comparable. Evidence from RAASi initiation studies also

suggests RAASi therapies to have additive effects, i.e. that patients on RAASi monotherapy or dual therapy receive further benefits when treated with additional RAASi therapies (i.e. dual therapy or triple therapy, respectively).[133] Furthermore, RCT evidence also demonstrate the effect of RAASi therapy to be dose-dependent.[136] Given the high-quality evidence available on the effect of RAASi initiation, it is appropriate to use RAASi initiation evidence as proxy for the effect of RAASi down-titration or discontinuation.

Furthermore, the cost-effectiveness model does not currently adjust the risk of mortality in HF patients according to RAASi use, due to limited time during the consultation period to incorporate additional model parameters. As such, the benefits of SZC as a RAASi enabler in HF are not taken into account, and model results should therefore be considered to be highly conservative with respect to HF mortality. Risk of hospitalisation in HF patients is however adjusted based on RAASi use in the cost-effectiveness model. Flather et al.[135] was a meta-analysis based on individual patient data and therefore provides more information than meta-analyses of aggregate data. Therefore, data from Flather et al. was used in the base case for HF hospitalisation and Xie et al. and Thomsen et al. were evaluated in scenario analyses.

4.3 Meta-analyses show the effect of RAASi in delaying progression of CKD and HF

AstraZeneca understand the Committee's concerns, about the possibility that CKD and HF patients may change from RAASi therapy to another antihypertensive drug in clinical practice, and that therefore the effect of RAASi discontinuation may be less pronounced.

Evidence identified from targeted literature searches show that RAASi therapy is associated with a significant reduction in disease progression compared to other antihypertensive therapies,[128,137] and as such, clinical benefits will be lost by replacing RAASi therapy with other antihypertensive treatments.

The network meta-analysis in CKD patients by Xie et al.[128] (described above in Section 4.1) showed that ACEi and ARB are associated with significant reductions in the odds for kidney failure (OR: 0.61 and 0.70, respectively; 95% CrI: 0.47–0.79 and 0.52–0.89; respectively) when compared to placebo. When ACEi and ARB were compared against active treatments, defined as active antihypertensive drugs other than ACEi and ARB, the reduction in odds for kidney failure remained significant (OR: 0.65 and 0.75, respectively; 95% CrI: 0.51–0.80 and 0.54–0.97, respectively).

Similarly, a meta-analysis by Kunz et al.[53] showed that ARB significantly reduced proteinuria compared with placebo or calcium channel blockers (OR: 0.57 and 0.69, respectively; 95% CI: 0.47–0.68 and 0.62–0.77, respectively). The combination of ARB with ACEi further reduced proteinuria compared to ARB monotherapy or ACEi monotherapy (OR: 0.76 and 0.78, respectively; 95% CI: 0.61–0.92 and 0.72–0.84, respectively).[53] In addition, results from other trials showed that the dose of ACEi is important, with maximal and supra-maximal doses being associated with improved outcomes and delayed disease progression.[54,55]

A meta-analysis of MRA in HFrEF patients by Phelan et al.[137] included 14 RCTs reporting on 1,575 patients in total. Overall, 73% of patients were concurrently treated with β-blockers and most patients were also treated with ACEi or ARB (93%). Overall, the weighted mean difference in ejection fraction between treatment and control groups were 3.2% (OR: 1.9; 95% CI: 1.4–2.7; p<0.001). Additionally, MRA treatment was also associated with an improvement in patients' functional capacity, measured as an improvement in the NYHA class by 0.13 (OR: 1.7; 95% CI: 1.2–2.2; p=0.001).[137] Similarly, published RCT evidence has also demonstrated the benefit of ACEi in delaying disease progression in HF patients.[138]

Whilst beta-blockers provide mortality and symptom benefits in HF patients,[139] typically both beta-blockers and RAASi therapy are used in combination to treat HF patients, and as such it may not be possible for patients to *change* [from RAASi therapy] to another antihypertensive with similar clinical benefits. Other 'anti-hypertensive' therapies have not been demonstrated to significantly impact outcomes.

Data from the UK CPRD show that a large proportion of CKD and HF patients are already treated with an antihypertensive at baseline. Amongst CKD patients with S-K ≥6.0, 35.00%, 44.42% and 31.40% of patients were treated with calcium-channel blockers, diuretics and β-blockers, respectively, collectively representing a significant proportion of patients, even when prevalence of dual or triple therapy is taken into account. Similarly, amongst HF patients with S-K ≥5.5, 25.93%, 77.65% and 58.46% of patients were treated with calcium-channel blockers, diuretics and β-blockers, respectively, representing the majority of HF patients.

4.4 Summary of evidence on RAASi and long-term outcomes

We recognise the Committee's concerns around the associations between RAASi down-titration and discontinuation and outcomes, as published in the ACD, and we have therefore conducted targeted literature reviews on these topics. The studies identified address most of the Committee's concerns, particularly in confirming the negative effect of RAASi down-titration and discontinuation on clinical outcomes which is likely to be of a larger magnitude than the cardiorenal benefits of RAASi initiation. The clinical benefits associated with RAASi therapy in CKD and HF patients are well recognised and emphasised in clinical guidelines and consensus statements, including those published by NICE, the European Society of Cardiology, and the British Society for Heart Failure, supporting the use of continuous and optimised RAASi therapy.[22-24]

We recognise, that due to time constraints, we were not able to systematically review the literature to ensure all relevant studies are identified. A systematic literature review on the topics discussed in Section 4 is underway, but outputs of this will not be available in advance of responding to the ACD. In the meantime, we are providing scenario analyses in Section 6, where we conservatively assume that there are no benefits associated with RAASi therapy, and that therefore RAASi down-titration or discontinuation are not associated with any loss in clinical benefits.

Whilst the Committee's concerns about the effect of "changing [from RAASi] to another antihypertensive" are valid, evidence from the literature indicates RAASi to be associated with significant clinical benefits in addition to reduced blood pressure alone.[128,137] Furthermore, because a substantial proportion of CKD and HF patients are already treated with other antihypertensive treatments, there is limited scope to "change [from RAASi] to other antihypertensives" in UK clinical practice.[66]

5 Key issue 5: Use of SZC in emergency admissions

5.1 A sub-group of patients with life-threatening HK was enrolled in ZS-004

ACD Section 3.10. '*[The Committee] noted that it had seen no data for people with life-threatening hyperkalaemia who would be treated in the emergency setting because this population was not included in the trial.*'

As previously stated, the Renal Association guidelines recommend that patients are treated with IV insulin dextrose when S-K is ≥6.0 mmol/L, with expert help required when S-K is ≥6.5 mmol/L. If ECG changes are apparent, guidelines recommend the use of calcium gluconate to stabilise the myocardium prior to treating with insulin-dextrose.[32]

As insulin-dextrose is a temporising agent, clinicians advised that repeat treatment is common. This results in the need for prolonged monitoring of patients due to the risk of re-bound, and the possible adverse effects associated with insulin. These risks were highlighted in a publication by Rajendran et al, and the need to improve treatment of patients with HK was recognised in a recent Patient Safety Alert published by NHS Improvement.[11,48] Therefore, we have positioned SZC as a treatment for HK following initial administration of insulin-dextrose to maintain normokalaemia, which may also mitigate the need for repeat treatment with IV insulin-dextrose.

As highlighted in the ACD, there is limited clinical trial data on the clinical effectiveness of SZC in patients with life-threatening HK (S-K ≥6.5). However, as there was no upper baseline S-K cut-off in the inclusion criteria for ZS-004, a sub-group (n=8[ii]) of patients with baseline S-K≥6.5 were included in the correction phase of the trial. The mean baseline S-K and the 48h absolute S-K reduction (SD) for these patients are summarised in Table 8.

[redacted] the patients in this sub-group achieved S-K <5.5 and S-K <6.0 at the end of the correction phase (outcomes of interest to clinicians), providing data on the effectiveness of SZC in reducing S-K levels in patients with life-threatening HK. However, as the trial protocol required patients to achieve S-K <5.1, only [redacted] of these patients continued to be treated in the maintenance phase of the trial and these patients were randomised to placebo ([redacted]), SZC 10 g OD ([redacted]) and SZC 15 g OD ([redacted]). [redacted]

Overall, the SZC treatment effect in the sub-group of patients with baseline S-K ≥6.5 (48h reduction: [redacted] mmol/L) is greater than the effect size observed in sub-groups with a lower baseline S-K (48h reduction: [redacted] to [redacted] mmol/L, see Table 4).

Table 8. ZS-004 correction phase S-K change in sub-group with baseline S-K ≤6.5

Sub-population	Baseline S-K (SD)	48h absolute reduction (SD)	Number of patients with S-K <5.5 mmol/L at 48h (%)	Number of patients with S-K <6.0 mmol/L at 48h (%)
Baseline S-K ≥6.5 (n=8[a])	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: S-K serum potassium, SD, standard deviation
Source: ZS-004 CSR Listings 16.2.6.1
[a] One patient with baseline S-K 7.2 mmol/L did not complete the correction phase of ZS-004 and was therefore not included in this analysis

[ii] One patient with baseline S-K 7.2 mmol/L did not complete the correction phase of the study and was therefore not included in this analysis (n=8)

5.2 The speed of response with SZC is fast and relevant for patients treated during an emergency admission

Submissions from professional organisations in advance of the first appraisal Committee meeting highlighted the importance of a fast response to treatment, within 2h, for HK therapies where emergency guidelines are followed.[47]

Secondary analyses of ZS-004 show the median time to normalisation of S-K values in the ITT population to be 2.2h after the first dose of SZC (see Document B, Section B.2.6.1), with normalisation defined as S-K ≤5.0. As such, the median time to normalisation to S-K <5.5 or S-K <6.0, levels relevant to UK clinical practice, is expected to be less than 2.2h and therefore relevant for use in this setting. This contrasts with other potassium binders, such as patiromer, which has a slower onset of 7h following the first administration.[140]

6 Key issue 6: Model uncertainty

ACD Section 3.11: *'[The Committee concluded that] cost-effectiveness results did not address the clinical problem. In addition, the committee noted further limitations:*

- *The company did not model the relationship between having a RAAS inhibitor and serum potassium.*
- *The model excluded outpatient follow-up of people who had had treatment for hyperkalaemia in hospital.*
- *The model did not account for the proportion of people whose hyperkalaemia was not corrected by sodium zirconium cyclosilicate.*
- *The modelling of sodium zirconium cyclosilicate in people with underlying chronic kidney disease or heart failure did not account for people having both conditions.*
- *The model did not address the possibility of a dose-dependent relationship between RAAS inhibitors and more advanced renal disease, cardiovascular disease and death.*
- *The model did not address the fact that some people may stop RAAS inhibitors for reasons other than hyperkalaemia.*
- *The ERG's utility values for chronic kidney disease were more plausible than the company's because utility is expected to decrease as kidney disease progresses.*
- *The ERG's assumptions on the costs of changing RAAS inhibitor dosage were more plausible than the company's because the consultations to change dosage would be expected to be done in an outpatient rather than an inpatient setting.'*

The economic model developed for this appraisal was based on a patient level simulation model which has recently been accepted for publication in the peer-reviewed Journal of Medical Economics.[141] The originally submitted cost-effectiveness model has been updated to address concerns raised in the ACD taking into account the new evidence presented in Sections □–5. A summary of the revised base case, focusing on the changes from the original company submission is provided in Table 9. Details of the model inputs used, along with justifications, and relevant scenario analyses are provided in Sections 6.1-6.6.

The incremental cost-effectiveness ratios associated with the revised base case are presented in Table 10 for CKD and HF, and for the outpatient setting and emergency admissions. Compared to standard care, SZC is associated with an ICER of £9,865 and £18,158 in the outpatient setting for CKD and HF patients, respectively, and dominates in patients admitted to A&E/AMU. Incremental costs and QALYs of the revised base case are reported in Table 11 and

Table 12.

The results from scenario analyses are presented in Table 11 and

Table 12 for the outpatient setting and emergency admissions, respectively.

Table 9. Summary model inputs used for revised base case

Parameter	Outpatient setting		Emergency admissions	
	CKD	HF	CKD	HF
SK – trajectories				
Threshold for treatment initiation	6.0 mmol/L, see Section 6.1.1	5.5 mmol/L, see Section 6.1.1	6.0 mmol/L, see Section 6.1.1	
Threshold for repeat treatment	6.0 mmol/L, see Section 6.1.1	5.5 mmol/L, see Section 6.1.1	6.0 mmol/L, see Section 6.1.1	
Threshold for "less severe" HK event	6.0 mmol/L, see Section 6.1.1	5.5 mmol/L, see Section 6.1.1	N/A	
Threshold for "severe" HK event	6.5 mmol/L, see Section 6.1.1	6.5 mmol/L, see Section 6.1.1	6.0 mmol/L, see Section 6.1.1	
RAASi down-titration (max to sub-optimal) – standard care	S-K ≥5.5,<6.0: 0% S-K ≥6.0: 0% See Section 6.1.1	S-K ≥5.5,<6.0: 80% S-K ≥6.0: 0% See Section 6.1.1	S-K ≥5.5,<6.0: 0% S-K ≥6.0: 0% See Section 6.1.1	
RAASi discontinuation (max to discontinuation; sub-optimal to discontinuation) – standard care	S-K ≥5.5,<6.0: 0% S-K ≥6.0: 100% See Section 6.1.1	S-K ≥5.5,<6.0: 20% S-K ≥6.0: 100% See Section 6.1.1	S-K ≥5.5,<6.0: 100% S-K ≥6.0: 100% See Section 6.1.1	
S-K trajectory in SZC arm	Based on pooled ZS-004 and ZS-005 data, from patients with baseline S-K of ≥6.0 mmol/L, see Section 6.1.2	Based on pooled ZS-004 and ZS-005 data, from patients with baseline S-K of ≥5.5 mmol/L, see Section 6.1.2	Based on pooled ZS-004 and ZS-005 data, from patients with baseline S-K of ≥6.0 mmol/L, see Section 6.1.2	
S-K trajectory in SoC arm	Based on placebo arm of ZS-003, adjusted to patients with baseline S-K **≥6.0**, see Section 6.2	Based on placebo arm of ZS-003, adjusted to patients with baseline S-K **≥5.5**, see Section 6.2	Based on placebo arm of ZS-003, adjusted to patients with baseline S-K ≥6.0, see Section 6.2	
S-K and outcomes				
Baseline mortality	Go et al. 2004	Levy et al. 2006 (SHFM)	Go et al. 2004	Levy et al. 2006 (SHFM)
Baseline MACE	Go et al. 2004	CPRD study, see Sections 6.3	Go et al. 2004	CPRD study, see Sections 6.3
Baseline hospitalisation	Go et al. 2004	Ford et al. 2012	Go et al. 2004	Ford et al. 2012
IRR: S-K and mortality	Luo et al. 2016, see Sections 6.3	Desai et al. 2018 (RCT), see Section 6.3	Luo et al. 2016, see Sections 3.1 and 6.3	Desai et al. 2018 (RCT), see Section 6.3
IRR: S-K and MACE		CPRD study, see Section 6.3		CPRD study, see Section 6.3
IRR: S-K and hospitalisation		Desai et al. 2018 (RCT), see Section 6.3		Desai et al. 2018 (RCT), see Section 6.3
RAASi and outcomes				
OR: RAASi and mortality	Xie et al. 2016a (NMA), see Section 4.1	Levy et al. 2006 (SHFM)	Xie et al. 2016a (NMA), see Section 4.1	Levy et al. 2006 (SHFM)

Parameter	Outpatient setting		Emergency admissions	
	CKD	HF	CKD	HF
OR: RAASi and MACE	Xie et al. 2016a (NMA), see Section 4.1	No evidence	Xie et al. 2016a (NMA), see Section 4.1	No evidence
OR: RAASi and hospitalisation	No evidence	Flather et al.	No evidence	Flather et al.
RAASi and S-K				
RAASi effect on S –K	-0.23, see Section 2.1.1	-0.23, see Section 2.1.1	-0.23, see Section 2.1.1	-0.23, see Section 2.1.1
Utilities				
Health state utility values	Ericsson et al. 2017 (EQ-5D), see Section 6.5			
ERG-based assumptions				
Time horizon	Life-time	Life-time	52 weeks	52 weeks
12 weeks RAASi withdrawal if S-K ≥ 6.0 mmol/L whilst on SZC*	Yes	Yes	No*	No*
Reduced RAASi adjustment cost	Lower as per ERG base case	Lower as per ERG base case	Lower as per ERG base case	Lower as per ERG base case

Abbreviations: CKD, chronic kidney disease; CPRD, clinical practice research datalink; CV, cardiovascular; ERG, evidence review group; HF, heart failure; HR: hazard ratio; ICER, incremental cost-effectiveness ratios; IRR: incidence rate ratio; MACE, major adverse cardiovascular events; N/A, not applicable; OR: odds ratio; RCT, randomised controlled trial; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SoC, standard care; SHFM, Seattle heart failure model; SZC, sodium zirconium cyclosilicate

* In the base case, all patients admitted to A&E/AMU withdraw RAASi, and cannot resume RAASi

Table 10. Cost-effectiveness results

ICER, £	Outpatient setting		Emergency setting	
	CKD	HF	CKD	HF
Original company submission base case	£26,111	£12,928	Dominates	£4,924
Revised base case	£11,644	£18,158	Dominates	Dominates

Abbreviations: CKD, chronic kidney disease; HF, heart failure; ICER, incremental cost-effectiveness ratios

Table 11. Scenario analyses in the outpatient setting

#	Parameter	Data source / details	Outpatient setting					
			CKD			HF		
			Incr. costs	Incr. QALYs	ICER	Incr. costs	Incr. QALYs	ICER
-	**Base case**		£8,249	0.708	£11,644	£14,860	0.818	£18,158
S-K trajectories (see Section 6.2.3)								
1	S-K trajectory	Alternative SoC S-K trajectory	£11,362	0.573	£19,815	£13,928	0.641	£21,729
S-K and outcomes – Alternate evidence sources – See Section 6.3								
2	CPRD: S-K and mortality (CKD)	Furuland et al. 2018	£8,774	0.876	£10,018	N/A	N/A	N/A
3	IRR: S-K and mortality (CKD)	Collins et al. 2017	£13,623	0.843	£16,157	N/A	N/A	N/A
4		Nakhoul et al. 2015	£2,689	0.570	£4,717	N/A	N/A	N/A
5	CPRD: S-K and MACE (CKD)	Furuland et al. 2018	£8,296	0.709	£11,694	N/A	N/A	N/A
6	IRR: S-K and mortality (HF)	Aldahl et al. 2017	N/A	N/A	N/A	£13,948	0.860	£16,225
7		Collins et al. 2017	N/A	N/A	N/A	£14,757	0.920	£16,042
8		Krogager et al. 2015	N/A	N/A	N/A	£12,401	0.912	£13,602
9		Nunez et al. 2018	N/A	N/A	N/A	£13,827	0.708	£19,520
10		Polcwiartek et al. 2018	N/A	N/A	N/A	£12,063	0.659	£18,313
S-K and outcomes – All statistical measures varied by +/- 20% apart from reference group (see Section 6.3)								
11	IRR: S-K and mortality (CKD)	Luo et al. 2016 (+20%)	£9,113	0.713	£12,785	N/A	N/A	N/A
12		Luo et al. 2016 (-20%)	£6,848	0.685	£9,990	N/A	N/A	N/A
13	IRR: S-K and MACE (CKD)	Luo et al. 2016 (+20%)	£8,106	0.709	£11,439	N/A	N/A	N/A
14		Luo et al. 2016 (-20%)	£8,402	0.708	£11,867	N/A	N/A	N/A
15	IRR: S-K and hospitalisation (CKD)	Luo et al. 2016 (+20%)	£7,750	0.709	£10,937	N/A	N/A	N/A
16		Luo et al. 2016 (-20%)	£8,843	0.708	£12,487	N/A	N/A	N/A
17	HR: S-K and mortality (HF)	Desai et al. 2018 (+20%)	N/A	N/A	N/A	£14,412	0.866	£16,645
18		Desai et al. 2018 (-20%)	N/A	N/A	N/A	£14,893	0.704	£21,165
19	HR: S-K and hospitalisation (HF)	Desai et al. 2018 (+20%)	N/A	N/A	N/A	£14,463	0.818	£17,670
20		Desai et al. 2018 (-20%)	N/A	N/A	N/A	£15,263	0.818	£18,655
RAASi and outcomes – alternative evidence sources (see Section 6.4)								
21	OR: RAASi and mortality (CKD)	Xie et al. 2016a analysis versus active control	£10,006	0.788	£12,703	N/A	N/A	N/A
22	OR: RAASi and CV event (CKD)	Xie et al. 2016a analysis versus active control	£8,532	0.707	£12,066	N/A	N/A	N/A

#	Parameter	Data source / details	Outpatient setting					
			CKD			HF		
			Incr. costs	Incr. QALYs	ICER	Incr. costs	Incr. QALYs	ICER
23	OR: RAASi and hospitalisation (HF)	Xie et al. 2016b	N/A	N/A	N/A	£14,937	0.818	£18,253
24	OR/HR: RAASi and outcomes in model	Assuming no RAASi effect on outcomes	£7,054	0.631	£11,173	£12,575	0.499	£25,208
RAASi and outcomes – sensitivity analyses with all ORs varied by +/- 20% (see Section 6.4)								
25	OR: RAASi and mortality (CKD)	Xie et al. 2016a (+20%)	£6,082	0.609	£9,981	N/A	N/A	N/A
26	OR: RAASi and mortality (CKD)	Xie et al. 2016a (-20%)	£10,729	0.820	£13,083	N/A	N/A	N/A
27	OR: RAASi and CV event (CKD)	Xie et al. 2016a (+20%)	£8,689	0.706	£12,301	N/A	N/A	N/A
28	OR: RAASi and CV event (CKD)	Xie et al. 2016a (-20%)	£7,804	0.711	£10,983	N/A	N/A	N/A
29	OR: RAASi and hospitalisation (HF)	Flather et al. 2016 (+ 20%)	N/A	N/A	N/A	£15,259	0.818	£18,650
30	OR: RAASi and hospitalisation (HF)	Flather et al. 2016 (- 20%)	N/A	N/A	N/A	£14,427	0.819	£17,625
Scenarios using ERG-based assumptions (see Section 6.6.3)								
31	Wastage: 30 sachet / 28 days	From ERG base case	£9,120	0.708	£12,873	£16,058	0.818	£19,623
32	Hospitalisation days in SZC equal to SoC (3 days)	Scenario analysis undertaken by the ERG	£8,329	0.708	£11,756	£14,876	0.818	£18,178

Abbreviations: CKD, chronic kidney disease; CPRD, clinical practice research datalink; CV, cardiovascular; ERG, evidence review group; HF, heart failure; HR: hazard ratio; ICER, incremental cost-effectiveness ratios; IRR: incidence rate ratio; MACE, major adverse cardiovascular events; N/A, not applicable; OR: odds ratio; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SoC, standard care; SZC, sodium zirconium cyclosilicate; QALY, quality-adjusted life year

Table 12. Scenario analyses for emergency admissions

#	Parameter	Data source / details	Emergency setting					
			CKD			HF		
			Incr. costs	Incr. QALYs	ICER	Incr. costs	Incr. QALYs	ICER
-	**Base case**		-£4,079	0.007	Dominates	-£3,536	0.009	Dominates
S-K trajectories (see Section 6.2.3)								
1	S-K trajectory	Alternative SoC S-K trajectory	-£3,444	0.004	Dominates	-£3,184	0.007	Dominates
S-K and outcomes – alternate evidence sources (see Section 6.3)								
2	CPRD: S-K and mortality (CKD)	Furuland et al. 2018	-£4,324	0.004	Dominates	N/A	N/A	N/A
3	IRR: S-K and mortality (CKD)	Collins et al. 2017	-£3,614	0.014	Dominates	N/A	N/A	N/A
4		Nakhoul et al. 2015	-£4,314	0.004	Dominates	N/A	N/A	N/A
5	CPRD: S-K and MACE (CKD)	Furuland et al. 2018	-£4,037	0.007	Dominates	N/A	N/A	N/A
6	IRR: S-K and mortality (HF)	Aldahl et al. 2017	N/A	N/A	N/A	-£3,198	0.014	Dominates
7		Collins et al. 2017	N/A	N/A	N/A	-£2,600	0.022	Dominates
8		Krogager et al. 2015	N/A	N/A	N/A	-£2,450	0.027	Dominates
9		Nunez et al. 2018	N/A	N/A	N/A	-£3,842	0.004	Dominates
10		Polcwiartek et al. 2018	N/A	N/A	N/A	-£3,691	0.006	Dominates
S-K and outcomes – sensitivity analyses with all statistical measures varied by +/- 20% apart from reference group (see Section 6.3)								
11	IRR: S-K and mortality (CKD)	Luo et al. 2016 (+20%)	-£3,978	0.008	Dominates	N/A	N/A	N/A
12		Luo et al. 2016 (-20%)	-£4,182	0.006	Dominates	N/A	N/A	N/A
13	IRR: S-K and MACE (CKD)	Luo et al. 2016 (+20%)	-£4,110	0.007	Dominates	N/A	N/A	N/A
14		Luo et al. 2016 (-20%)	-£4,062	0.007	Dominates	N/A	N/A	N/A
15	IRR: S-K and hospitalisation (CKD)	Luo et al. 2016 (+20%)	-£4,159	0.007	Dominates	N/A	N/A	N/A
16		Luo et al. 2016 (-20%)	-£4,013	0.007	Dominates	N/A	N/A	N/A
17	HR: S-K and mortality (HF)	Desai et al. 2018 (+20%)	N/A	N/A	N/A	-£3,346	0.012	Dominates
18		Desai et al. 2018 (-20%)	N/A	N/A	N/A	-£3,718	0.006	Dominates
19	HR: S-K and hospitalisation (HF)	Desai et al. 2018 (+20%)	N/A	N/A	N/A	-£3,606	0.009	Dominates
20		Desai et al. 2018 (-20%)	N/A	N/A	N/A	-£3,469	0.009	Dominates
RAASi and outcomes – alternative evidence sources (see Section 6.4)								

#	Parameter	Data source / details	Emergency setting					
			CKD			HF		
			Incr. costs	Incr. QALYs	ICER	Incr. costs	Incr. QALYs	ICER
21	OR: RAASi and mortality (CKD)	Xie et al. 2016a active control	-£4,079	0.007	Dominates	N/A	N/A	N/A
22	OR: RAASi and CV event (CKD)	Xie et al. 2016a active control	-£4,079	0.007	Dominates	N/A	N/A	N/A
23	OR: RAASi and hospitalisation (HF)	Xie et al. 2016b	N/A	N/A	N/A	-£3,536	0.009	Dominates
24	OR/HR: RAASi and outcomes in model	Assuming no RAASi effect on outcomes	-£4,079	0.007	Dominates	-£3,535	0.009	Dominates
RAASi and outcomes – sensitivity analyses with all ORs varied by +/- 20% (see Section 6.4)								
25	OR: RAASi and mortality (CKD)	Xie et al. 2016 (+20%)	-£4,079	0.007	Dominates	N/A	N/A	N/A
26	OR: RAASi and mortality (CKD)	Xie et al. 2016 (-20%)	-£4,079	0.007	Dominates	N/A	N/A	N/A
27	OR: RAASi and CV event (CKD)	Xie et al. 2016 (+20%)	-£4,079	0.007	Dominates	N/A	N/A	N/A
28	OR: RAASi and CV event (CKD)	Xie et al. 2016 (-20%)	-£4,079	0.007	Dominates	N/A	N/A	N/A
29	OR: RAASi and hospitalisation (HF)	Flather et al. 2016 (+ 20%)	N/A	N/A	N/A	-£3,536	0.009	Dominates
30	OR: RAASi and hospitalisation (HF)	Flather et al. 2016 (- 20%)	N/A	N/A	N/A	-£3,536	0.009	Dominates
Scenarios using ERG-based assumptions (see Section 6.6.3)								
31	Wastage: 30 sachet / 28 days	From ERG base case	-£4,028	0.007	Dominates	-£3,488	0.009	Dominates
32	Hospitalisation days in SZC equal to SoC	Scenario analysis undertaken by the ERG	-£3,770	0.007	Dominates	-£3,228	0.009	Dominates
33	Allow patients to restart RAASi	Scenario analysis undertaken by the ERG	-£2,988	0.009	Dominates	-£2,543	0.011	Dominates

#	Parameter	Data source / details	Emergency setting					
			CKD			HF		
			Incr. costs	Incr. QALYs	ICER	Incr. costs	Incr. QALYs	ICER
Disutilities and costs associated with emergency admissions (see Section 6.6.1)								
34	Emergency admission disutility	Sullivan et al. Disutility = -0.06675	-£6,037	0.011	Dominates	-£6,900	0.009	Dominates
35	Emergency admission additional costs	NHS reference costs Cost = £2,390.34						

Abbreviations: CKD, chronic kidney disease; CPRD, clinical practice research datalink; CV, cardiovascular; ERG, evidence review group; HF, heart failure; HR: hazard ratio; ICER, incremental cost-effectiveness ratios; IRR: incidence rate ratio; MACE, major adverse cardiovascular events; N/A, not applicable; OR: odds ratio; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SoC, standard care; SZC, sodium zirconium cyclosilicate; QALY, quality-adjusted life year

6.1 Generalisability of clinical trials data

6.1.1 S-K treatment thresholds

Following extensive engagement with clinical experts (Section 1.1), the S-K thresholds in the model have been revised to better reflect UK clinical practice. In the outpatient setting, treatment would be initiated when S-K ≥6.0 mmol/L for CKD patients and S-K ≥ 5.5 mmol/L for HF patients. For emergency admissions, treatment would be initiated when S-K ≥ 6.0 mmol/L for both CKD and HF patients. In line with this, the threshold for "less severe" HK events in CKD patients, in the outpatient setting, has been updated from S-K ≥5.5 mmol/L to S-K ≥6.0 mmol/L. Similarly, the proportions of patients who down-titrate or discontinue RAASi in standard care have been updated to reflect the S-K ≥6.0 mmol/L threshold in the outpatient setting for CKD patients (see Table 9), i.e. management for HK in CKD outpatients occurs at S-K ≥6.0 mmol/L through RAASi discontinuation (100% of patients), as per CG182.[22]

6.1.2 S-K trajectories for the SZC arm

To ensure that the economic model better reflects UK clinical practice, updated S-K thresholds to initiate treatment (Section 6.1.1) were implemented and subgroups of clinical trial data relevant to UK clinical practice were used to generate two new S-K trajectories– one to reflect treatment initiation at S-K ≥ 6.0 mmol/L and one to reflect treatment initiation at S-K ≥ 5.5 mmol/L. The updated S-K profiles were simulated using mixed effects regression models.

For the treatment initiation threshold of S-K ≥ 6.0 mmol/L, data from 126 patients with baseline S-K ≥6.0 mmol/L in ZS-004 and ZS-005 were pooled to create the S-K trajectory in the corrective phase. Data from 92 patients were used to inform the S-K trajectory in the maintenance phase.

For the treatment initiation threshold of S-K ≥ 5.5 mmol/L threshold, data from 469 patients with baseline S-K ≥5.5 mmol/L in ZS-004 and ZS-005 were pooled to create the S-K trajectories in the corrective phase. Data from 357 patients were used to inform the S-K trajectory in the maintenance phase.

The new S-K trajectories for treatment initiation at S-K ≥ 6.0 mmol/L and S-K ≥ 5.5 mmol/L are presented in Table 13 and Table 14, respectively.

Table 13. S-K profile for SZC, based on pooled ZS-004 and ZS-005, from patients with baseline S-K ≥6.0 mmol/L who were randomised to 5 g OD or 10 g OD

	Corrective phase	Maintenance phase		
	Day 0 – 3	**Day 4 – 14**	**Day 15 - 28**	**Day 29+**
Fixed effects				
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Time (days)	[redacted]	N/A		
Random effects as standard deviations (normally distributed with mean 0)				
Patient	[redacted]	[redacted]		
Observation	[redacted]	[redacted]		

Abbreviations: OD, once a day; S-K, serum potassium; SZC, sodium zirconium cyclosilicate.

Table 14. S-K profile for SZC, based on pooled ZS-004 and ZS-005, from patients with baseline S-K ≥5.5 mmol/L who were randomised to 5 g OD or 10 g OD

	Corrective phase	Maintenance phase		
	Day 0 - 3	**Day 4 - 14**	**Day 15 - 28**	**Day 29+**
Fixed effects				
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Time (days)	[redacted]	N/A		

Random effects as standard deviations (normally distributed with mean 0)		
Patient	[redacted]	[redacted]
Observation	[redacted]	[redacted]

Abbreviations: OD, once a day; S-K, serum potassium; SZC, sodium zirconium cyclosilicate.

6.2 Comparative data to inform the effect of standard care

6.2.1 S-K trajectories for the standard care arm

As discussed in Section 2.2, in the absence of relevant published evidence to inform the clinical effectiveness of standard care, data from ZS-003 was used to provide the S-K trajectory for the model.

The adjusted 48h absolute reduction was applied as the absolute reduction in S-K at the end of the correction phase of the model (Day 3). As such, the time (days) slope coefficient was calculated by dividing the adjusted 48h absolute reduction by 3.

As the S-K levels in the placebo arm of ZS-003 were generally stable during the maintenance treatment, the S-K trajectory during the maintenance phase was modelled to be constant. The random effects have been kept the same as those in the revised S-K trajectories for SZC.

Table 15. S-K profile for standard care, based on ZS-003, from patients with baseline S-K ≥6.0 mmol/L

	Corrective phase	Maintenance phase		
	Day 0 – 3	Day 4 – 14	Day 15 – 28	Day 29+
Fixed				
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Time (days)	[redacted]	N/A		
Random effects as standard deviations (normally distributed with mean 0)				
Patient	[redacted]	[redacted]		
Observation	[redacted]	[redacted]		

Abbreviations: S-K, serum potassium

Table 16. S-K profile for standard care, based on ZS-003, from patients with baseline S-K ≥5.5 mmol/L

	Corrective phase	Maintenance phase		
	Day 0 – 3	Day 4 – 14	Day 15 – 28	Day 29+
Fixed				
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Time (days)	[redacted]	N/A		
Random effects as standard deviations (normally distributed with mean 0)				
Patient	[redacted]	[redacted]		
Observation	[redacted]	[redacted]		

Abbreviations: S-K, serum potassium

6.2.2 Effect of RAASi down-titration or discontinuation on S-K levels

As indicated in Section 2.22.2.3, there was a low level of RAASi discontinuation amongst patients in the ZS-003 trial based on which the S-K trajectories for standard care patients were derived. As such, it could be expected that some patients in clinical practice may have a further S-K reduction compared to ZS-003, attributed to RAASi down-titration or discontinuation.

As per the ERG's base case, a S-K decrement when RAASi treatment is discontinued (0.23 mmol/L) or down-titrated (0.115mmol/L) was applied in the revised base case presented in Table 10. These S-

K decrements were considered conservative in light of the evidence retrieved in the targeted literature review describing potential changes in S-K following RAASi discontinuation or down-titration (Section 2.1.1). [redacted] In the model, as per clinical experts' opinion, 80% of patients with S-K ≥5.5 mmol/L are expected to down-titrate, leading to a 0.115mmol/L reduction in S-K, and 20% are expected to discontinue RAASi, resulting in a 0.23mmol/L reduction in S-K. For both standard care and SZC arms, all patients discontinue RAASi when S-K ≥6.0 mmol/L, resulting in both patients groups having a 0.23mmol/L reduction in S-K.

6.2.3 Alternative standard care S-K trajectory used in scenario analyses

Alternative standard care S-K trajectories were generated for patients starting treatment at S-K ≥6.0 mmol/L and S-K ≥5.5 mmol/L. For these alternative trajectories, the 48h placebo effect observed in ZS-003 was applied to Day 2 of the S-K trajectory, and then extrapolated linearly to Day 3, resulting in a further reduction in S-K. For the maintenance phase trajectory, the S-K value at Day 3 was assumed to remain constant.

The alternative S-K trajectories from ZS-003 for standard care are presented in Table 17 and Table 18 for S-K ≥6.0 mmol/L and S-K ≥5.5 mmol/L, respectively.

Table 17: Alternative S-K profile for standard care, based on ZS-003, from patients with baseline S-K ≥6.0 mmol/L

	Corrective phase	Maintenance phase		
	Day 0 – 3	Day 4 – 14	Day 15 – 28	Day 29+
Fixed				
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Time (days)	[redacted]	N/A		
Random effects as standard deviations (normally distributed with mean 0)				
Patient	[redacted]	[redacted]		
Observation	[redacted]	[redacted]		

Abbreviations: S-K, serum potassium

Table 18: Alternative S-K profile for standard care, based on ZS-003, from patients with baseline S-K ≥5.5 mmol/L

	Corrective phase	Maintenance phase		
	Day 0 - 3	Day 4 - 14	Day 15 - 28	Day 29+
Fixed				
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Time (days)	[redacted]	N/A		
Random effects as standard deviations (normally distributed with mean 0)				
Patient	[redacted]	[redacted]		
Observation	[redacted]	[redacted]		

Abbreviations: S-K, serum potassium

6.3 Evidence on S-K and outcomes

As discussed in Section 3, an SLR was conducted to investigate the relationship between S-K and outcomes, from which a range of relevant studies were found and evaluated for use within the economic model (see Section 3).

6.3.1 S-K and outcomes for patients with CKD

Of the nine studies[1,5,10,99-102,104,105] considered to be relevant to the decision problem in Section 3.1 only four[1,101,104,105] were considered relevant for use in the economic model. Of the five studies not considered relevant for the economic model, two [5,102] did not report rate ratios for S-K intervals

covering hypo-, normo-, and hyperkalaemia, one[99] only reported in-hospital mortality, one[100] did not mention adjustments made for confounders and one[10] only assessed the hazard at specific S-K values.

For the relationship between S-K and mortality in CKD patients, Luo et al. was chosen for the base case (as per the originally submitted model). Whilst Furuland et al. provide a risk equation to predict the mortality risk based on multiple risk factors, including S-K levels and RAASi use, it is not straightforward to remove the dependency of individual risk factors for the purpose of conducting scenario analyses (including the scenario analysis assuming no impact of RAASi on mortality). As such, Furuland et al. was not selected for the base case, but instead evaluated in a scenario analysis. The two remaining relevant studies, by Collins et al. and Nakhoul et al., have also been evaluated in scenario analyses. The results of these scenario analyses can be found in Table 11 and

Table 12 for the outpatient setting and emergency admissions, respectively.

For relationship between S-K and MACE in CKD patients, only two studies[1,105] were relevant for use in the economic model. Luo et al. was again used in the base case whilst Furuland et al. was implemented in a scenario analysis with the results presented in Table 11 and

Table 12 for the outpatient setting and emergency admissions, respectively.

Data from Luo et al.[1] was also used in the base case to inform the relationship between S-K and hospitalisation, as Luo et al. was the only relevant study reporting risk ratios for hypo-, normo, and hyperkalaemia.

Using the same large, well-conducted and appropriately adjusted study consistently across outcomes was the main reason for selecting Luo et al. over other data sources. However, scenario analyses indicated that the use of other sources led to similar results.

In addition to the scenario analyses discussed above, the published studies constructing the base case were subject to further sensitivity analyses. With the exception of the reference category, all relative statistical measures were varied by ±20%.

The results of scenario analyses for the outpatient setting and emergency admissions are presented in Table 11 and

Table 12, respectively. Irrespective of the evidence sources used in the model for the relationship between S-K and outcomes, SZC remained cost-effective.

6.3.2 S-K and outcomes for patients with HF

As described in Section 3.2**Error! Reference source not found.**, the SLR identified a single RCT conducted by Desai et al.,[70] which assessed the relationship between S-K and mortality. This was used in the revised base case model. Additionally, five observational studies[21,97,101,114,119] identified in the SLR reported risk ratios for hypo-, normo-, and hyperkalaemia and adjusted for relevant covariates. Scenario analyses were presented using these five relevant studies in Table 11 for the outpatient setting and in

Table 12 for emergency admissions.

No relevant studies on the relationship between S-K and MACE in patients with HF were identified in the SLR. Therefore, unpublished data on the relationship between S-K and MACE from a CPRD analysis in HF patients was used to explore this relationship in a UK context.[66] Data were collected from 21,334 patients with HF between 2006 and 2015 and risk equations were derived. All statistically significant covariates were adjusted for and included age, gender, time, S-K interval, history of MACE, cancer and PVD, white blood cell count and prescription of diuretics and beta blockers ±3 months from baseline. The risk equations produced event probability estimates for six S-K categories, with S-K ≥ 4.5, < 5.0 mmol/L set as the reference category. Where there was insufficient evidence to support a deviation in risk from the reference category (i.e. there was no statistically significant difference from unity at the 5% level), the coefficient was assumed to be zero.

RCT evidence from Desai et al.[70] was also used to estimate the relationship between S-K and hospitalisation in the model. No relevant observational studies were identified for scenario analyses.

In addition to the scenario analyses discussed above, the published studies constructing the base case were subject to further sensitivity analyses. With the exception of the reference category, all IRRs were varied by ±20%.

The results of scenario analyses for the outpatient setting and emergency admissions are presented in Table 11 and

Table 12, respectively. Irrespective of the evidence sources used in the model for the relationship between S-K and outcomes, SZC remained cost-effective.

6.4 Evidence on RAASi and outcomes

As described in Section 4**Error! Reference source not found.**, targeted literature searches were conducted to identify evidence on the effect of RAASi down-titration and discontinuation on clinical outcomes.

6.4.1 RAASi and outcomes for patients with CKD

For CKD patients, Xie et al. 2016a[128] was identified as the most relevant source to inform the relationship between RAASi and mortality, and RAASi and CV events. The results from the targeted literature review, confirm the relevance of the use ORs for RAASi versus placebo from the Xie et al. 2016a meta-analyses in the original company submission. No evidence was identified in the targeted literature review on the relationship between RAASi and hospitalisation, as such this relationship is not modelled.

As a scenario analysis, the ORs from Xie et al. 2016a[128] for ACEi/ARB versus active control treatment were applied, with active control treatment defined as antihypertensives other than RAASi therapies (Table 19). This scenario analysis was carried out to address the Committee's concern about alternative antihypertensive drugs and reflects a scenario where patients switch to other antihypertensive treatments when discontinuing RAASi (see Section 4.1). In addition, the model inputs from Xie et al. 2016a for the relationship (RAASi vs placebo) between RAASi and mortality, and RAASi and CV events, were varied by ±20% in scenario analyses to evaluate the robustness of the model. Finally, a worst-case scenario assuming that RAASi discontinuation or down-titration have no effect on outcomes was also conducted.

The results of these scenario analyses are presented in Table 11 and

Table 12 for the outpatient setting and emergency admissions, respectively. Irrespective of the evidence sources used in the model for the relationship between RAASi and outcomes, SZC remained cost-effective.

Table 19: Scenario analysis inputs for the relationship between RAASi and outcomes in patients with CKD

Model input	Value	Reference
Mortality (CKD)		
Max RAASi	0.74	Weighted average of the ORs for ACEi and ARB as reported in Xie et al. 2016a[128] weighting by type of RAASi from CPRD data[66]
Sub-max RAASi	0.87	Assumed 50% reduction in efficacy compared to max RAASi
CV events (CKD)		
Max RAASi	0.92	Weighted average of the ORs for ACEi and ARB as reported in Xie et al. 2016a[128], weighting by type of RAASi from CPRD data[66]
Sub-max RAASi	0.96	Assumed 50% reduction in efficacy compared to max RAASi

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blockers; CKD, chronic kidney disease; CPRD, clinical practice research datalink; OR; odds ratio; RAASi, renin-angiotensin-aldosterone system inhibitor

6.4.2 RAASi and outcomes for patients with HF

For HF patients, several meta-analyses on the relationship between RAASi and mortality, and RAASi and hospitalisation were identified from the targeted literature review.[130,133-135] Flather et al., the study used in the original company submission, was selected to inform the relationship between RAASi and hospitalisation in the revised base case, as this study was a meta-analysis based on individual patient data (see Section 4.2). Despite the supporting evidence from several meta-analyses on the relationship between RAASi and mortality,[130,133-135] this relationship was not included in the model, and as such the model should be considered to be highly conservative.

As scenario analyses, ORs from Xie et al. 2016b[133] on the relationship between ACEi, ARB, and MRA were applied as a weighted average based on the relative prevalence of ACEi, ARB and MRA use in UK clinical practice (Table 20).[66] Additional scenario analyses were also conducted by varying the base case model inputs by ±20% to test the robustness of the model. Finally, a worst-case scenario assuming that RAASi discontinuation or down-titration have no effect on outcomes was also conducted.

The results of these scenario analyses are presented in Table 11 and

Table 12 for the outpatient setting and emergency admissions, respectively. Irrespective of the evidence sources used in the model for the relationship between RAASi and outcomes, SZC remained cost-effective.

Table 20: Scenario analysis inputs for the relationship between RAASi and outcomes in patients with HF

Model input	Value	Reference
Hospitalisation		
Max RAASi	0.70	Weighted average of the ORs for ACEi, ARB and MRA as reported in Xie et al. 2016b,[133] weighting by type of RAASi from CPRD data
Sub-max RAASi	0.92	Based on data from ATLAS showing a 24% lower risk of hospitalisation with a high RAASi dose compared to a low RAASi dose (statistically significant)

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blockers; CPRD, clinical practice research datalink; HF, heart failure; MRA, mineralocorticoid receptor antagonist; OR; odds ratio; RAASi, renin-angiotensin-aldosterone system inhibitor

6.5 EQ-5D and utilities SLR

As explained in the proforma response following the ERG report, a systematic literature review on the impact of CKD on quality of life was conducted by AstraZeneca. Two studies that reported EQ-5D utility values by severity of CKD were identified: one US study of hypertensive patients with and without CKD,[142] and one European study of CKD patients with and without anaemia.[143] Both studies reported patients with more severe CKD to have lower EQ-5D utility values. Because the Eriksson et al. studied European patients, the results from this study is considered more generalisable than Wolfgram et al. (US study) to the current decision problem.

Furthermore, since EQ-5D is the preferred measure of health-related quality of life as per the NICE reference case, values from Eriksson et al. are used in the revised base case, instead of the values used in the original company submission based on HUI-3 from Gorodetskaya et al.[144]

CKD Stage	Company alternative source (SD) EQ-5D-3L Eriksson et al. 2016 * (N=313)
3a	0.85 (0.21)
3b	0.85 (0.21)
4	0.81 (0.22)
5 (pre-RRT)	0.74 (0.29) (CKD stage 5, dialysis patients used a proxy)

Abbreviations: CKD, chronic kidney disease; RRT, renal replacement therapy; SD, standard deviation

6.6 *Not adjusted by 0.79, the ERG-assumed population norm for the patients aged 63 to 65 years because the adjustment would lead to values capped to 1 Other modelling assumptions

6.6.1 Disutilities and costs for emergency admissions

For emergency admissions only, a scenario analysis which includes disutilities and costs associated with emergency admission patients was conducted. Disutilities for sepsis and pneumonia reported by Sullivan et al.[145] were applied, assuming that 50% of patients would present with sepsis and 50% with pneumonia. These disutilities were applied for 14 days every time a patient experienced an emergency admission with HK. Event costs, calculated using non-elective long stay costs for sepsis (NHS reference costs WJ06G-WJ06J) and pneumonia (DZ11R-DZ11V)/2) were also applied every time a patient experienced an emergency admission with HK.

Table 21: Disutilities and costs associated with emergency admissions

	Sepsis		Pneumonia		Input data used in the model
	Value	Source	Value	Source	
14-day event disutilities	-0.0559	Infection from Sullivan et al.	-0.0776	Other lung diseases from Sullivan et al.	-0.06675
One-off event costs	£2,441	NHS reference costs 2017-2018 Weighted average of a non-elective long stay WJ06G-WJ06J	£2,339	NHS reference costs 2017-2018 Weighted average of a non-elective long stay DZ11R-DZ11V	£2,390

Abbreviations: NHS, National Health Service

6.6.2 Assumptions made by the ERG and implemented in the revised base case analysis

The following assumptions and changes from the ERG were implemented in the revised base case:

- The time horizon for emergency admissions has been reduced from life-time to 52 weeks as patients identified in A&E/AMU would be followed-up in the outpatient setting following multiple episodes. However, it should be noted that this would assume all patients with HK in the emergency episode would transition into chronic management, which is not necessarily the case.
- Lower costs have been implemented in the revised base case for RAASi dose changes as per the ERG's base case. It is now assumed that all secondary care visits to change RAASi dosage occur in an outpatient setting rather than an inpatient setting.
- RAASi treatment is withheld for 12 weeks for patients with S-K > 6.0 mmol/L in the SZC arm in the revised base case.

6.6.3 Assumptions made by the ERG and implemented in a scenario analysis

The following assumptions from the ERG were implemented as scenario analyses:

- Wastage equivalent to 2 sachets for every 30 sachets prescribed during the 52-week maintenance phase of patients in the outpatient setting. This was an assumption from the ERG, but AstraZeneca consider this assumption to be highly pessimistic with limited justification, as sachets would be stored at home and prescribed again once they have been consumed. Please see AstraZeneca's response to the ERG report and clarification questions for a more detailed explanation of why this assumption is not considered to be relevant.
- Patients admitted to A&E/AMU with HK can restart RAASi

There is no reduction in hospital length of stay associated with SZC treatment

7 Factual inaccuracies identified in the ACD

Table 22: Factual inaccuracies identified in the ACD

Section and page number in the ACD	ACD statement	Comments
3.5 page 8	The clinical expert explained that such a diet is considered worth trying to help manage serum potassium levels, is recommended by NICE.	This sentence is unclear and needs to be rephrased.
3.5 page 8	The diet lowers serum potassium compared with an unrestricted diet.	This statement is unsubstantiated and needs to be removed or rephrased. AstraZeneca conducted a systematic literature review to identify RCT-based evidence in patients with hyperkalaemia but did not retrieve any relevant RCT.

8 References

1. Luo J, Brunelli SM, Jensen DE, Yang A. Association between Serum Potassium and Outcomes in Patients with Reduced Kidney Function. *Clin J Am Soc Nephrol.* 2016;11(1):90-100.
2. Qin L, McEwan P, Evans M, Bergenheim K, Horne L, Grandy S. #325 Association Between Serum Potassium and Clinical Outcomes in UK Patients with Heart Failure (Poster). European Society of Cardiology; 2017.
3. Qin L, McEwan P, Evans M, Bergenheim K, Horne L, Grandy S. MO067 The relationship between serum K+ and incidence rates of major adverse cardiovascular events and mortality in UK patients with CKD. (Oral presentation). *Nephrol Dial Transplant.* 2017;32(3):ii73-74.
4. Thomsen RW, Nicolaisen SK, Hasvold P. Elevated potassium levels in patients with congestive heart failure: incidence and clinical outcomes - a Danish population based cohort study: Poster ESC 2017. 2017.
5. Thomsen RW, Nicolaisen SK, Hasvold P, et al. Elevated potassium levels in patients with chronic kidney disease: occurrence, risk factors and clinical outcomes-a Danish population-based cohort study. *Nephrol Dial Transplant.* 2017.
6. Goyal A, Spertus JA, Gosch K, et al. Serum Potassium Levels and Mortality in Acute Myocardial Infarction. *JAMA.* 2012;307(2):157-164.
7. Thomsen RW, Nicolaisen SK, Kim K, Palaka E, Sorensen CM. SP318 Healthcare Resource Utilisation Associated with Elevated Potassium Levels in Patients with Chronic Kidney Disease (Poster). *Nephrol Dial Transplant.* 2017;32(Suppl 3):iii214-215.
8. Park S, Baek SH, Lee SW, et al. Elevated baseline potassium level within reference range is associated with worse clinical outcomes in hospitalised patients. *Scientific reports.* 2017;7(1):2402.
9. McEwan P, Qin L, Evans M, Horne L, Palaka E, Grandy S. TH-PO1106 Associations Between Serum Potassium and Clinical Outcomes in Patients with CKD in a Real-World Setting (Poster). American Society of Nephrology; 2017.
10. Kovesdy CP, Matsushita K, Sang Y, et al. Serum potassium and adverse outcomes across the range of kidney function: a CKD Prognosis Consortium meta-analysis. *Eur Heart J.* 2018;39(17):1535-1542.
11. NHS Improvement. Patient Safety Alert: Resources to support safe and timely management of hyperkalaemia (high level of potassium in the blood). 2018; https://improvement.nhs.uk/documents/3121/Patient_Safety_Alert_-_Resources_to_support_safe_management_of_hyperkalaemia.pdf, 7 November 2018.
12. Kovesdy CP. Management of hyperkalaemia in chronic kidney disease. *Nat Rev Nephrol.* 2014;10(11):653-662.
13. Vardeny O, Claggett B, Anand I, et al. Incidence, predictors, and outcomes related to hypo- and hyperkalemia in patients with severe heart failure treated with a mineralocorticoid receptor antagonist. *Circ Heart Fail.* 2014;7(4):573-579.
14. Montford JR, Linas S. How Dangerous Is Hyperkalemia? *J Am Soc Nephrol.* 2017;28(11):3155-3165.
15. Einhorn LM, Zhan M, Hsu VD, et al. The Frequency of Hyperkalemia and Its Significance in Chronic Kidney Disease. *Arch Intern Med.* 2009;169(12):1156-1162.
16. Horne L, Ashfaq A, MacLachlan S, Sinsakul M, Qin L, Locasale R. MP370 Incidence of and Risk Factor for Hyperkalemia in Adults in the UK (Poster). *Nephrol Dial Transplant.* 2017;32(Suppl 3):iii563.
17. Nilsson E, Gasparini A, Arnlov J, et al. Incidence and determinants of hyperkalemia and hypokalemia in a large healthcare system. *Int J Cardiol.* 2017.
18. Thomsen RW, Nicolaisen SK, Hasvold P, Sorenson HT. MO066 Elevated potassium levels in patients with chronic kidney disease: incidence, risk factors and clinical outcomes. (Oral presentation). *Nephrol Dial Transplant.* 2017;32(Suppl 3):iii73.
19. Desai AS, Liu J, Pfeffer MA, et al. Incident hyperkalemia, hypokalemia, and clinical outcomes during spironolactone treatment of heart failure with preserved ejection fraction: analysis of the TOPCAT Trial. *J Card Fail.* 2018;24(5):313-320.
20. Furuland H, McEwan P, Evans M, et al. Recurrent Hyperkalaemia and Association with Length of Stay and Mortality following Hospitalisation: Real World Evidence from UK Patients with CKD. *Poster ERA-EDTA.* 2018.
21. Nunez J, Bayes-Genis A, Zannad F, et al. Long-Term Potassium Monitoring and Dynamics in Heart Failure and Risk of Mortality. *Circulation.* 2018;137(13):1320-1330.

22. National Institute of Clinical and Care Excellence (NICE). Chronic kidney disease in adults: assessment and management [CG182]. 2015; https://www.nice.org.uk/guidance/cg182. Accessed 23 November 2018.
23. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2016;37(27):2129-2200.
24. British Society of Heart Failure, Renal Association UK, Kidneys T. *Changes in kidney function and serum potassium during ACEI/ARB/diruetic treatment in primary care, A position statement from Think Kidneys, the Renal Association and the British Society for Heart Failure.* 2017.
25. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med.* 1987;316(23):1429-1435.
26. Investigators S, Yusuf S, Pitt B, Davis CE, Hood WB, Jr., Cohn JN. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med.* 1992;327(10):685-691.
27. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. *JAMA.* 1995;273(18):1450-1456.
28. Rosano GMC, Tamargo J, Kjeldsen KP, et al. Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with renin angiotensin aldosterone system inhibitors: coordinated by the Working Group on Cardiovascular Pharmacotherapy of the European Society of Cardiology. *European heart journal Cardiovascular pharmacotherapy.* 2018;4(3):180-188.
29. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J.* 2013;34(28):2159-2219.
30. AstraZeneca. *Data on file: Key External Expert Engagement Outputs.*
31. Kalantar-Zadeh K, Tortorici AR, Chen JL, et al. Dietary restrictions in dialysis patients: is there anything left to eat? *Seminars in dialysis.* 2015;28(2):159-168.
32. Renal Association UK. Emergency Management of Hyperkalaemia in Adults Algorithm. 2014; https://renal.org/wp-content/uploads/2017/10/HYPERKALAEMIA-ALGORITHM-MARCH-2014.pdf. Accessed 23 November 2018.
33. Michel A, Martin-Perez M, Ruigomez A, Garcia Rodriguez LA. Risk factors for hyperkalaemia in a cohort of patients with newly diagnosed heart failure: a nested case-control study in UK general practice. *European journal of heart failure.* 2015;17(2):205-213.
34. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *New England Journal of Medicine.* 1999;341(10):709-717.
35. Ouwerkerk W, Voors AA, Anker SD, et al. Determinants and clinical outcome of uptitration of ACE-inhibitors and beta-blockers in patients with heart failure: a prospective European study. *Eur Heart J.* 2017;38(24):1883-1890.
36. Group G. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *The Lancet.* 1997;349(9069):1857-1863.
37. Burnett H, Earley A, Voors A, et al. Thirty years of evidence on the efficacy of drug treatments for chronic heart failure with reduced ejection fraction: a network metaanalysis. Circ Heart Fail 2017; 10 (1). In.
38. Brenner BM, Cooper ME, De Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *New England Journal of Medicine.* 2001;345(12):861-869.
39. Basi S, Lewis JB. Microalbuminuria as a target to improve cardiovascular and renal outcomes. *American Journal of Kidney Diseases.* 2006;47(6):927-946.
40. Linde C, McEwan P, Bakhai A, et al. Real-world Dosing of Renin-angiotensin-aldosterone System Inhibitors in Heart Failure Patients, and Associations between Hyperkalaemia and Down-titration or Discontinuation [poster]. Presented at: European Society of Cardiology (ESC). 2018 #86896.

41. Qin L, McEwan P, Evans M, et al. The relationship between serum potassium concentration and discontinuation of renin–angiotensin–aldosterone system inhibitors in UK patients with CKD [poster]. Presented at: European Renal Association–European Dialysis and Transplant Association (ERA–EDTA) 54th Annual Congress; June 3–6, 2017; Madrid, Spain; Poster MP373.
42. AstraZeneca. *Data on file: Clinical Engagement Document.*
43. Maggioni AP, Dahlstrom U, Filippatos G, et al. EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). *European journal of heart failure.* 2013;15(7):808-817.
44. Gheorghiade M, Albert NM, Curtis AB, et al. Medication dosing in outpatients with heart failure after implementation of a practice-based performance improvement intervention: findings from IMPROVE HF. *Congestive heart failure (Greenwich, Conn).* 2012;18(1):9-17.
45. Shirazian S, Grant CD, Mujeeb S, et al. Underprescription of renin-angiotensin system blockers in moderate to severe chronic kidney disease. *The American journal of the medical sciences.* 2015;349(6):510-515.
46. Molnar MZ, Kalantar-Zadeh K, Lott EH, et al. Angiotensin-converting enzyme inhibitor, angiotensin receptor blocker use, and mortality in patients with chronic kidney disease. *J Am Coll Cardiol.* 2014;63(7):650-658.
47. National Institute of Clinical and Care Excellence (NICE). Sodium zirconium cyclosilicate for treating hyperkalaemia [ID1293] - ACM1 Committee Papers. 2018; https://www.nice.org.uk/guidance/gid-ta10307/documents/committee-papers-2. Accessed 7 November 2018.
48. Rajendran R, Rayman G. Serious harm from inpatient hypoglycaemia: a survey of hospitals in the UK. *Diabetic medicine : a journal of the British Diabetic Association.* 2014;31(10):1218-1221.
49. Imperial College Healthcare. *CKD Guidelines.* 2018.
50. K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis.* 2004;43(5 Suppl 1):S1-290.
51. Alfonzo A, Soar J, MacTier R, et al. Clinical Practice Guidelines, Treatment of Acute Hyperkalaemia in Adults, UK Renal Association. 2014; https://renal.org/wp-content/uploads/2017/06/hyperkalaemia-guideline-1.pdf. Accessed 23 November 2018.
52. Sarafidis PA, Khosla N, Bakris GL. Antihypertensive therapy in the presence of proteinuria. *American Journal of Kidney Diseases.* 2007;49(1):12-26.
53. Kunz R, Friedrich C, Wolbers M, Mann JF. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin–angiotensin system on proteinuria in renal disease. *Annals of internal medicine.* 2008;148(1):30-48.
54. Aranda P, Segura J, Ruilope LM, et al. Long-term renoprotective effects of standard versus high doses of telmisartan in hypertensive nondiabetic nephropathies. *American journal of kidney diseases.* 2005;46(6):1074-1079.
55. Burgess E, Muirhead N, de Cotret PR, et al. Supramaximal dose of candesartan in proteinuric renal disease. *Journal of the American Society of Nephrology.* 2009;20(4):893-900.
56. Chalisey A, Ross C, Weavers N. *Joint Trust Guideline for the management of hyperkalaemia in adults, James Paget University Hospitals and Norfolk and Norwich University Hospitals.* 2017.
57. Nottingham University Hosptial NHS Trust. *Guideline for the management of acute hyperkalaemia in adults.* 2017.
58. St George's Hospital. *Guidelines for the Management of Common Medical Emergencies and for the Use of Anti-Microbial Drugs.* August 2017 2017.
59. European Medicines Agency (EMA). Lokelma Summary of Product Characteristics. 2017; https://www.ema.europa.eu/documents/product-information/lokelma-epar-product-information_en.pdf. Accessed 23 November 2018.
60. AstraZeneca. *Data on file: White Paper, Lokelma (sodium zirconium cyclosilicate [ZS]) oral suspension, Subgroups based on comorbid conditions at baseline in ZS clinical studies.*
61. Lambert K, Mullan J, Mansfield K. An integrative review of the methodology and findings regarding dietary adherence in end stage kidney disease. *BMC nephrology.* 2017;18(1):318.
62. Ribeiro SC, Figueiredo AE, Barretti P, Pecoits-Filho R, de Moraes TP, Investigators B. Impact of Renin-Angiotensin Aldosterone System Inhibition on Serum Potassium Levels among Peritoneal Dialysis Patients. *American journal of nephrology.* 2017;46(2):150-155.
63. Weir MR, Rolfe M. Potassium homeostasis and renin-angiotensin-aldosterone system inhibitors. *Clinical Journal of the American Society of Nephrology.* 2010:CJN. 07821109.

64. MacKinnon M, Shurraw S, Akbari A, Knoll GA, Jaffey J, Clark HD. Combination therapy with an angiotensin receptor blocker and an ACE inhibitor in proteinuric renal disease: a systematic review of the efficacy and safety data. *American Journal of Kidney Diseases.* 2006;48(1):8-20.
65. Ng KP, Arnold J, Sharif A, Gill P, Townend JN, Ferro CJ. Cardiovascular actions of mineralocorticoid receptor antagonists in patients with chronic kidney disease: A systematic review and meta-analysis of randomized trials. *J Renin Angiotensin Aldosterone Syst.* 2015;16(3):599-613.
66. AstraZeneca. Natural History and Disease Burden of Hyperkalemia in Patients with Chronic Kidney Disease or Heart Failure in the United Kingdom. Study Report (June 2017). In.
67. Nasir K, Ahmad A. Treatment of hyperkalemia in patients with chronic kidney disease: a comparison of calcium polystyrene sulphonate and sodium polystyrene sulphonate. *Journal of Ayub Medical College, Abbottabad : JAMC.* 2014;26(4):455-458.
68. Arnold R, Pianta TJ, Pussell BA, et al. Randomized, controlled trial of the effect of dietary potassium restriction on nerve function in CKD. *Clinical Journal of the American Society of Nephrology.* 2017;12(10):1569-1577.
69. Alderman MH, Piller LB, Ford CE, et al. Clinical significance of incident hypokalemia and hyperkalemia in treated hypertensive patients in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. *Hypertension.* 2012;59(5):926-933.
70. Desai AS, Liu J, Pfeffer MA, et al. Incident Hyperkalemia, Hypokalemia, and Clinical Outcomes During Spironolactone Treatment of Heart Failure With Preserved Ejection Fraction: Analysis of the TOPCAT Trial. *J Card Fail.* 2018;24(5):313-320.
71. Anutrakulchai S, Pongskul C, Sirivongs D, et al. Factors associated with mortality and high treatment expense of adult patients hospitalized with chronic kidney disease in Thailand. *Asian Biomedicine.* 2016;10(1):15-24.
72. Hoss S, Elizur Y, Luria D, Keren A, Lotan C, Gotsman I. Serum potassium levels and outcome in patients with chronic heart failure. *The American journal of cardiology.* 2016;118(12):1868-1874.
73. Nishihara T, Tokitsu T, Sueta D, et al. Serum potassium and cardiovascular events in heart failure with preserved left ventricular ejection fraction patients. *American journal of hypertension.* 2018;31(10):1098-1105.
74. Wajner A, Zuchinali P, Olsen V, Polanczyk CA, Rohde LE. Causes and predictors of in-hospital mortality in patients admitted with or for heart failure at a tertiary hospital in Brazil. *Arquivos brasileiros de cardiologia.* 2017(AHEAD):0-0.
75. Lee S, Kang E, Yoo KD, et al. Lower serum potassium associated with increased mortality in dialysis patients: A nationwide prospective observational cohort study in Korea. *PloS one.* 2017;12(3):e0171842.
76. Zhang Y, Chen P, Chen J, Wang L, Wei Y, Xu D. Association of Low Serum Potassium Levels and Risk for All-Cause Mortality in Patients With Chronic Kidney Disease: A Systematic Review and Meta-Analysis. *Therapeutic Apheresis and Dialysis.* 2018.
77. Huang C-W, Lee M-J, Lee P-T, et al. Low potassium dialysate as a protective factor of sudden cardiac death in hemodialysis patients with hyperkalemia. *PloS one.* 2015;10(10):e0139886.
78. Hwang J-C, Wang C-T, Chen C-A, Chen H-C. Hypokalemia is associated with increased mortality rate in chronic hemodialysis patients. *Blood purification.* 2011;32(4):254-261.
79. Kurnik D, Vesterman-Landes J, Bialik M, et al. Hyperkalemia and renal function during monotherapy and dual renin-angiotensin blockade in the community setting. *Clinical therapeutics.* 2011;33(4):456-464.
80. Legrand M, Ludes P-O, Massy Z, et al. Association between hypo-and hyperkalemia and outcome in acute heart failure patients: the role of medications. *Clinical Research in Cardiology.* 2018;107(3):214-221.
81. Younis A, Goldenberg I, Goldkorn R, et al. Elevated Admission Potassium Levels and 1-Year and 10-Year Mortality Among Patients With Heart Failure. *The American journal of the medical sciences.* 2017;354(3):268-277.
82. Chen Y, Sang Y, Ballew SH, et al. Race, serum potassium, and associations with ESRD and mortality. *American Journal of Kidney Diseases.* 2017;70(2):244-251.
83. Durfey N, Lehnhof B, Bergeson A, et al. Severe hyperkalemia: Can the electrocardiogram risk stratify for short-term adverse events? *Western Journal of Emergency Medicine.* 2017;18(5):963.

84. Epstein M, Reaven NL, Funk SE, McGaughey KJ, Oestreicher N, Knispel J. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. *Am J Manag Care.* 2015;21(11 Suppl):S212-220.
85. Krogager ML, Torp-Pedersen C, Mortensen RN, et al. Short-term mortality risk of serum potassium levels in hypertension: a retrospective analysis of nationwide registry data. *European heart journal.* 2017;38(2):104-112.
86. Johnson LS, Mattsson N, Sajadieh A, Wollmer P, Söderholm M. Serum potassium is positively associated with stroke and mortality in the large, population-based Malmö Preventive Project cohort. *Stroke.* 2017;48(11):2973-2978.
87. Hughes-Austin JM, Rifkin DE, Beben T, et al. The relation of serum potassium concentration with cardiovascular events and mortality in community-living individuals. *Clinical Journal of the American Society of Nephrology.* 2017:CJN. 06290616.
88. Thomsen R, Nicolaisen S, Adelborg K, et al. Hyperkalaemia in people with diabetes: occurrence, risk factors and outcomes in a Danish population-based cohort study. *Diabetic Medicine.* 2018.
89. Velavan P, Khan NK, Goode K, et al. Predictors of short term mortality in heart failure—insights from the Euro Heart Failure survey. *International journal of cardiology.* 2010;138(1):63-69.
90. Karaboyas A, Zee J, Brunelli SM, et al. Dialysate Potassium, Serum Potassium, Mortality, and Arrhythmia Events in Hemodialysis: Results From the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis.* 2017;69(2):266-277.
91. Kim T, Rhee CM, Streja E, et al. Racial and Ethnic Differences in Mortality Associated with Serum Potassium in a Large Hemodialysis Cohort. *American journal of nephrology.* 2017;45(6):509-521.
92. Korgaonkar S, Tilea A, Gillespie BW, et al. Serum potassium and outcomes in CKD: insights from the RRI-CKD cohort study. *Clin J Am Soc Nephrol.* 2010;5(5):762-769.
93. Torlen K, Kalantar-Zadeh K, Molnar MZ, Vashistha T, Mehrotra R. Serum potassium and cause-specific mortality in a large peritoneal dialysis cohort. *Clin J Am Soc Nephrol.* 2012;7(8):1272-1284.
94. Yusuf AA, Hu Y, Singh B, Menoyo JA, Wetmore JB. Serum Potassium Levels and Mortality in Hemodialysis Patients: A Retrospective Cohort Study. *American journal of nephrology.* 2016;44(3):179-186.
95. Bowling CB, Pitt B, Ahmed MI, et al. Hypokalemia and outcomes in patients with chronic heart failure and chronic kidney disease: findings from propensity-matched studies. *Circ Heart Fail.* 2010;3(2):253-260.
96. Pun PH, Goldstein BA, Gallis JA, Middleton JP, Svetkey LP. Serum Potassium Levels and Risk of Sudden Cardiac Death Among Patients With Chronic Kidney Disease and Significant Coronary Artery Disease. *Kidney Int Rep.* 2017;2(6):1122-1131.
97. Polcwiartek C, Hansen SM, Kragholm K, et al. Prognostic role of serum sodium levels across different serum potassium levels in heart failure patients: A Danish register-based cohort study. *Int J Cardiol.* 2018;272:244-249.
98. Wagner S, Metzger M, Flamant M, et al. Association of plasma potassium with mortality and end-stage kidney disease in patients with chronic kidney disease under nephrologist care - The NephroTest study. *BMC Nephrol.* 2017;18(1):295.
99. Cheungpasitporn W, Thongprayoon C, Kittanamongkolchai W, Sakhuja A, Mao MA, Erickson SB. Impact of admission serum potassium on mortality in patients with chronic kidney disease and cardiovascular disease. *QJM : monthly journal of the Association of Physicians.* 2017;110(11):713-719.
100. Gasparini A, Evans M, Barany P, et al. Plasma potassium ranges associated with mortality across stages of chronic kidney disease: the Stockholm CREAtinine Measurements (SCREAM) project. *Nephrol Dial Transplant.* 2018.
101. Collins AJ, Pitt B, Reaven N, et al. Association of Serum Potassium with All-Cause Mortality in Patients with and without Heart Failure, Chronic Kidney Disease, and/or Diabetes. *American journal of nephrology.* 2017;46(3):213-221.
102. Hayes J, Kalantar-Zadeh K, Lu JL, Turban S, Anderson JE, Kovesdy CP. Association of hypo- and hyperkalemia with disease progression and mortality in males with chronic kidney disease: the role of race. *Nephron Clin Pract.* 2012;120(1):c8-16.
103. Thomsen RW, Nicolaisen SK, Hasvold P, et al. Elevated Potassium Levels in Patients With Congestive Heart Failure: Occurrence, Risk Factors, and Clinical Outcomes: A Danish Population-Based Cohort Study. *J Am Heart Assoc.* 2018;7(11).

104. Nakhoul GN, Huang H, Arrigain S, et al. Serum Potassium, End-Stage Renal Disease and Mortality in Chronic Kidney Disease. *American journal of nephrology.* 2015;41(6):456-463.
105. Furuland H, McEwan P, Evans M, et al. Serum potassium as a predictor of adverse clinical outcomes in patients with chronic kidney disease: new risk equations using the UK clinical practice research datalink. *BMC Nephrol.* 2018;19(1):211.
106. Chang AR, Sang Y, Leddy J, et al. Antihypertensive Medications and the Prevalence of Hyperkalemia in a Large Health System. *Hypertension.* 2016;67(6):1181-1188.
107. Ahmed A, Zannad F, Love TE, et al. A propensity-matched study of the association of low serum potassium levels and mortality in chronic heart failure. *European heart journal.* 2007;28(11):1334-1343.
108. Ahmed MI, Ekundayo OJ, Mujib M, et al. Mild hyperkalemia and outcomes in chronic heart failure: a propensity matched study. *International journal of cardiology.* 2010;144(3):383-388.
109. Cosei II, Antohi L, Radu R, et al. Serum potassium levels at admission and in-hospital all-cause mortality in patients hospitalised for acute heart failure (insights from RO-AHFS registry). *European journal of heart failure.* 2017;19:540-541.
110. Tromp J, ter Maaten JM, Damman K, et al. Serum potassium levels and outcome in acute heart failure (data from the PROTECT and COACH trials). *The American journal of cardiology.* 2017;119(2):290-296.
111. Formiga F, Chivite D, Montero A, et al. Association between diabetes and mortality in elderly patients admitted for a first episode of acute heart failure. *Geriatrics & gerontology international.* 2018;18(4):554-560.
112. Formiga F, Moreno-Gonzalez R, Chivite D, Casado J, Escrihuela-Vidal F, Corbella X. Clinical characteristics and one-year mortality according to admission renal function in patients with a first acute heart failure hospitalization. *Revista portuguesa de cardiologia.* 2018;37(2):159-165.
113. Krittanawong C, Thongprayoon C, Peeraphatdit T, Naksuk N. SP354OPTIMAL SERUM POTASSIUM, CALCIUM AND MAGNESIUM IN THE CORONARY CARE UNIT. *Nephrology dialysis transplantation.* 2015;30(suppl_3):iii496-iii496.
114. Aldahl M, Jensen AC, Davidsen L, et al. Associations of serum potassium levels with mortality in chronic heart failure patients. *Eur Heart J.* 2017;38(38):2890-2896.
115. Alper AB, Campbell RC, Anker SD, et al. A propensity-matched study of low serum potassium and mortality in older adults with chronic heart failure. *International journal of cardiology.* 2009;137(1):1-8.
116. Jain N, Kotla S, Little BB, et al. Predictors of hyperkalemia and death in patients with cardiac and renal disease. *The American journal of cardiology.* 2012;109(10):1510-1513.
117. Kiernan MS, Wentworth D, Francis G, et al. Predicting adverse events during angiotensin receptor blocker treatment in heart failure: results from the HEAAL trial. *European journal of heart failure.* 2012;14(12):1401-1409.
118. Spinar J, Parenica J, Vitovec J, et al. Baseline characteristics and hospital mortality in the Acute Heart Failure Database (AHEAD) Main registry. *Critical care.* 2011;15(6):R291.
119. Krogager ML, Eggers-Kaas L, Aasbjerg K, et al. Short-term mortality risk of serum potassium levels in acute heart failure following myocardial infarction. *European heart journal Cardiovascular pharmacotherapy.* 2015;1(4):245-251.
120. Formiga F, Chivite D, Corbella X, et al. Influence of potassium levels on one-year outcomes in elderly patients with acute heart failure. *European Journal of Internal Medicine.* 2018.
121. Bennet H, Ayoubkhan D, Evans M, et al. Quantifying the relationship between hyperkalaemia and outcomes in Patients with heart failure and chronic kidney disease. *Value in Health.* 2017;20(9):A682.
122. Qin Y, Chen T, Chen Q, et al. The effect of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use on mortality in patients with chronic kidney disease: a meta-analysis of observational studies. *Pharmacoepidemiol Drug Saf.* 2016;25(5):503-511.
123. Liu Y, Ma X, Zheng J, Jia J, Yan T. Effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on cardiovascular events and residual renal function in dialysis patients: a meta-analysis of randomised controlled trials. *BMC Nephrol.* 2017;18(1):206.
124. Tai DJ, Lim TW, James MT, et al. Cardiovascular effects of angiotensin converting enzyme inhibition or angiotensin receptor blockade in hemodialysis: a meta-analysis. *Clin J Am Soc Nephrol.* 2010;5(4):623-630.
125. Lu R, Zhang Y, Zhu X, et al. Effects of mineralocorticoid receptor antagonists on left ventricular mass in chronic kidney disease patients: a systematic review and meta-analysis. *International urology and nephrology.* 2016;48(9):1499-1509.

126. Quach K, Lvtvyn L, Baigent C, et al. The Safety and Efficacy of Mineralocorticoid Receptor Antagonists in Patients Who Require Dialysis: A Systematic Review and Meta-analysis. *Am J Kidney Dis.* 2016;68(4):591-598.
127. Balamuthusamy S, Srinivasan L, Verma M, et al. Renin angiotensin system blockade and cardiovascular outcomes in patients with chronic kidney disease and proteinuria: a meta-analysis. *American heart journal.* 2008;155(5):791-805.
128. Xie X, Liu Y, Perkovic V, et al. Renin-angiotensin system inhibitors and kidney and cardiovascular outcomes in patients with CKD: A Bayesian network meta-analysis of randomized clinical trials. *Am J Kidney Dis.* 2016;67(5):728-741.
129. Gilstrap LG, Fonarow GC, Desai AS, et al. Initiation, Continuation, or Withdrawal of Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers and Outcomes in Patients Hospitalized With Heart Failure With Reduced Ejection Fraction. *J Am Heart Assoc.* 2017;6(2).
130. Miller RJ, Howlett JG, Exner DV, Campbell PM, Grant AD, Wilton SB. Baseline Functional Class and Therapeutic Efficacy of Common Heart Failure Interventions: A Systematic Review and Meta-analysis. *Can J Cardiol.* 2015;31(6):792-799.
131. Fu M, Zhou J, Sun A, et al. Efficacy of ACE inhibitors in chronic heart failure with preserved ejection fraction--a meta analysis of 7 prospective clinical studies. *Int J Cardiol.* 2012;155(1):33-38.
132. Tai C, Gan T, Zou L, et al. Effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on cardiovascular events in patients with heart failure: a meta-analysis of randomized controlled trials. *BMC Cardiovasc Disord.* 2017;17(1):257.
133. Xie W, Zheng F, Song X, Zhong B, Yan L. Renin-angiotensin-aldosterone system blockers for heart failure with reduced ejection fraction or left ventricular dysfunction: Network meta-analysis. *Int J Cardiol.* 2016;205:65-71.
134. Thomsen MM, Lewinter C, Kober L. Varying effects of recommended treatments for heart failure with reduced ejection fraction: meta-analysis of randomized controlled trials in the ESC and ACCF/AHA guidelines. *ESC Heart Fail.* 2016;3(4):235-244.
135. Flather MD, Yusuf S, Kober L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. *Lancet (London, England).* 2000;355(9215):1575-1581.
136. Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. *Circulation.* 1999;100(23):2312-2318.
137. Phelan D, Thavendiranathan P, Collier P, Marwick TH. Aldosterone antagonists improve ejection fraction and functional capacity independently of functional class: a meta-analysis of randomised controlled trials. *Heart.* 2012;98(23):1693-1700.
138. Kleber FX, Niemöller L. Long-term survival in the Munich Mild Heart Failure Trial (MHFT). *American Journal of Cardiology.* 1993;71(13):1237-1239.
139. Kotecha D, Manzano L, Krum H, et al. Effect of age and sex on efficacy and tolerability of β blockers in patients with heart failure with reduced ejection fraction: individual patient data meta-analysis. *bmj.* 2016;353:i1855.
140. Bushinsky DA, Williams GH, Pitt B, et al. Patiromer induces rapid and sustained potassium lowering in patients with chronic kidney disease and hyperkalemia. *Kidney international.* 2015;88(6):1427-1433.
141. Bakhai A, Palaka E, Linde C, et al. Development of a health economic model to evaluate the potential benefits of optimal serum potassium management in patients with heart failure. *Journal of medical economics.* 2018:1-11.
142. Wolfgram DF, Garcia K, Evans G, et al. Association of Albuminuria and Estimated Glomerular Filtration Rate with functional performance measures in older adults with chronic kidney disease. *American journal of nephrology.* 2017;45(2):172-179.
143. Eriksson D, Goldsmith D, Teitsson S, Jackson J, van Nooten F. Cross-sectional survey in CKD patients across Europe describing the association between quality of life and anaemia. *BMC nephrology.* 2016;17(1):97.
144. Gorodetskaya I, Zenios S, McCulloch CE, et al. Health-related quality of life and estimates of utility in chronic kidney disease. *Kidney International.* 2005;68(6):2801-2808.
145. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. *Med Decis Making.* 2011;31(6):800-804.

9 Appendices

Appendix A. S-K and outcomes SLR methods

Table 23 shows the Population-Intervention-Comparators-Outcomes-Study (PICOS) eligibility criteria for the review.

Table 23: PICOS eligibility criteria

	Inclusion criteria	Exclusion criteria
Population	[redacted]	[redacted]
Intervention and comparators	[redacted]	[redacted]
Outcomes	[redacted]	[redacted]
Study	[redacted]	[redacted]
Language restrictions	[redacted]	[redacted]
Date restrictions	[redacted]	[redacted]

Abbreviations: CKD, chronic kidney disease; HF, heart failure; HK, hyperkalaemia; IRR, incident rate ratio; MACE, major adverse cardiac event; N/A, not applicable; OR, odds ratio; RAASi, renin–angiotensin–aldosterone system inhibitor; S-K; serum potassium.

The search was initially conducted from [redacted] across the following databases:

[redacted]

An SLR update was undertaken on [redacted] to identify any additional studies that had not been indexed or published at the time of the initial review. The SLR update was restricted to studies published from [redacted], using the same search strategies on the same databases as the initial SLR.

In addition, supplementary searches of “grey” literature searching were performed to complement the literature database searches.

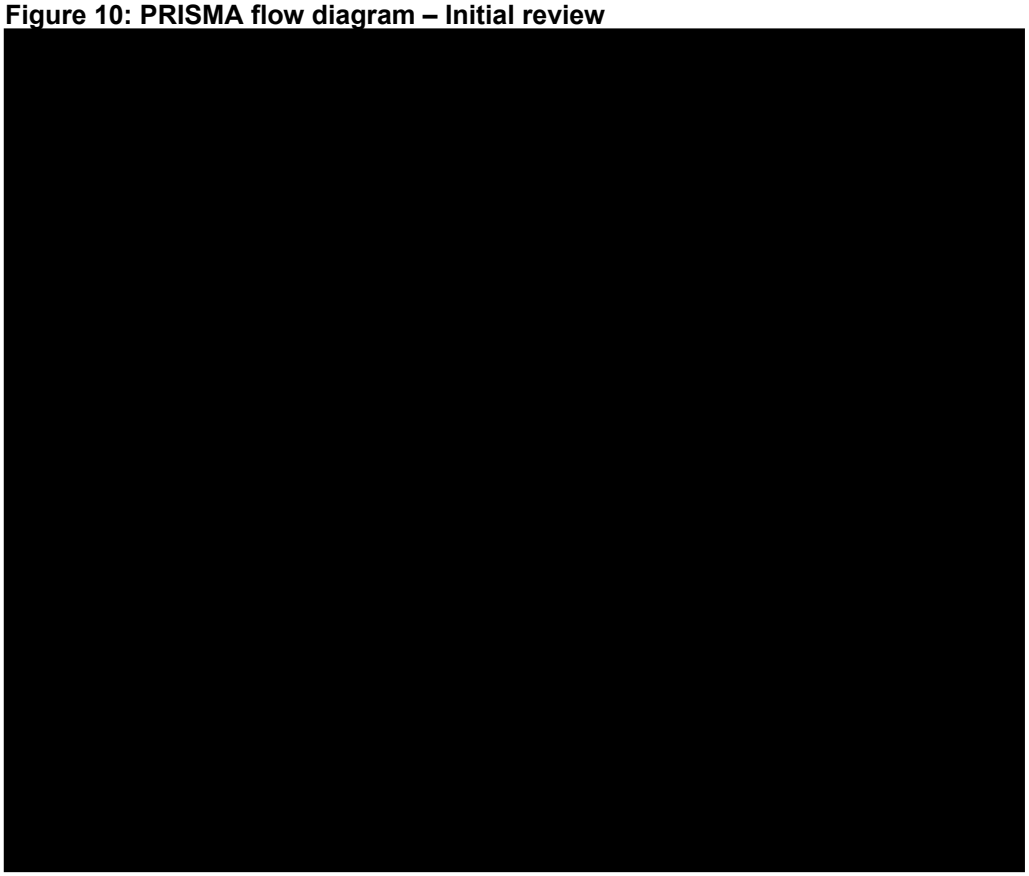
Following the removal of any duplicate records across the searched databases, two independent reviewers assessed the relevance of identified studies based on title and abstract. Full-texts of potentially eligible studies were retrieved and assessed against the PICOS eligibility criteria outlined in Table 23. Disagreements were discussed, and a third reviewer was involved when required.

The review focussed on studies reporting relative and absolute measures of the risk of mortality, hospitalisation, and MACE. These associations were reported in terms of event incidence rate, probability of event, hazard ratio (HR), odds ratio (OR), relative risk ratio (RR) and incidence rate ratio

(IRR). Where possible, absolute measures of risk were converted to the appropriate relative measure for consistency.

The searches identified [redacted] references after the removal of duplicates. After reviewing titles and abstracts, a further [redacted] references were excluded. Full texts of the remaining references were retrieved and reviewed, with [redacted] references excluded at this stage. A total of [redacted] references met the inclusion criteria. The SLR update identified [redacted] references, after the removal of duplicates. A further [redacted] references were removed after reviewing titles and abstracts. Of the remaining [redacted] references, [redacted] had been identified as part of the initial review and were consequently excluded. Full texts were retrieved and reviewed for the remaining [redacted] references with [redacted] studies satisfying the inclusion criteria. Of the [redacted] relevant studies identified, [redacted] reported associations between a patient's S-K level and outcomes and were therefore fully assessed. The PRISMA flow diagrams for the initial SLR and for the SLR update are presented in Figure 10 and Figure 11, respectively.

Figure 10: PRISMA flow diagram – Initial review



Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

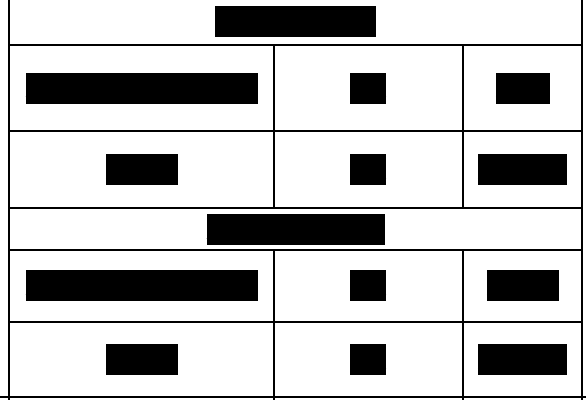
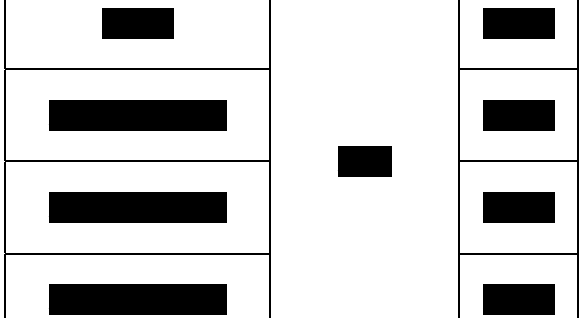
Figure 11: PRISMA flow diagram – 2nd November 2018 update

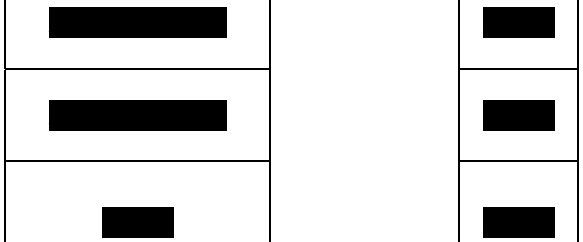
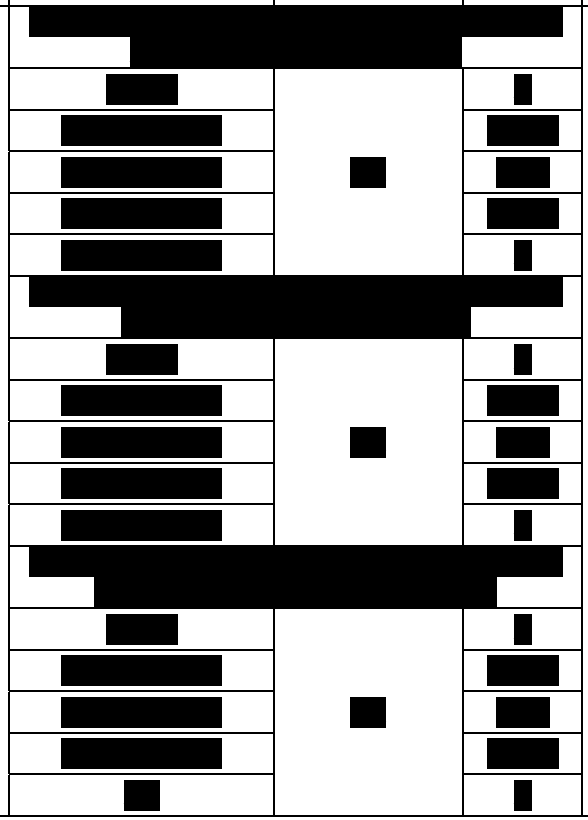
Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Appendix B. S-K and outcomes SLR results

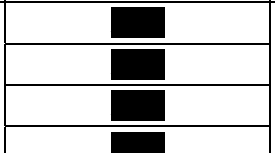
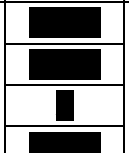
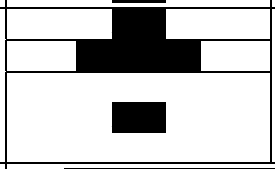
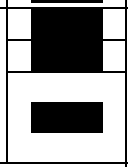
Table 24: Studies reporting the relationship between S-K and mortality in CKD patients

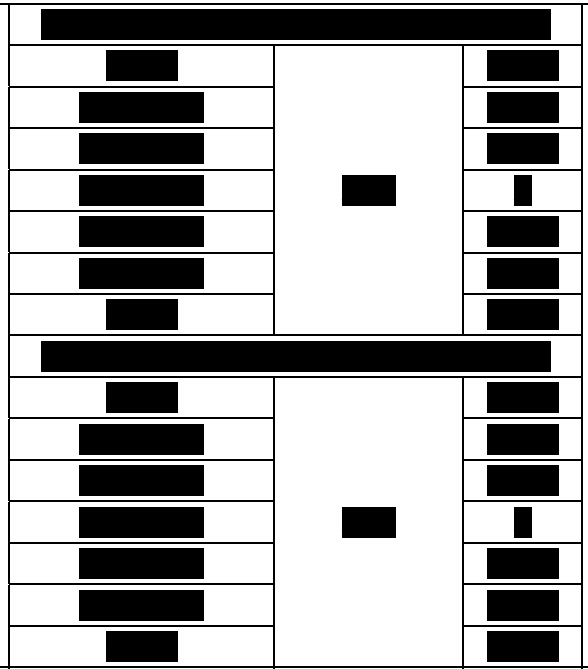
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Study relevance and rationale***
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Not relevant** The study only examined the effect of hypokalaemia
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Not relevant** Adjusted for age, sex, race, eGFR, principal diagnosis, Charlson comorbidity score, comorbidities and medications. Patients with ESRD excluded ORs reported for 7 S-K intervals However, only in-hospital mortality was considered, making the paper un suitable for use in the economic model
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Relevant** Adjusted for age group, gender; HTN, CVD, AMI, CKD

								stage, HF, DM, RAASi, and loop, thiazide, and potassium-sparing diuretic prescriptions RAASi Patients with ESRD and AKI excluded IRRs reported for 9 S-K intervals
								**Not relevant** Only death events on the day of the S-K measurement was considered (authors stated that this avoids confounding) CV comorbidities included in analysis as a composite measure No adjustment for eGFR
								**Relevant** Model output for risk equations provided adjusting for age, gender, time, S-K, history of diabetes, cancer, dementia, MACE, PVD and smoking, time-updated eGFR and RAASi, time-updated

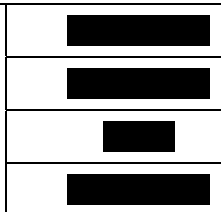
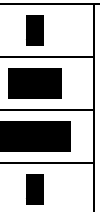
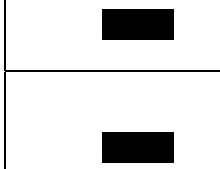
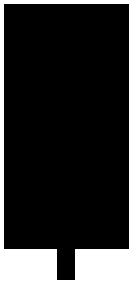
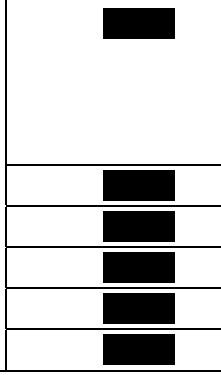
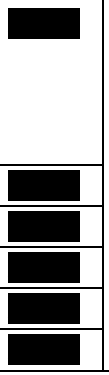
								presence of HF, and prescription of diuretics, bronchodilators, insulin and statins ± 3 months from baseline Model output for 6 S-K intervals included
								**Not relevant** Abstract reports 365-day mortality but does not mention how confounders were adjusted for

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Not relevant** Only reported a HR for one S-K interval
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Not relevant** Haemodialysis patients only
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Not relevant** In maintenance haemodialysis patients only

								**Not relevant** Cox regression analyses were not adjusted for relevant pharmacotherapies
								**Not relevant** Only assessed hazard at specific S-K values
								**Relevant** Adjusted for age, sex, race/ethnicity, diabetes, congestive heart failure, coronary artery disease, cerebrovascular disease, β-blocker use, RAAS blocker use, nondihydropyridine calcium channel blocker use, thiazide diuretic use, loop diuretic use, and eGFR. Kidney transplant and dialysis patients were excluded

								IRRs were reported for 7 S-K intervals stratified by eGFR
								Relevant Adjusted for age, gender, race, body mass index (BMI), eGFR, diabetes, hypertension, malignancy, coronary artery disease, heart failure, chronic obstructive pulmonary disease (COPD) and/or asthma, use of ACE/ARB, and use of beta blockers

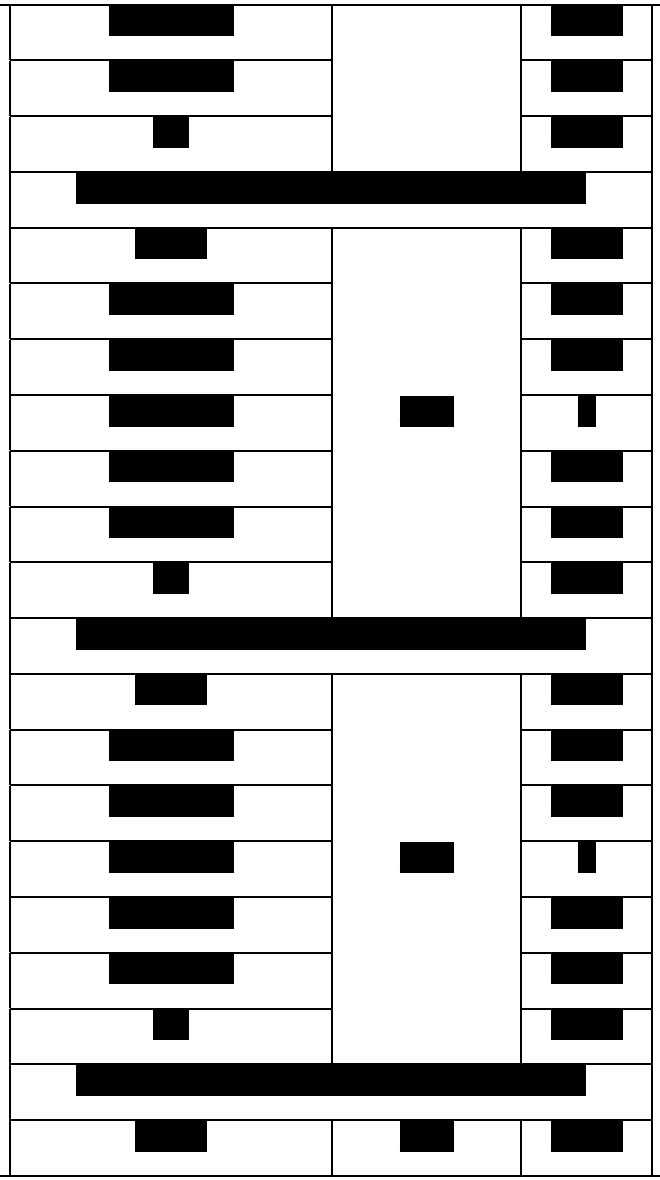
								ESRD and dialysis patients were excluded
								Not relevant Assessed patients with impaired estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 m^2 meaning that patients with dialysis or RRT are potentially included
								Not relevant All patients had acute coronary artery disease (post catherization patients) Outcome was sudden cardiac arrest and sudden cardiac death, i.e. not all-cause mortality
								Not relevant Only looking at HK
								Not relevant

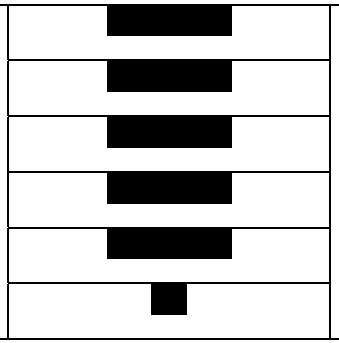
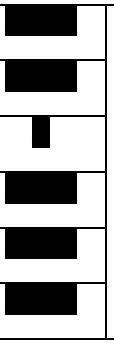
								All patients on peritoneal maintenance dialysis
								**Not relevant** Only provided hazard ratios for ‘before ESKD’ and ‘after ESRD’
								**Not relevant** All patients on dialysis

* The following was considered for study relevance: covariate adjustment (baseline characteristics, relevant pharmacotherapies and comorbidities), population (CKD stage I-V pre-dialysis), range of potassium values reported (covering hypo- and hyperkalaemia, with at least 3 S-K increments)

Table 25: Studies reporting the relationship between S-K and MACE in CKD patients

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Study relevance and rationale*
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Relevant** Model output for risk equations provided adjusting for age, gender, time, S-K, baseline cholesterol, history of diabetes, rheumatologic disease, MACE, chronic pulmonary disease and smoking, time-updated eGFR, and prescription of CCBs, insulin and beta blockers ± 3 months from baseline Model output for 6 S-K intervals included
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Relevant** Adjusted for age, sex, race/ethnicity, diabetes, congestive heart failure, coronary artery disease, cerebrovascular disease, β-blocker

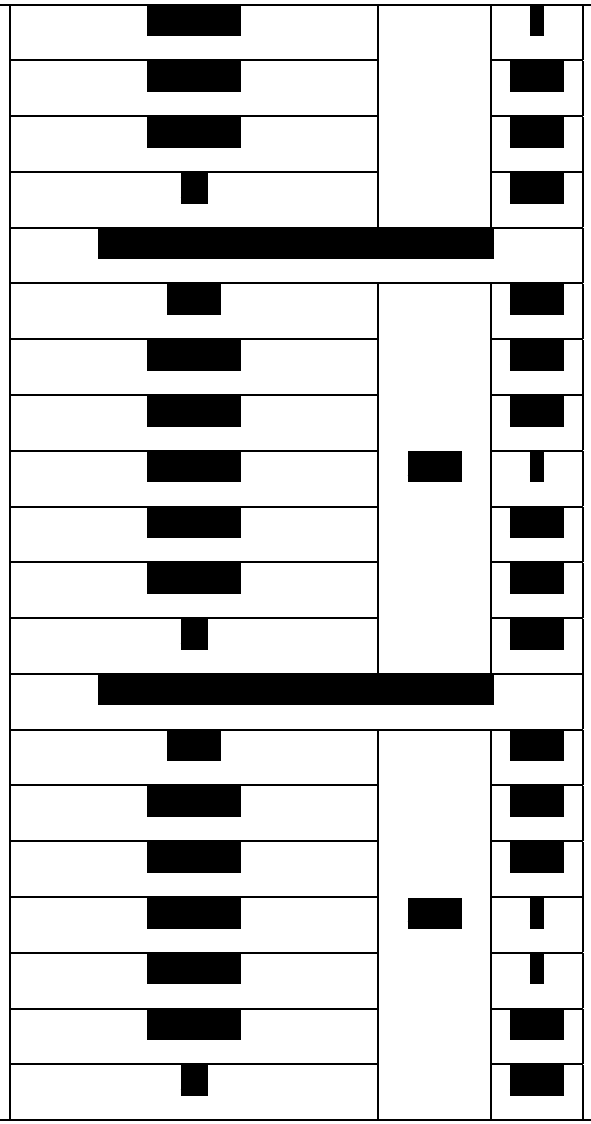
						use, RAAS blocker use, nondihydropyridine calcium channel blocker use, thiazide diuretic use, loop diuretic use, and eGFR. Kidney transplant and dialysis patients were excluded IRRs were reported for 7 S-K intervals stratified by eGFR

*The following was considered for study relevance: covariate adjustment (baseline characteristics, relevant pharmacotherapies and comorbidities), population (CKD stage I-V pre-dialysis), range of potassium values reported (covering hypo- and hyperkalaemia, with at least 3 S-K increments)

Table 26: Studies reporting the relationship between S-K and hospitalisation in CKD patients

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Study relevance and rationale***
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Not relevant** The study only examined the effect of hypokalaemia
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Not relevant** The study only looks at HK
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Relevant** Adjusted for age, sex, race/ethnicity, diabetes, congestive heart failure, coronary artery disease, cerebrovascular disease, β-blocker use, RAAS blocker use, nondihydropyridine calcium channel blocker use, thiazide diuretic use, loop diuretic

						use, and eGFR. Kidney transplant and dialysis patients were excluded IRRs were reported for 7 S-K intervals stratified by eGFR

								**Not relevant** The study assessed patients before and after HK and so a clear reference category was not stated, potentially covering any S-K level below 5mmol/L

*The following was considered for study relevance: covariate adjustment (baseline characteristics, relevant pharmacotherapies and comorbidities) , population (CKD stage I-V pre-dialysis), range of potassium values reported (covering hypo- and hyperkalaemia, with at least 3 S-K increments)

Table 27: Studies reporting the relationship between S-K and mortality in HF patients

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Study relevance for economic model and rationale***
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Not relevant** Limited range of potassium values – only looked at low S-K
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Not relevant** Limited range of potassium values – only assessed mild HK
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Relevant** Clinically relevant comorbidities, conditions, and relevant concomitant cardiovascular pharmacotherapies were used as covariates in the analysis HRs were provided for 8 S-K intervals
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Not relevant**

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Study relevance for economic model and rationale***
									Only looked at patients ≥65 years of age
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Not relevant** Limited range of potassium values – only assessed patients with low S-K
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Relevant** Adjusted for age group, gender; HTN, CVD, AMI, CKD stage, HF, DM, RAASi, and loop, thiazide, and potassium-sparing diuretic prescriptions RAASi IRRs were reported for 9 S-K intervals
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Relevant** Adjusted for region, age, gender, race, baseline GFR, baseline potassium, and

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Study relevance for economic model and rationale***
						[redacted]			baseline pharmacologic treatment (renin-angiotensin-aldosterone antagonists, beta blockade and loop diuretics, spironolactone) Reported HRs for 6 S-K intervals covering hypo- and HK
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Not relevant** Only looked at patients ≥65 years of age
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Not relevant** Only evaluated patients ≥50 years of age
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Not relevant** Only looked at patients ≥75 years of age

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Study relevance for economic model and rationale***
						[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Not relevant** No mention of covariate adjustment and no consideration of HK
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Not relevant** Limited range of potassium values – only looked at HK
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Not relevant** Limited range of potassium values – only looked at HK
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Not relevant** The abstract did not specify

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Study relevance for economic model and rationale***
						[redacted]		[redacted]	which covariates were adjusted for
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Relevant** There was adjustment for age, sex, biologically relevant comorbidities (e.g. stroke) and medication, including RAAS inhibitors HRs provided for 7 S-K intervals
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Not relevant** The study did not look at hypokalaemia

									Study relevance for economic model and rationale*
									Relevant Adjusted for sex, estimated glomerular filtration rate time-varying <60 mL/min/1.73 m2 (0/1), diabetes mellitus time-varying (0/1), and the use of potassium-modifying treatments (none, MRA, ACEI/ARB, and both) at baseline HRs were reported for hypo-, normo- and hyperkalaemia.
									Relevant

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Study relevance for economic model and rationale***
						[redacted]		[redacted]	Adjusted for age, sex, ischemic cause of HF, atrial flutter or fibrillation, second- or third-degree atrioventricular block, ventricular tachycardia or fibrillation, hypertension, chronic obstructive pulmonary disease, renal insufficiency, chronic liver disease, diabetes, hypothyroidism, alcohol abuse, ACEIs, ARBs, MRAs, potassium supplements, betablockers digoxin, thiazide diuretics,
				[redacted]		[redacted]		[redacted]	
				[redacted]		[redacted]		[redacted]	

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Study relevance for economic model and rationale***
									NSAIDs, antidepressants, and antiepileptics HRs presented for 5 S-K intervals
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Not relevant** Limited range of potassium values – only looked at HK
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Not relevant** Limited range of potassium values – only looked at HK
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Not relevant** S-K range for HRs not reported

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor, AMI, acute myocardial infarction, ARB, angiotensin receptor blockers, CKD, chronic kidney disease, CVD, cardiovascular disease, DM, diabetes mellitus, GFR, glomerular filtration rate, HF, heart failure, HK, hypokalaemia, HR, hazard ratio, HTN, hypertension, IRR, incident rate ratio,MRA, mineralocorticoid receptor antagonist, NSAID, non-steroidal anti-inflammatory drug, RAASi, renin-angiotensin-aldosterone system inhibitor, S-K, serum potassium

*The following was considered for study relevance: covariate adjustement (baseline characteristics, concomitant pharmcotherapies, comorbidities), population (HF), range of potassium values reported (covering hypo- and hyperkalaemia, with at least 3 S-K increments)

Table 28: Studies reporting the relationship between S-K and hospitalisation in HF patients

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Study relevance for economic model and rationale***
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Not relevant** Limited range of potassium values – only looked at low S-K
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Not relevant** Limited range of potassium values – only assessed mild HK

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Study relevance for economic model and rationale***
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Not relevant** Only looked at patients ≥65 years of age
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Not relevant** Limited range of potassium values – only assessed patients with low S-K
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Relevant** Adjusted for region, age, gender, race, baseline GFR, baseline potassium, and baseline pharmacologic treatment (renin-angiotensin-aldosterone antagonists, beta blockade and loop

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Study relevance for economic model and rationale***
									diuretics, spironolactone) Reported HRs for 6 S-K intervals covering hypo- and hyperkalaemia
									Not relevant Only looked at patients ≥75 years of age
									Not relevant Limited range of potassium values – only looked at HK

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Study relevance for economic model and rationale***
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Not relevant** The study assessed patients before and after HK and so a clear reference category was not stated, potentially covering any S-K level below 5mmol/L

Abbreviations: GFR, glomerular filtration rate, HF, heart failure, S-K, serum potassium

*The following was considered for study relevance: covariate adjustement (baseline characteristics, concomitant pharmcotherapies, comorbidities), population (HF), range of potassium values reported (covering hypo- and hyperkalaemia, with at least 3 S-K increments)

Appendix C. S-K and outcomes full SLR

Please see separate document.

Appendix D. Efficacy and safety data using MedDRA SMQ (narrow) definitions of HF and CKD

Please see separate document.

Appendix C: S-K and outcomes full SLR

Table of Contents

1 Introduction

Hyperkalaemia (HK) refers to the presence of elevated serum potassium concentration (in excess of 5.5 mmol/L), and develops when there is excessive production, or ineffective elimination, of potassium.[1] Elevated potassium in the bloodstream can have severe consequences and is associated with increased risk of hospitalisation and mortality. The risk of cardiac-related morbidity and mortality is particularly elevated, as raised serum potassium levels can cause severe alterations to cardiac electrophysiology.[1]

The incidence of hyperkalaemia in hospitalised patients is between 1.1% and 10%, and the most common causes of hyperkalaemia are renal failure (77%), pharmacological (63%) and hyperglycaemia (49%). In patients with chronic kidney disease (CKD), several factors increase susceptibility to hyperkalaemia, including reduced glomerular filtration rate (GFR), metabolic acidosis, and a high dietary potassium intake relative to residual renal function.[1]

Sodium zirconium cyclosilicate (ZS9 [Lokelma®]) is an inorganic cation exchange crystalline compound with a capacity to entrap potassium in the gastrointestinal tract, with a higher specificity over other cations such as calcium and magnesium.[2] The trapped potassium ions are excreted from the body, thereby reducing any excess and resolving hyperkalaemia. The efficacy and safety of ZS9 has been assessed in three Phase II/III open label clinical trials.[3-5] ZS9 demonstrates improved capacity, selectivity and speed for entrapping excess potassium over currently available options for the treatment of hyperkalaemia.[2]

In order to robustly estimate the impact of effective serum potassium management on clinical and health economic outcomes, it is necessary to systematically identify appropriate evidence characterising the association between serum potassium and patient outcomes such as major adverse cardiac events (MACE), hospitalisation, discontinuation or dose-adjustment of renin–angiotensin–aldosterone system inhibitors (RAASi) and mortality.

2 Methods

2.1 Review objectives and inclusion criteria

The primary objective of this study was to perform a systematic literature review (SLR) to identify studies to support the estimation of hyperkalaemia risk and associations between hyperkalaemia and long-term events. Table 1 shows the Population-Intervention-Comparators-Outcomes-Study (PICOS) eligibility criteria for the review.

Table 1. PICOS eligibility criteria for the identification of studies to inform RAIT development

	Inclusion criteria	Exclusion criteria
Population	[redacted]	[redacted]
Intervention and comparators	[redacted]	[redacted]
Outcomes	[redacted]	[redacted]
Study	[redacted]	[redacted]
Language restrictions	[redacted]	[redacted]
Date restrictions	[redacted]	[redacted]

	Inclusion criteria	Exclusion criteria
RAASi: renin–angiotensin–aldosterone system inhibitor		

2.2 Identifying research evidence and study selection

The review was comprised of two components: an initial SLR, undertaken to identify studies published between [redacted] to identify any additional studies not yet indexed or published at the time of the initial review; the SLR update was restricted to studies published [redacted]. Both reviews were conducted according to the PRISMA statement, with consistent multi-string search strategies employed to retrieve published studies. Searches were conducted across the following electronic databases:

[redacted]The Medline, Embase and Cochrane electronic search strategies are listed in Appendix A.

In addition to the searching of databases and conference proceedings, a free text internet search was conducted and reference lists from relevant studies were used to identify further studies that may meet eligibility criteria.

Bibliographic details and abstracts of all citations retrieved by the literature search were downloaded into Endnote version X7, in which titles and abstracts were independently assessed for eligibility by two reviewers. Full-texts of potentially eligible studies were retrieved and assessed against the PICOS eligibility criteria.

[redacted]. Any discrepancies between the two reviewers concerning eligibility were resolved by consensus.

[redacted].

2.3 Data extraction

All data were extracted in a consistent manner from studies meeting the eligibility criteria, collated and analysed in Microsoft Excel 2016. Data were extracted by a single reviewer and quality-checked by a second reviewer. Studies were checked for overlap in terms of authors, their affiliations, study periods and locations, to reduce risk of including duplicate or overlapping cohorts in the review.

2.4 Measuring associations between serum potassium and patient outcomes

The review question concerned studies reporting [redacted]

[redacted].

These associations were reported in terms of event incidence rate, probability of event, hazard ratio (HR), odds ratio (OR), relative risk ratio (RR) and incidence rate ratios (IRR). Where possible, absolute measures of risk were converted to the appropriate relative measure for consistency.

Where associations were presented by categorical serum potassium values, the midpoint of the categorical range was used in graphical presentation of results, and where a category had an undefined limit (e.g. serum potassium ≥ 6.5 mmol/L) the defined limit of the range was used (e.g. 6.5 mmol/L). Where a binary comparison was made (serum potassium <5.0 mmol/L compared with serum potassium ≥5.0 mmol/L), the reported measure of relative risk was recorded and associated with a value representing the boundary between categories. Where definitions of hyperkalaemia were not provided, a threshold of 5.5 mmol/L was assumed. All estimates are presented, regardless of statistical significance.

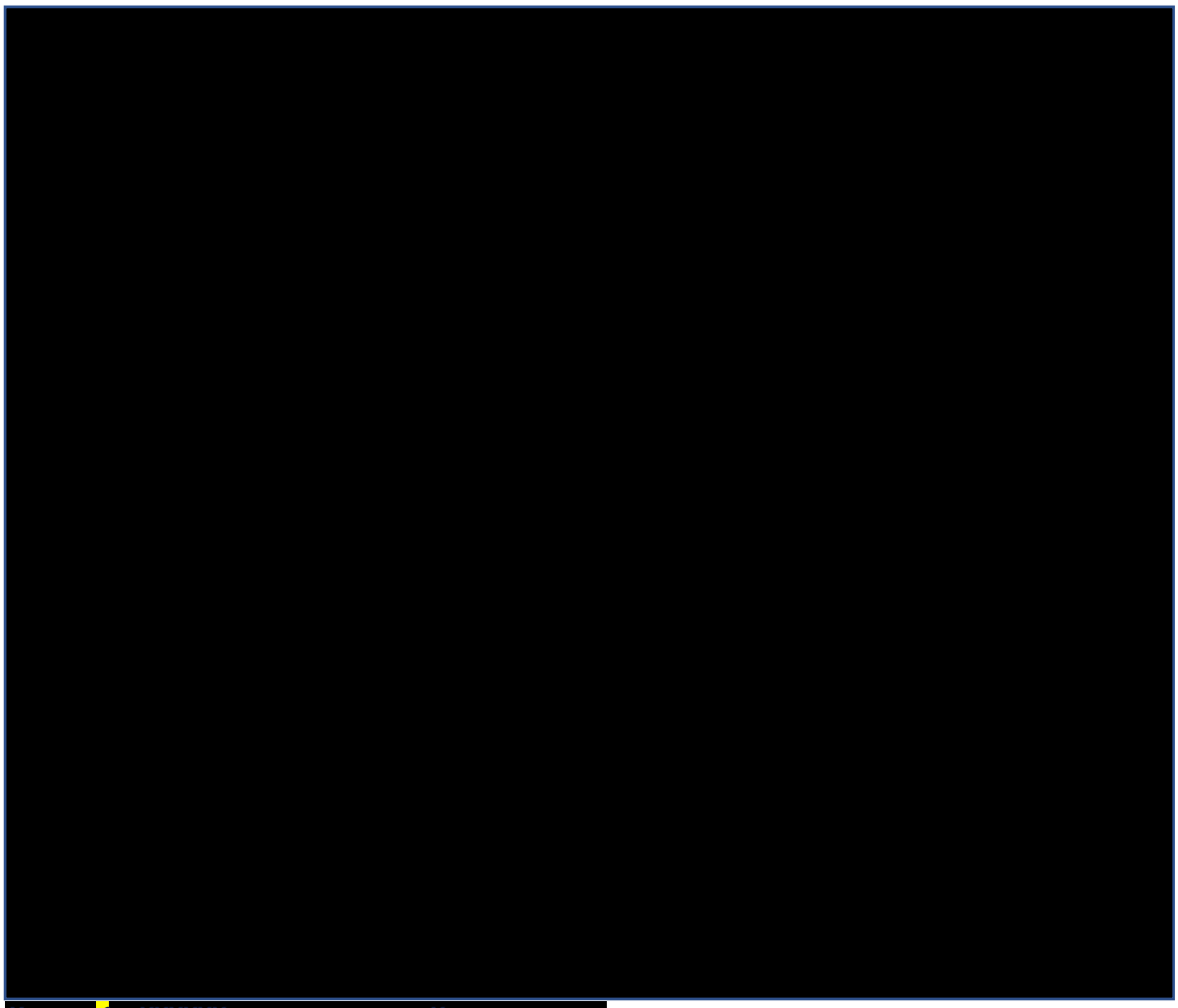
Given the heterogeneity of the included studies, formal hypothesis testing would be inappropriate, and instead a qualitative discussion of associations between serum potassium and outcomes is presented.

3 Results

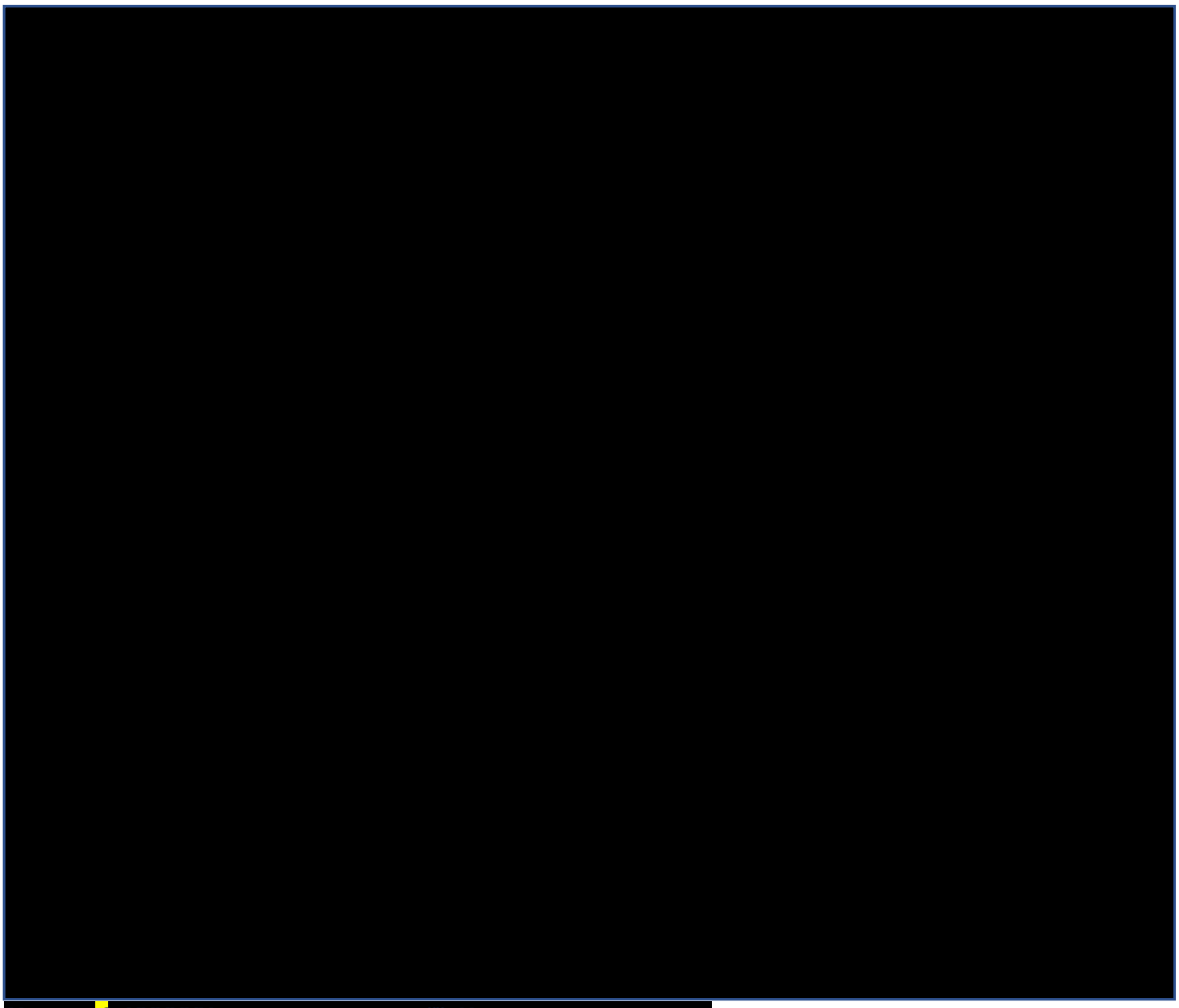
3.1 Literature Search Results

The initial review identified xxxxx references after removal of duplicates. After reviewing titles and abstracts, a further xxxxx references were excluded. Full texts of the remaining references were retrieved and reviewed, with xx references excluded at this stage. A total of xxx references met the inclusion criteria (Xxxxxxx1). The review update identified xxx references, after the removal of duplicates. A further xx references were removed after reviewing titles and abstracts. Of the remaining xx references, xx had been identified as part of the initial review and were consequently excluded; full texts were retrieved and reviewed for the remaining xx references. Of the full text references reviewed, six satisfied the inclusion criteria (Xxxxxxx2).

xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx reported associations between patient characteristics and long-term outcomes and are described in the following sections. A list of all included studies can be seen in Appendix B.



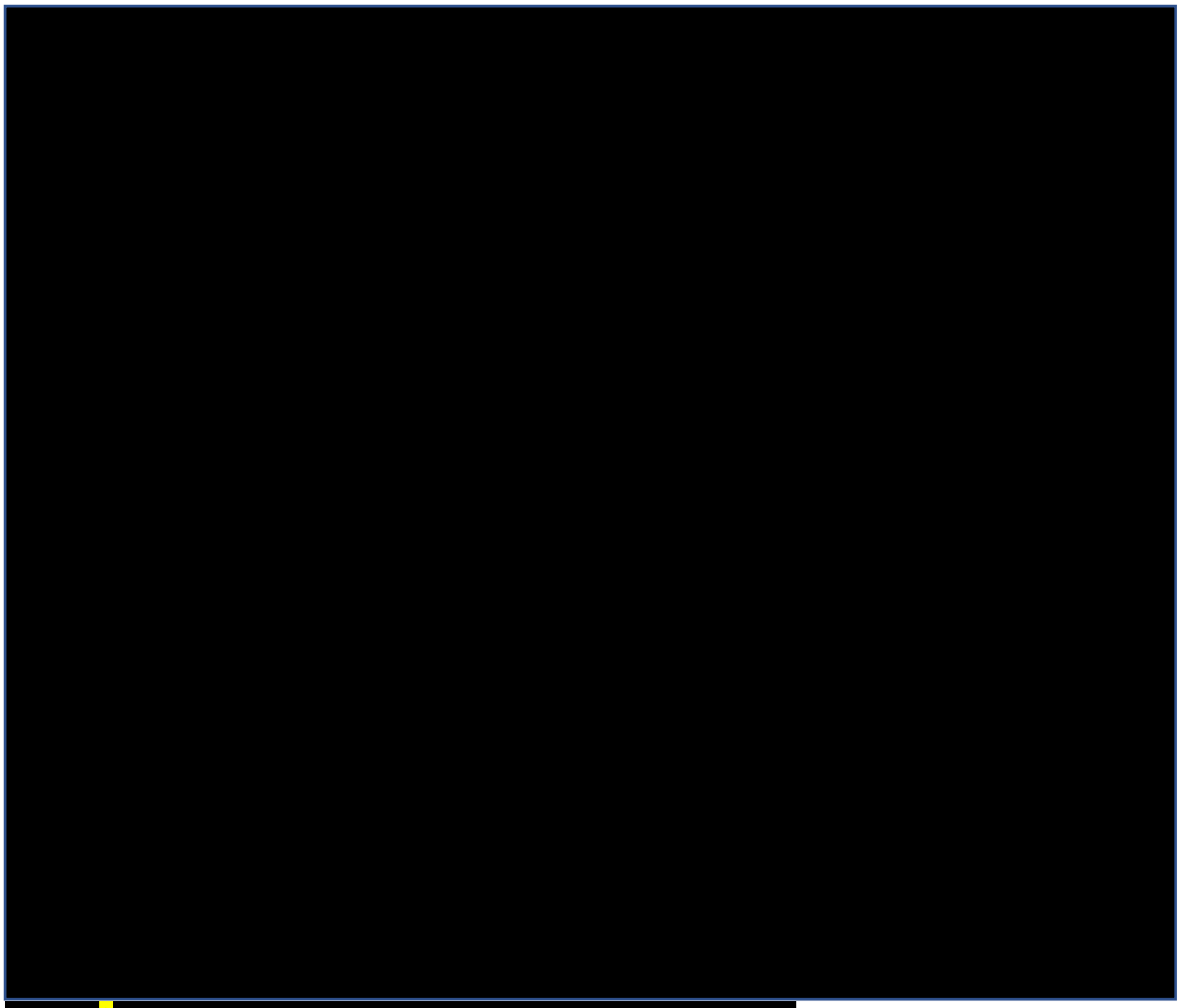
Xxxxxxxx1 xxXXXXXXxxxxxxxxxxxxxxxxxxXxxxxxxxxxxxxxx



Xxxxxxx2 xXXXXXXXxxxxxxxxxxxxxxxxxxxxx3xXxxxxxxxxxxxxxxxxxxx.

3.2 Study Characteristics

The frequency of relevant study publication has increased in recent years, with more than half of the included studies being published since xxxx (Xxxxxxx3).



Of the xx included studies, seven were prospective, xx were retrospective, xx were observational and two were randomised controlled trials, with total cohort sizes ranging from xxxxxxxxxxxxxxx. Xxxx included studies were conducted internationally, xx in North America, xx in Europe, xxxx in Asia and xxx in South America. Although all identified studies included a mixture of comorbidities, they were predominately in patients with CKD (xxxxxx) or heart failure (HF, xxxxxx), with the remaining studies (xxxxxx) undertaken in populations that contained a combination of patients with or without HF, CKD, diabetes and hypertension. Studies were conducted across both inpatient (xxxxxx) and outpatient settings (xxxxxx).

Of the adverse outcomes included in the review question, the association between serum potassium and mortality was most frequently reported (xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx) in the included studies. Associations between serum potassium levels and the incidence of MACE were reported by xxxx studies, the requirement to discontinue or down-titrate RAASi treatment in xxxx studies, and the incidence of hospitalisation in xx studies. Included studies reporting outcomes associated with hyperkalaemia or serum potassium are shown in Table 2.

Table 2. Characteristics of included studies

Author	Year	Country	Population	N	Mortality	Hospitalisation	MACE	RAASi dose adjustment
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Author	Year	Country	Population	N	Mortality	Hospitalisation	MACE	RAASi dose adjustment
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Author	Year	Country	Population	N	Mortality	Hospitalisation	MACE	RAASi dose adjustment
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CKD: chronic kidney disease; HF: heart failure; NR: not reported; RAASi: renin–angiotensin–aldosterone system inhibitor

3.3 Associations between serum potassium and mortality

The majority of included studies reporting evidence on the association between serum potassium and patient mortality found that patients with higher serum potassium were at a higher risk of death than those patients with lower serum potassium values, with relative measures of risk ranging from [redacted] when compared to normokalaemic patients. There were three exceptions to this observation:

[redacted]

Collectively, the relative measures of risk associated with serum potassium measurements reported across all included studies reporting mortality outcomes ([redacted] indicates that both hyperkalaemia and hypokalaemia are associated with increased risk of all-cause and cardiovascular mortality, with the risk to patients increasing as serum potassium levels increase in patients with hyperkalaemia, and decrease in patients with hypokalaemia ([redacted]). Reported effect sizes were typically comparable between CKD, HF and mixed comorbidity cohorts.

[redacted]

[redacted]

For patients with CKD, the most granular descriptions of the association between serum potassium and mortality were presented by [redacted] with estimates stratified by serum potassium level by [redacted]. Estimates were further stratified by eGFR categories in both the [redacted] studies. Despite differences in study design, estimates were similar across studies with [redacted], with eGFR included as a continuous variable, and potassium levels between [redacted].

In patients with HF, [redacted]. both provided detailed stratifications of the relationship between serum potassium levels and risk of mortality, with serum potassium values of over [redacted]. respectively.

3.4 Associations between serum potassium and hospitalisation

The patterns of association between serum potassium and hospitalisation observed in the included studies were similar to the patterns of association observed between serum potassium and mortality described in Section 3.3; both hyper- and hypo-kalaemic patients were at increased risk of hospitalisation, and risks increased with increasing severity of either condition ([redacted]5). However, the relative risks of hospitalisation associated with hyperkalaemia were substantially higher in HF patient cohorts when compared with CKD patient cohorts. In contrast, the relative risk of hospitalisation associated with hypokalaemia was greater in CKD patient cohorts.

[redacted]

[redacted] 5 [redacted]

In CKD patient cohorts, the study by [redacted] provided the most comprehensive stratifications of the relationship between serum potassium and hospitalisation, with adjusted incidence rates and IRRs stratified across a wide range of both serum potassium and eGFR categories, due to a significant interaction observed between serum potassium and eGFR. [redacted].

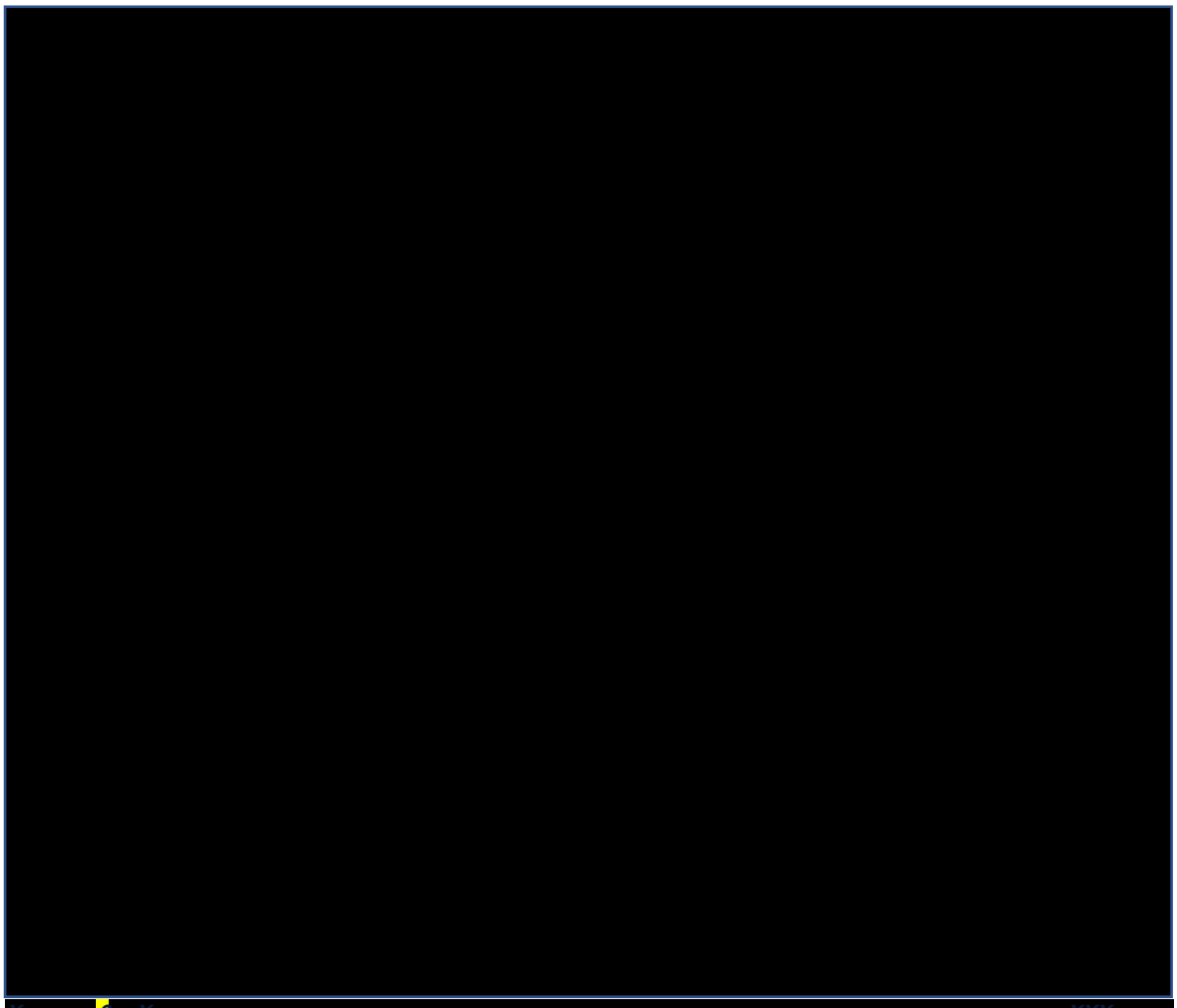
For patients with HF, [redacted] described the HR associated with serum potassium categories ranging from ≤[redacted]. [redacted] described the HRs associated with hyperkalaemia for all-cause hospitalisation, hospitalisation for cardiovascular reasons and hospitalisation for HF independently, with HRs associated with serum potassium [redacted] respectively, relative to patients with normokalaemia.

3.5 Associations between serum potassium and major adverse cardiac events

[redacted]. were the only identified studies that reported on the association of serum potassium and MACE events in an exclusively CKD cohort. Across both eGFR subgroup [redacted] and overall populations, U-shaped relationships between MACE and potassium were consistently reported (Xxxxxxx6). For the overall populations[redacted] report adjusted IRRs for the incidence of MACE to increase from [redacted]

[redacted] was the only study to report associations between serum potassium and MACE in a HF cohort. Relative to patients with serum potassium levels of [redacted] at discharge, significantly higher probabilities of both cardiovascular and HF-related events were observed among patients with lower [redacted] serum potassium levels. Cox proportional hazard analysis of serum potassium by quartile revealed J-shaped associations between serum potassium and both cardiovascular events (plotted in Xxxxxxx6) and HF-related events. The authors presented HRs estimated via alternative models adjusted for different sets of patient characteristics, where serum potassium levels of

[redacted]



[redacted]

3.6 Associations between serum potassium and RAASi dose-adjustments

Although a similar U-shaped relationship between serum potassium and RAASi dose-adjustments was observed (Xxxxxxx7) in included studies to that described in previous sections (Sections 3.3-3.5), only a limited number of studies were identified ([redacted]), and, of those, only studies by [redacted]., [redacted] (not plotted) explored the impact of serum potassium on RAASi dose-adjustments at more than one serum potassium level. [redacted]. reported the IRR associated with multiple serum potassium and eGFR categories in CKD patients, with IRRs for RAASi discontinuation in patients with serum potassium [redacted], relative to normokalaemia. Similarly, [redacted] et al. report IRRs for RAASi discontinuation across a range of serum potassium levels in patients with CKD stage 3 or higher, with eGFR included as a continuous variable; relative to the reference category ([redacted]), reported IRRs for RAASi discontinuation were [redacted]

The only study identified not in an exclusively CKD cohort was Epstein et al. who estimated the proportion of patients that discontinued or down-titrated RAASi treatment following mild ([redacted] or moderate-to-severe hyperkalaemia [redacted]) in cohort combining patients with CKD, HF, diabetes and hypertension. The proportion of patients discontinuing maximum dose with RAASi treatment were [redacted] for mild and moderate-to-severe hyperkalaemia respectively, with [redacted] and [redacted] down-titrating to a sub-maximum dose for mild and moderate-to-severe hyperkalaemia respectively. Similarly, in patients receiving a sub-maximum dose RAASi treatment, [redacted] discontinued treatment following a mild or moderate-to-severe hyperkalaemia event respectively.

4 Conclusion

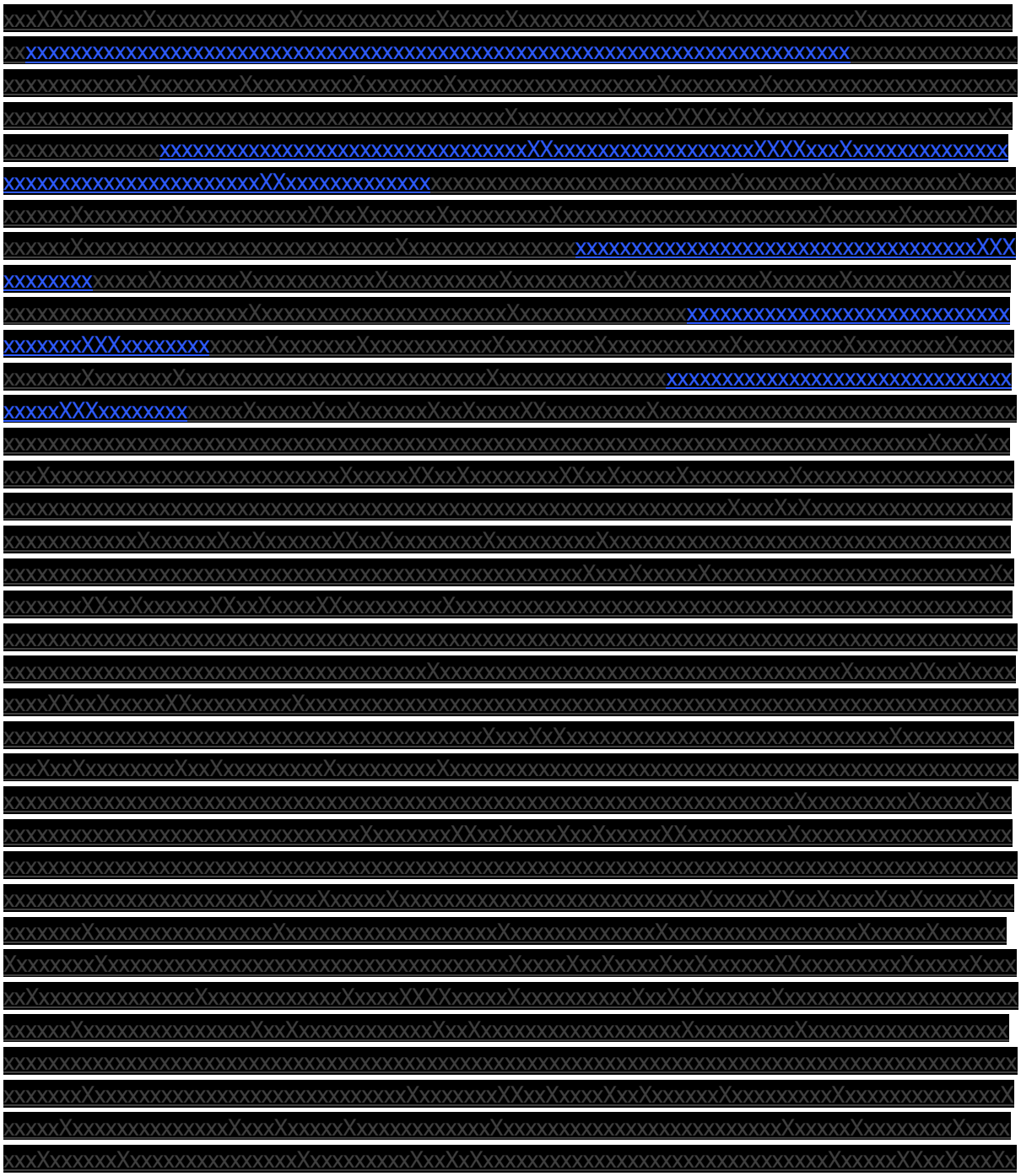
This review identified [redacted] studies that reported information characterising the association between serum potassium and patient outcomes including mortality, hospitalisation, MACE and RAASi dose-adjustments. The majority of identified studies described the impact of serum potassium in HF or CKD comorbid cohorts.

The relationship between hyperkalaemia and long-term outcomes was generally consistent across all outcomes assessed in this review, with relative and absolute risks of adverse patient outcomes

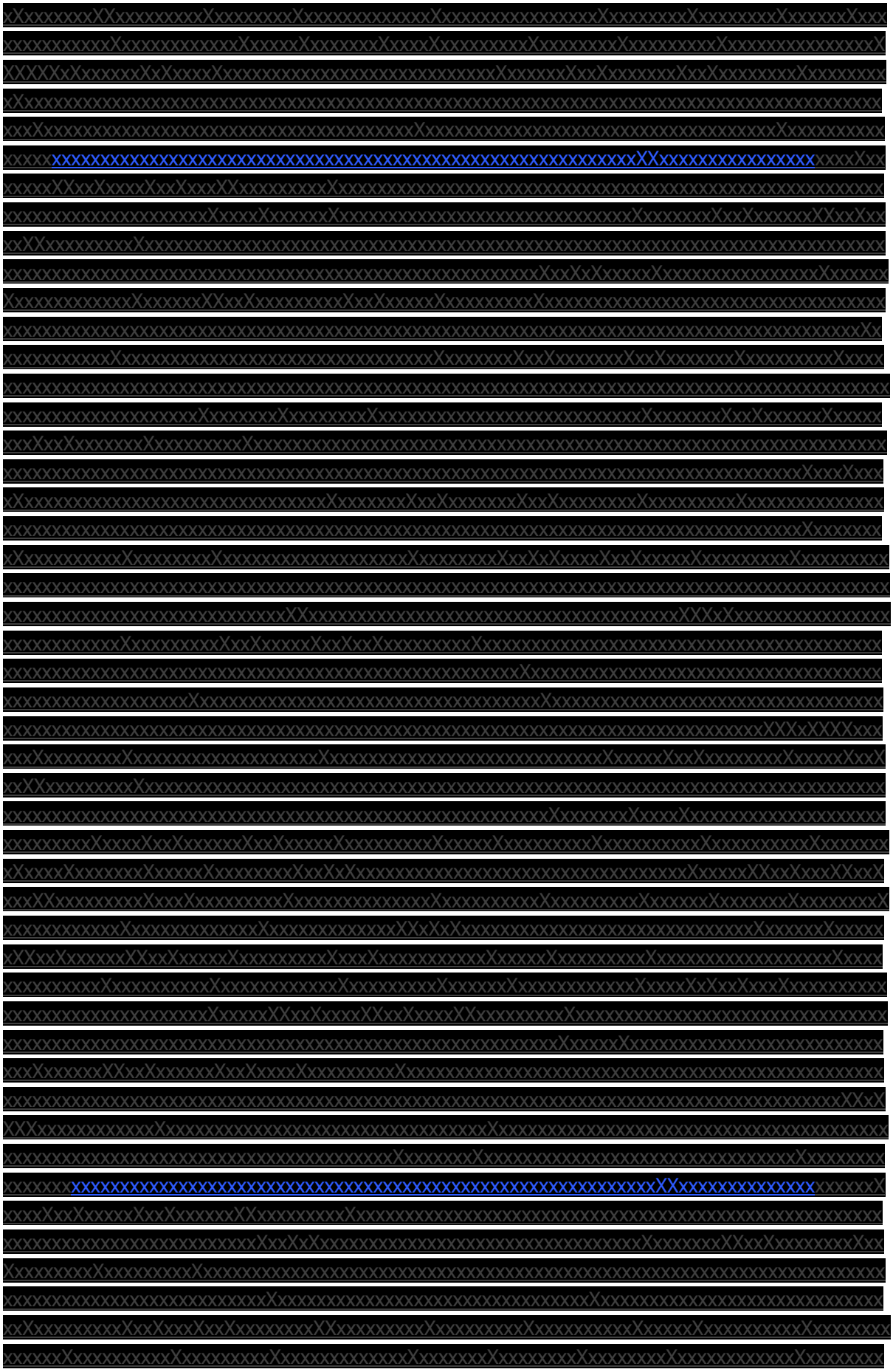
increasing with severity of hyperkalaemia. Key studies characterising the observed relationships have been identified; however, despite a rapidly growing evidence base quantifying the associations between serum potassium and patient outcomes, this review has also identified areas where evidence is most limited, notably the association between serum potassium, MACE and RAASi dose-adjustment in HF patients.

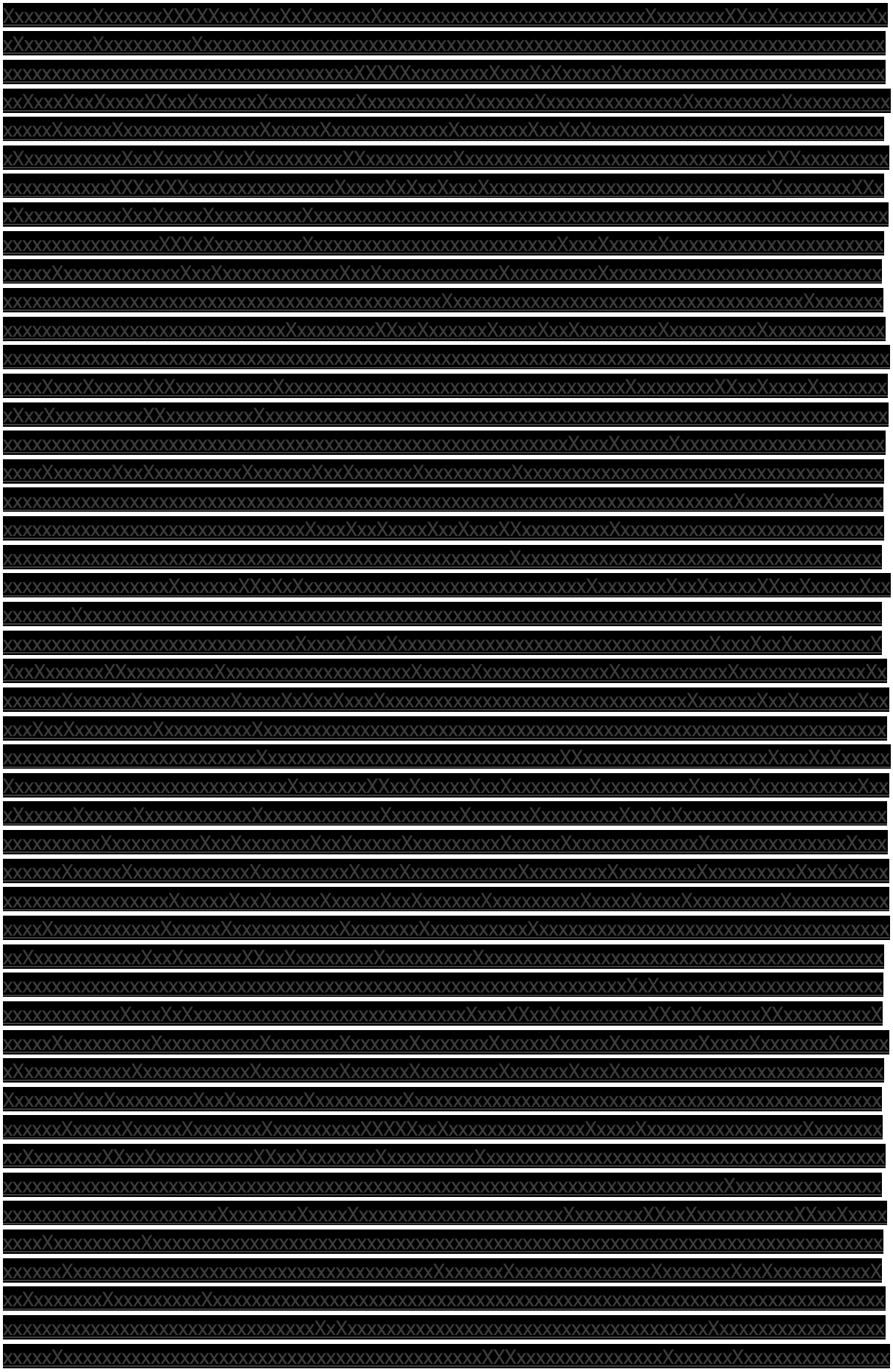
The review also highlighted the heterogeneity in the characterisation of hyperkalaemia and consequently associations between serum potassium and patient outcomes, making formal comparisons between studies difficult.

5 References

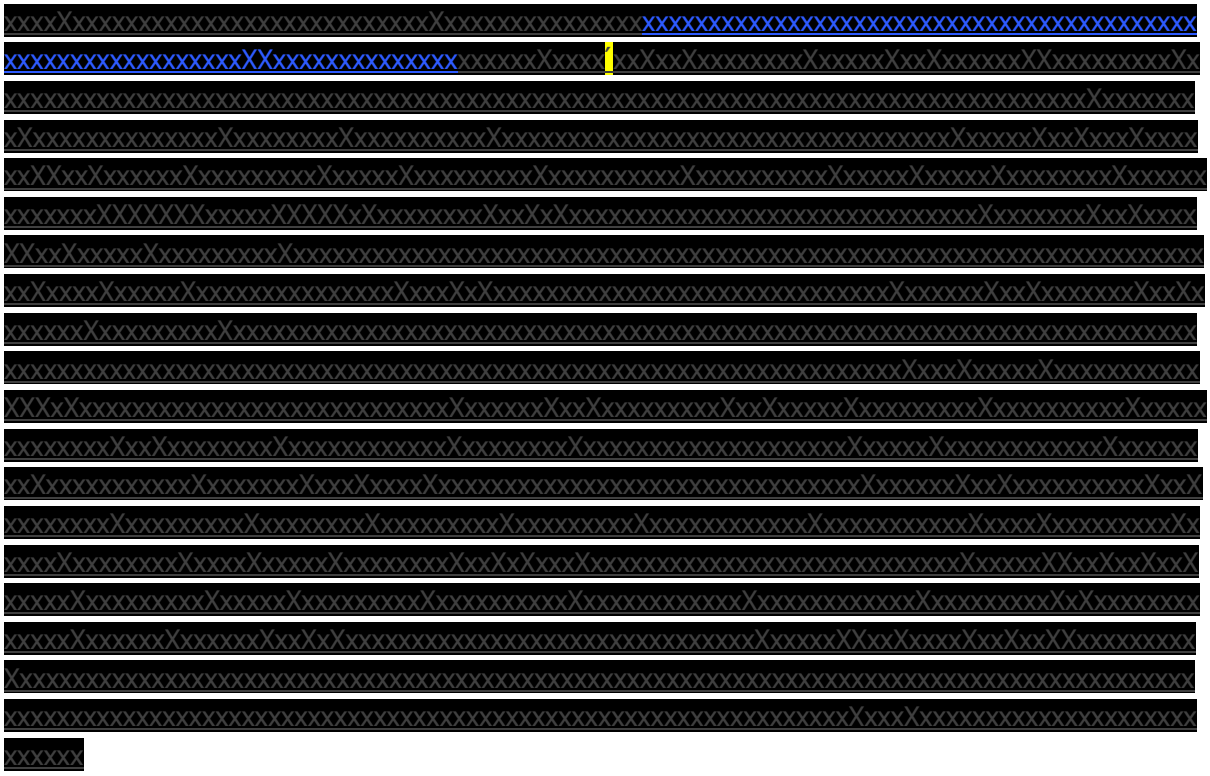


Associations Between Hyperkalaemia and Patient Outcomes: A Systematic Literature Review
Study Report





Associations Between Hyperkalaemia and Patient Outcomes: A Systematic Literature Review
Study Report



Appendix A. Search Strategies

Initial review

Table 3. Medline search strategy for the identification of studies to inform RAIT development

#	Search terms	Number of hits
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	[redacted]	[redacted]

Table 4. Embase search strategy for the identification of studies to inform RAIT development

#	Search terms	Number of hits
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]

Table 5. Cochrane search strategy for the identification of studies to inform RAIT development

#	Search terms	Number of hits
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	[redacted]	[redacted]
9	[redacted]	[redacted]
10	[redacted]	[redacted]
11	[redacted]	[redacted]
12	[redacted]	[redacted]
13	[redacted]	[redacted]
14	[redacted]	[redacted]
15	[redacted]	[redacted]
16	[redacted]	[redacted]

Table 6. Summary of search results

Database	Number of hits
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Review update

Table 7. Medline search strategy for the identification of studies to inform RAIT development

#	Search terms	Number of hits
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	[redacted]	[redacted]

Table 8. Embase search strategy for the identification of studies to inform RAIT development

#	Search terms	Number of hits
1	[redacted]	[redacted]
2	[redacted]	[redacted]

#	Search terms	Number of hits
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	[redacted]	[redacted]

Table 9. Cochrane search strategy for the identification of studies to inform RAIT development

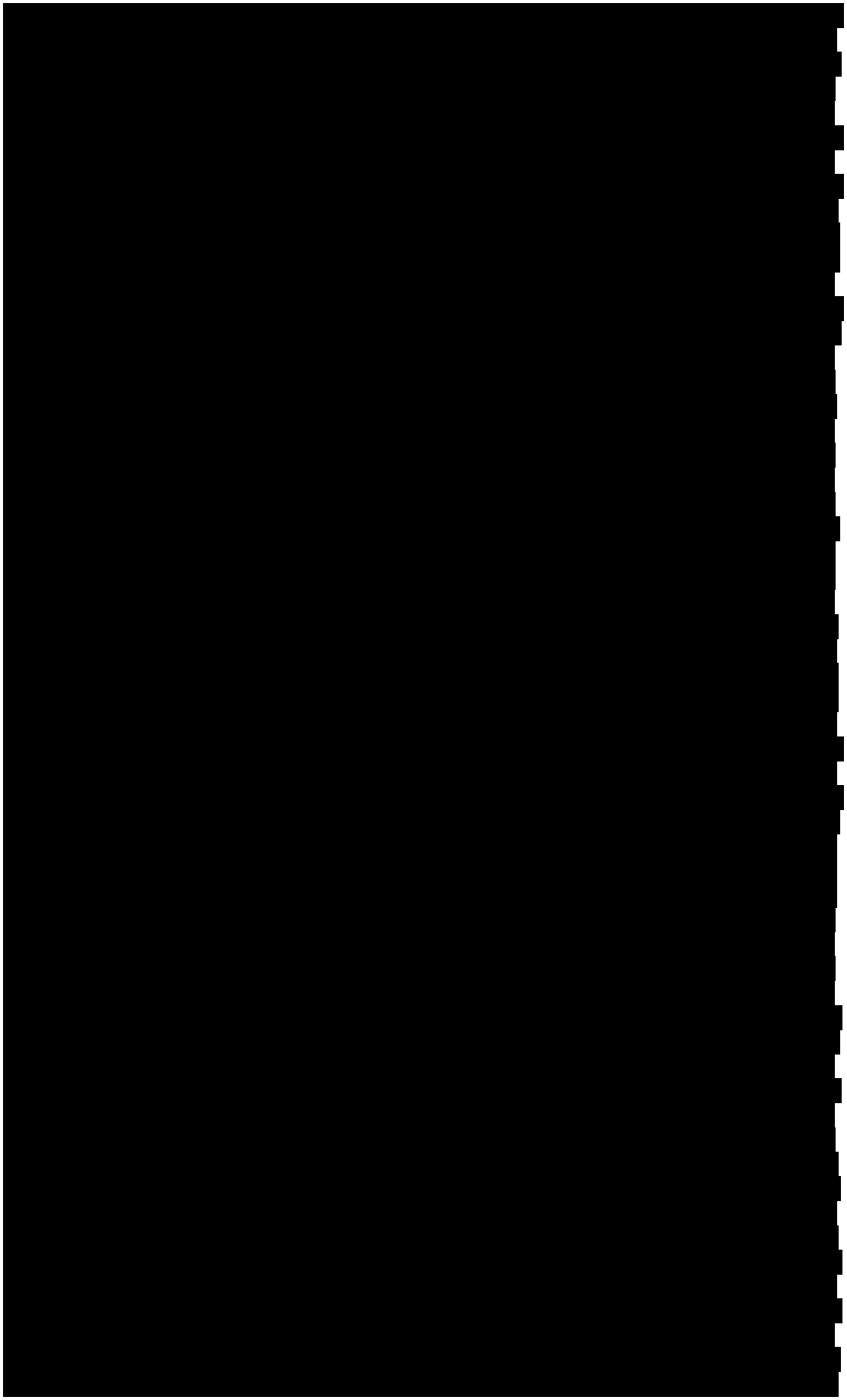
#	Search terms	Number of hits
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	[redacted]	[redacted]
9	[redacted]	[redacted]
10	[redacted]	[redacted]
11	[redacted]	[redacted]
12	[redacted]	[redacted]
13	[redacted]	[redacted]
14	[redacted]	[redacted]
15	[redacted]	[redacted]
16	[redacted]	[redacted]
17	[redacted]	[redacted]

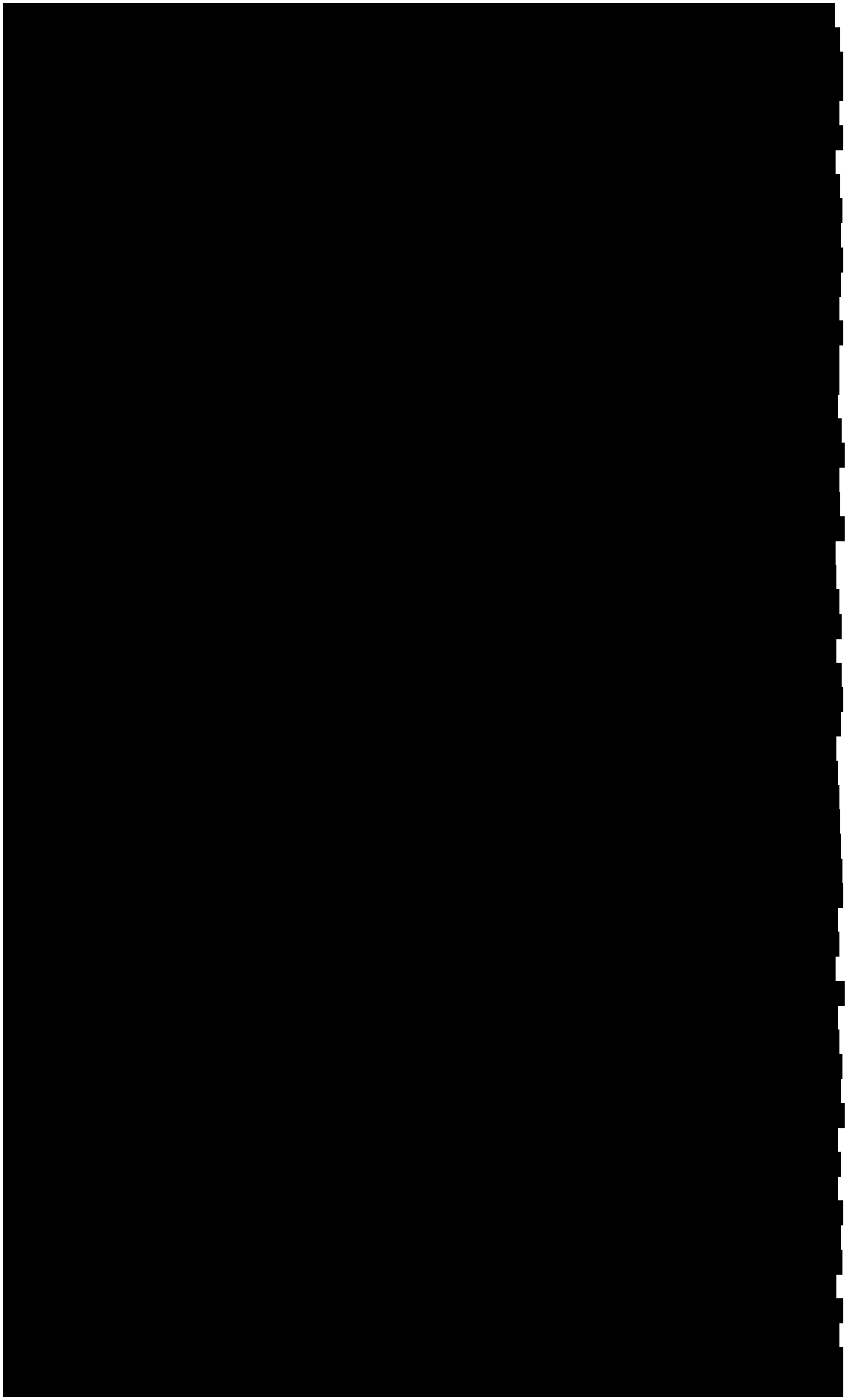
Table 10. Summary of search results

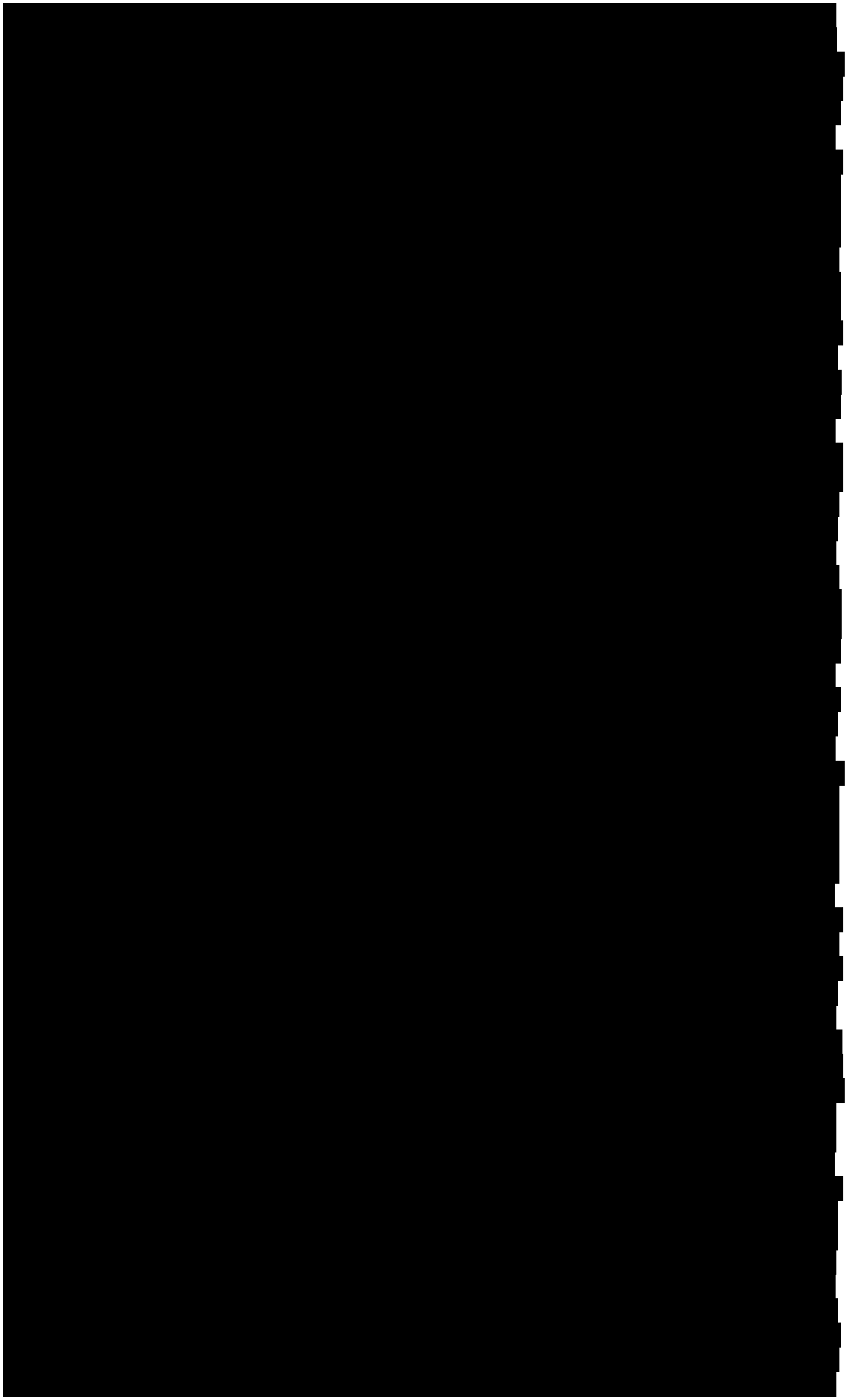
Database	Number of hits
PubMed	[redacted]
Embase	[redacted]
Cochrane	[redacted]
Total	[redacted]
Total (after removal of duplicates)	[redacted]

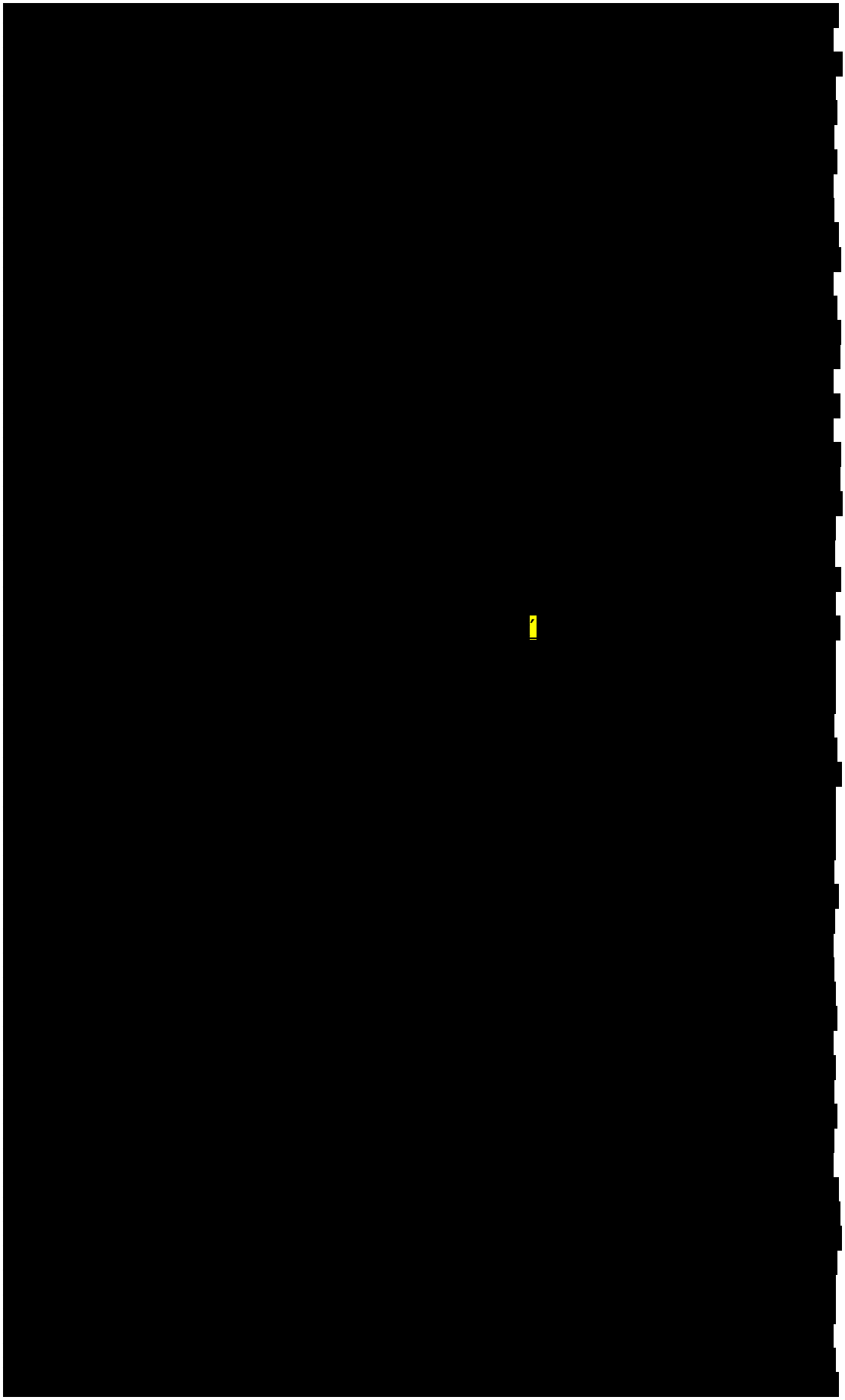
Appendix B. Included Studies

[redacted]









Appendix D. Efficacy and safety data using MedDRA SMQ (narrow) definitions of HF and CKD

[redacted]

[redacted]

[redacted] 1

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]		
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]

[redacted]

[redacted]	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
	[redacted]
	[redacted]

[redacted]

[redacted]

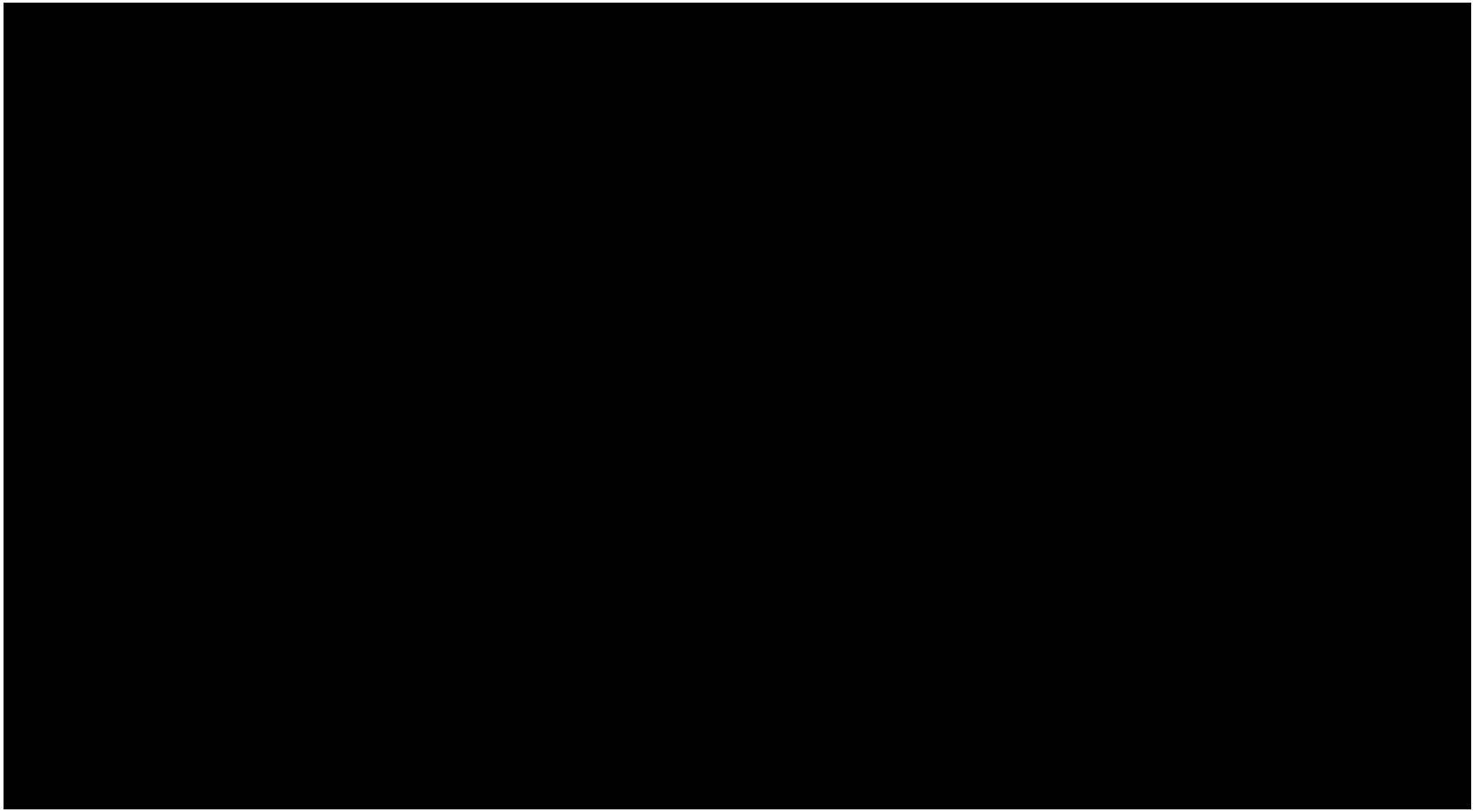
[redacted]

[redacted]

[redacted]

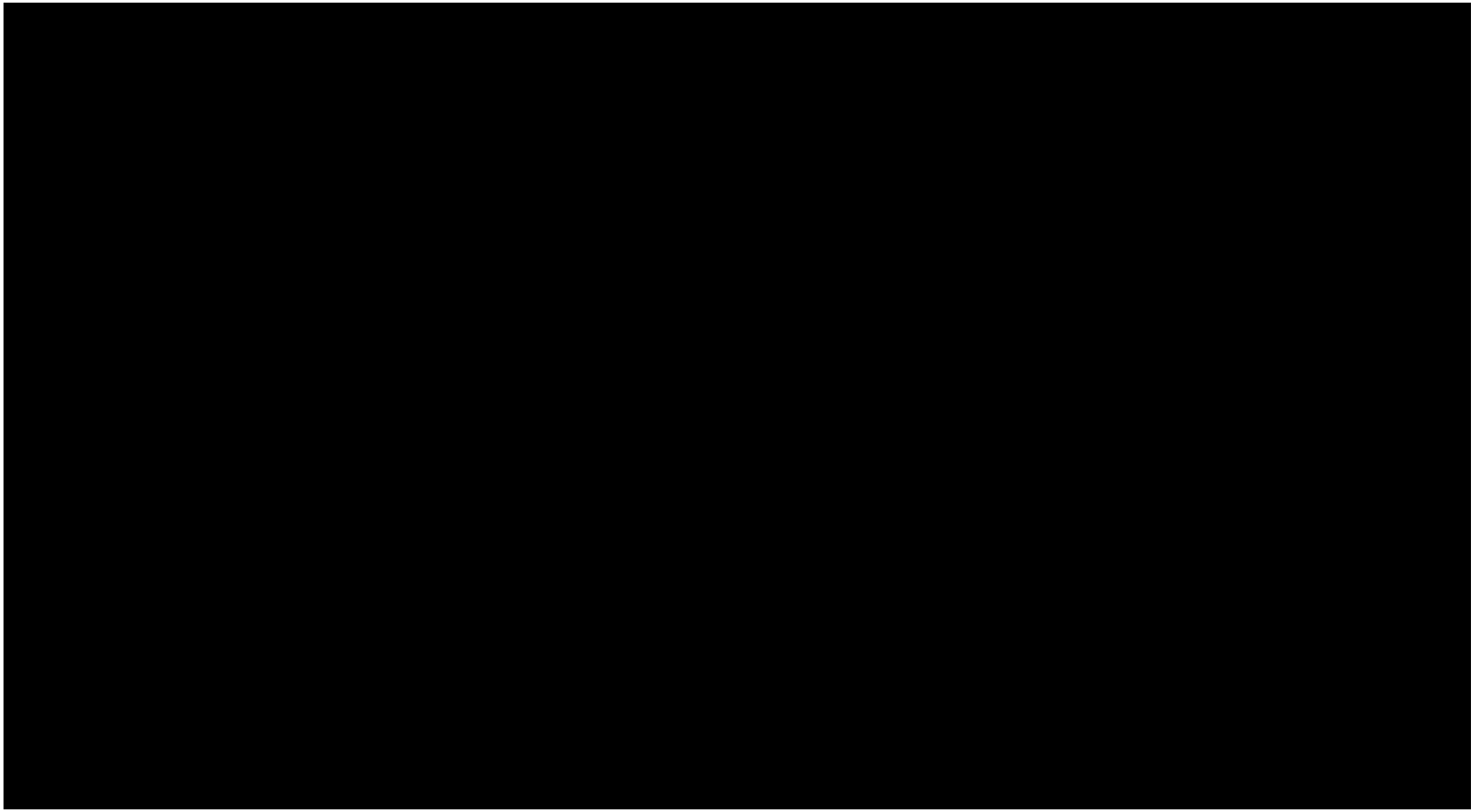
[redacted]

[redacted]



[redacted]

[redacted]



[redacted]

[redacted]

[redacted]

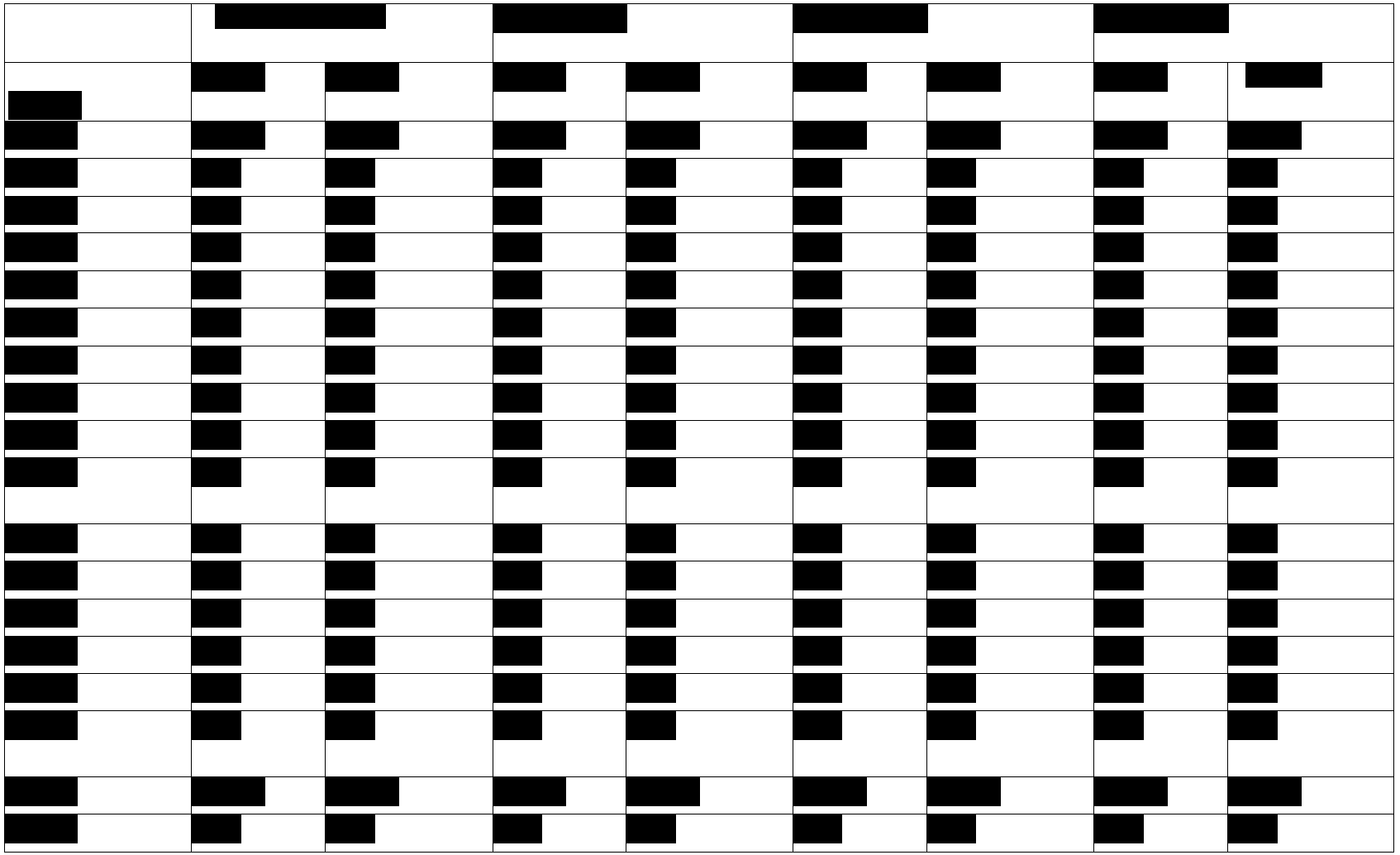
[redacted]

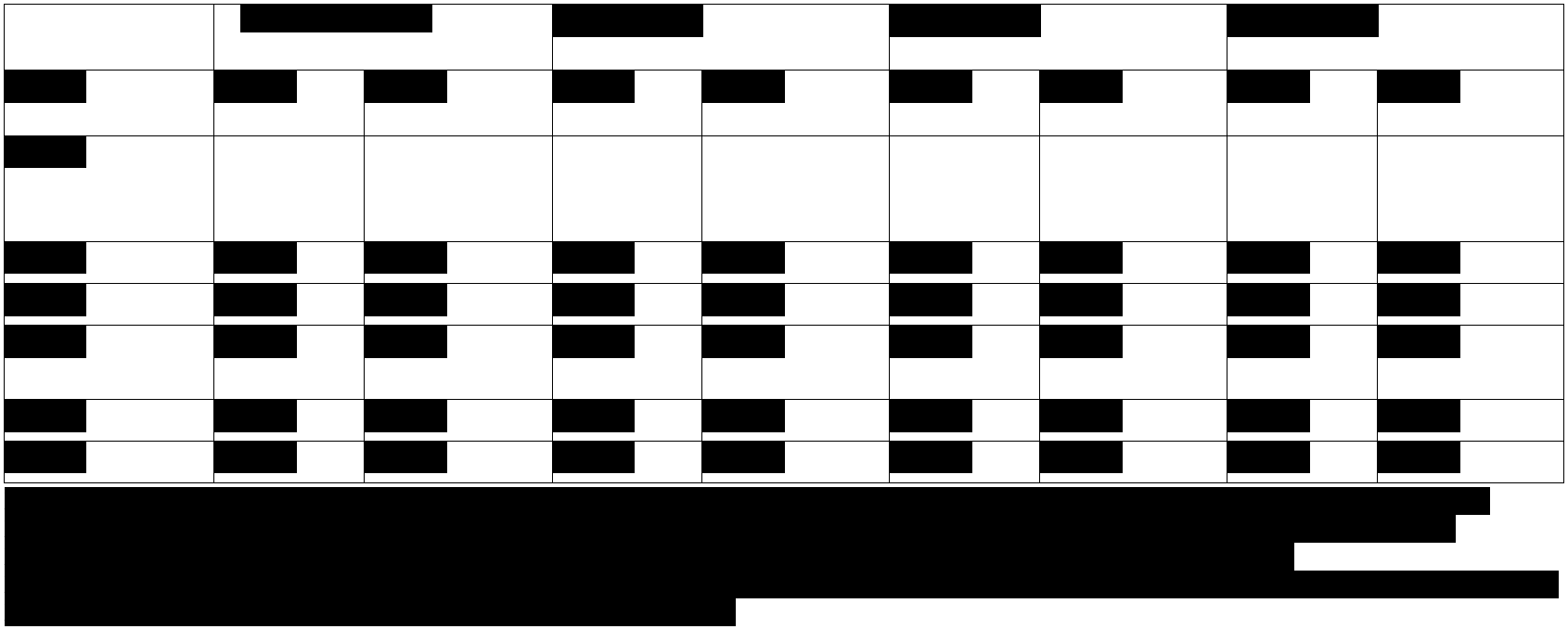
[redacted]

[redacted]

[redacted]

	[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]





[redacted]

	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

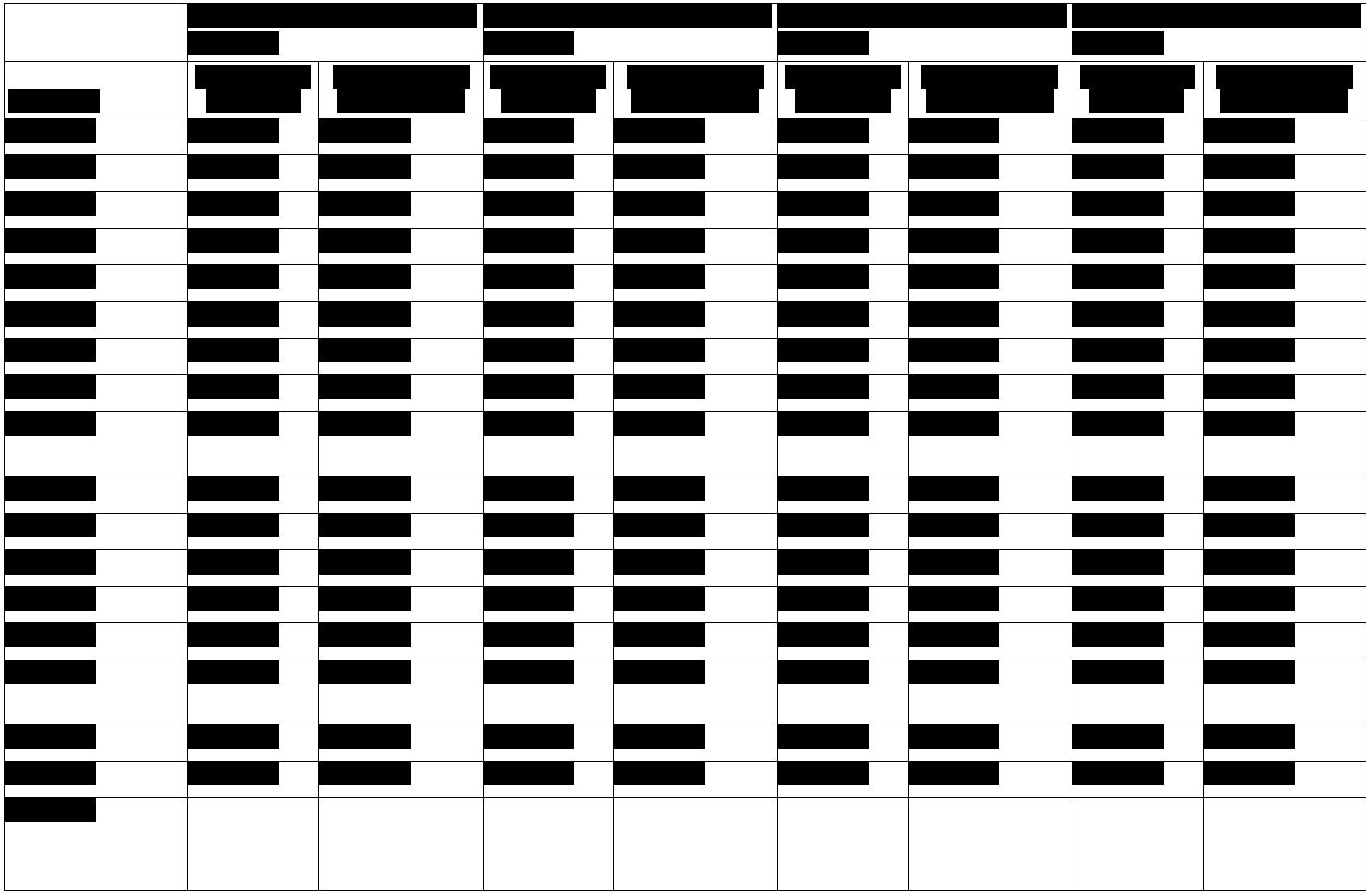
[redacted]

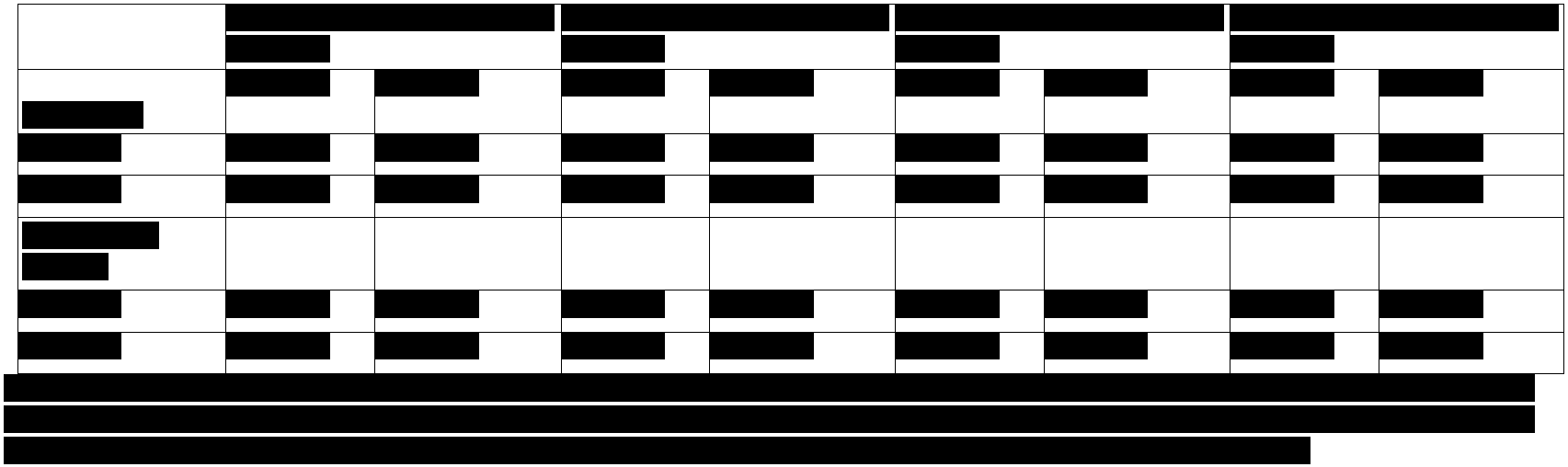
[redacted]

[redacted]

[redacted]

	[redacted]		[redacted]		[redacted]		[redacted]	
			[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]								





[redacted]

	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

Sodium Zirconium Cyclosilicate for Hyperkalaemia: A Single Technology Appraisal. A critique of the company's response to the Appraisal Consultation Document

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK Lesley Uttley, Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Jean Hamilton, Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Andrew Rawdin, Research Assistant, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
Date completed	31st January 2019

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 18/54/08.

Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Stevenson M, Uttley L, Hamilton J, Rawdin A. Sodium Zirconium Cyclosilicate for Hyperkalaemia: A Single Technology Appraisal. A critique of AstraZeneca's response to the Appraisal Consultation Document. School of Health and Related Research (ScHARR), 2019.

Contributions of authors

Matt Stevenson and Andrew Rawdin critiqued the health economic analysis submitted by the company. Lesley Uttley summarised and critiqued the clinical effectiveness data reported within the company's submission. Jean Hamilton critiqued the statistical aspects. All authors were involved in drafting and commenting on the final report.

1. Executive Summary

Sodium Zirconium Cyclosilicate (SZC) for the treatment of hyperkalaemia (HK) was appraised by NICE in October 2018, which culminated in a negative recommendation within an Appraisal Consultation Document (ACD).[1] The company manufacturing SZC (AstraZeneca) provided a response to the ACD which consisted of a document of 73 pages, two appendices of 32 and 52 pages, a revised mathematical model and a five-page document detailing the changes to the model, and the parameter values which produce the company's base case incremental cost-effectiveness ratios (ICERs). Collectively, these will be termed the company's response to the ACD.[2]

The company focussed on six 'key issues' related to the ACD, which are:

1. Generalisability of clinical trials data
2. Comparative data to inform standard of care (SOC)
3. Evidence relating to serum potassium (S-K) levels and long-term outcomes
4. Evidence relating to the impact of renin-angiotensin-aldosterone system inhibitors (RAASi) on long-term outcomes
5. The potential use and efficacy of SZC in the emergency setting
6. Model uncertainty

The company's responses to the ACD based on these issues are critiqued, in turn within this report by the evidence review group (ERG) for the initial single technology appraisal (STA). The impact of the company's changes on the base case ICERs (provided in terms of cost per quality-adjusted life-year (QALY) gained are then provided. Finally, ERG-preferred ICERs are estimated which incorporate changes to the company model made by the ERG.

The base case results produced by the ERG within an acute setting are higher values than the estimates by the company, and are approximately £17,000 per QALY gained for patients with CKD and £24,000 per QALY gained for patients with HF. Within the emergency setting the estimated results by both the company and the ERG is that SZC dominates.

Whilst the ERG believes that the base case values in the chronic setting are a relatively unbiased estimate the ERG acknowledges considerable uncertainty within the results. The multiple reasons for this are detailed in Section 4.3. The ERG comments that many of these limitations could be resolved if a trial, or trials were conducted comparing SZC to an active control which represents standard care in emergency and outpatient settings in patients who would be treated for HK in UK clinical practice. Preferably this trial would be of sufficient duration to establish the effects on mortality and major adverse cardiac events that are potentially associated with reduced S-K levels and potentially improved management of RAASi therapy.

2. The key issues

2.1 Key Issue 1 – Generalisability of clinical trials data

ACD comment (Section 1.2): *The evidence on how well sodium zirconium cyclosilicate works is not considered relevant to NHS clinical practice because it comes mostly from people with a level of serum potassium that would not be treated in the NHS.*

2.1.1 Relevant thresholds for treatment of HK in the UK

Within Section 3.1 of the ACD it is stated that the '*Committee and the clinical expert agreed they would not usually consider treating hyperkalaemia at serum potassium levels lower than 6.0 mmol/litre.*' The company have stated in response to the ACD that they have received clinical advice that suggests that a value of 6.0 mmol/L would be the lower limit at which treatment would be initiated for patients with chronic kidney disease (CKD), but that the lower threshold for treatment in patients with heart failure (HF) would be 5.5 mmol/L.

The ERG notes that the changing of the threshold of S-K levels to 6.0 mmol/L was requested by the ERG in clarification question B2, but the company refused to perform this analysis as the decision '*to initiate treatment in patients with S-K ≥5.5 mmol/L is based on clinical expert opinion and relevant and European guidance on the management of hyperkalaemia. Therefore, a scenario where treatment is not initiated until S-K reaches ≥6.0 mmol/L is not aligned with clinical guidelines, or UK clinical practice, and as such this scenario has not been provided.*'[3] It is unclear what further evidence has garnered by the company to reverse this view in patients with CKD and whether the threshold for with HF should remain at 5.5mmol/L. However, clinical advice provided to the ERG, suggested that a value of 5.5 mmol/L for the initiation of treatment in patients with HF was reasonable whereas nephrologists had suggested that a value of 6.0 mmol/L was more appropriate in patients with CKD. The ERG notes some differences in clinical practice between cardiology and nephrology departments highlighted by its clinical advisors which are summarised in

Table 1.

Table 1: Differences in treatment of HK in clinical practice: cardiology and nephrology

Cardiology	Nephrology
Fewer patients seen per week for high S-K levels in emergency and outpatient settings. S-K levels >5.5 mmol/L seen as clinically meaningful threshold	Frequently see patients in emergency and outpatient setting with S-K levels >6.0 mmol/L and much higher.
Low potassium diet advice is not really used in cardiology	Diet advice to restrict potassium for people with CKD always given
RAASi therapy is never permanently stopped (only ever temporarily withheld) or reduced	RAASi/MRA frequently discontinued if S-K >6.0 mmol/L.
The S-K levels of patients (often, older with comorbidities and therefore vulnerable) are monitored carefully in nurse-led clinics (not consultants)	Responsibility of re-initiation of RAASi/MRA is passed back to GPs where many are reluctant to re-initiate following an episode of HK.
RAASi is typically initiated and an increase in S-K levels is anticipated upon administration	RAASi is typically not initiated

The ERG considers that the post-hoc analyses to focus on patients with baseline S-K levels of >6.0 mmol/L are a valid attempt to better represent a population who would be treated for HK in clinical practice in the CKD/emergency admission setting whilst the baseline S-K of >5.5 mmol/L is intended to represent those patients seen in a HF outpatient setting.

2.1.2 Outcomes in ZS-004 and ZS005

Within the ACD it was stated that a key outcome would be the proportion of patients whose serum potassium (S-K) levels dropped below 6.0 mmol/L "*although this was not an outcome in the trial*". The company have provided post-hoc analyses of the ZS-004[4] and ZS-005[5] studies to look at the proportion of patients with an S-K level above 6.0 mmol/L that reduced to a value between 4.0 mmol/L and 6.0 mmol/L. The data provided by the company, which is marked as academic-in-confidence (AIC) is reproduced in Table 2. A total of 115 patients from the company's relevant clinical trials (26 from ZS-004, 89 from ZS-005) are reported as having an S-K level > 6.0 mmol/L at baseline. These subgroups represent 10.0% (26/258) and 11.9% (89/751) of the full study populations of trials ZS-004 and ZS-005 respectively. Table 2 shows that [redacted] of this subgroup of patients from ZS-004 were in the 4.0 mmol/L ≤ S-K level ≤ 6.0 mmol/L band at the end of the correction phase. The ERG highlights that this band is

different to the range of S-K levels which define normokalaemia, (3.5 mmol/L to 5.0 mmol/L) and which were used in the SZC clinical trials.

Table 2: The distribution of patients with an S-K level > 6.0 mmol/L at baseline across S-K categories in ZS-004 and ZS-005

	ZS-004 (N=26)			ZS-005 (N=89)
No of patients at end of correction phase (%) - 10g SZC thrice daily for up to 3 days				
S-K level > 6.0 mmol/L	[redacted]			[redacted]
4.0 mmol/L ≤ S-K level ≤ 6.0 mmol/L	[redacted]			[redacted]
S-K level < 4.0 mmol/L	[redacted]			[redacted]
	ZS-004 (N=21)			ZS-005 (N=76)
	Placebo (N=9)	SZC 5g OD (N=4)	SZC 10g OD (N=8)	
No of patients at end of maintenance phase (%) – In ZS-005 5g SZC daily with potential up titrating to 10g once daily or down titrating to 5g every other day.				
S-K level > 6.0 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]
4.0 mmol/L ≤ S-K level ≤ 6.0 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]
S-K level < 4.0 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]

The proportion of this subgroup of patients whose S-K level fell below 4.0 mmol/L is also shown in Table 2. Within the maintenance phase of ZS-004 [redacted]) receiving placebo in the maintenance phase and had an S-K level > 6.0 mmol/L compared with [redacted] patients ([redacted]) in those who continued with SZC. In ZS-005 the S-K levels of [redacted] of patients in the correction phase and [redacted] of patients within the maintenance phase dropped below 4.0 mmol/L. The company state that "*In clinical practice, these patients would be identified through routine testing and their low S-K levels would be resolved through dose adjustment or discontinuation of SZC, as per the SPC.*" The ERG comments that this facet has not be included in the model and that it is unclear how this would impact the ICER as there would be increased risks of adverse events if a patient becomes hypokalaemic, but if the SZC dose is reduced or the intervention discontinued then the costs of the SZC strategy would be reduced. The company's response to the ACD provides similar data for patients with an S-K level > 5.5 mmol/L, (Table 2) which is not reproduced here. Of note, the percentage of patients with S-K levels < 4.0 mmol/L is smaller in this group in ZS-004, being [redacted] in the correction phase and [redacted] in the maintenance phase. The data presented by the company relating to baseline S-K levels were not provided by whether patients had CKD or HF, however, the company believes that the reduction in S-K levels is generalisable to both data as detailed in Section 2.1.3.

The ERG comments that the numbers of patients with an S-K level > 6.0 mmol/L are small and thus there is considerable uncertainty in the results. Within ZS-004 it is observed that following correction with SZC, that [redacted] patients receiving SZC were in the range of 4.0 mmol/L ≤ S-K level ≤ 6.0 mmol/L compared with [redacted] patients in the placebo arm. Whilst it is acknowledged that banding of S-K levels

can mask important differences between apparently similar data, the values presented in Table 2show no clear advantage for patients receiving SZC.

The ERG notes that the maintenance phase data for patients in ZS-005 was restricted to those patients with an S-K level ≤ 5.1 mmol/L, as only patients with a 3.5mmol/L ≤ S-K level ≤ 5.0 mmol/L during the correction phase were eligible for the maintenance phase. It is unclear whether exclusion of patients who did not respond adequately to SZC treatment would experience equivalent events to if they had received SOC.

2.1.3 Response to treatment is independent of whether the patient has CKD, HF or diabetes mellitus (DM)

The company assert that treatment with SZC was effective regardless of underlying comorbidities. The company provide data (in Figures 2 to 6 of the company response to the ACD) on the mean changes in S-K levels in patients enrolled in ZS-004 and ZS-005, categorised by whether the patient had CKD, HF or DM. These data are further divided into changes within the correction phase and within the maintenance phase although these are not restricted to patients with S-K levels > 5.5mmol/L or >6.0mmol/L. The company state that "*the treatment effects are in the same direction for all sub-populations evaluated and none of the 95% confidence intervals [CI] substantially overlap with 0 (a difference of 0 versus placebo indicates no treatment effect)".* The ERG notes some heterogeneity in response to treatment for the presence of CKD in the maintenance phases of ZS-004 and ZS-005. Figure 5 of the company's response to the ACD[2] shows that the CIs for presence of CKD vs no CKD do not overlap with each other, with a more beneficial effect favouring those with CKD. Figure 6 of the response to the ACD shows the CIs for presence of CKD vs no CKD barely overlap with each other with the more beneficial response being again seen in people with CKD. Further analysis of statistical difference is not provided but the forest plots provided do suggest a differential beneficial response for mean change in S-K for CKD compared with people without CKD. The corollary to this is that the reduction in S-K levels for people with HF and DM may be less than estimated by the company.

The company state that "*the treatment effects are in the same direction for all sub-populations evaluated and none of the 95% confidence intervals substantially overlap with 0 (a difference of 0 versus placebo indicates no treatment effect)*". However, the ERG highlights that a proportion of these data is again reliant on a trial population with S-K levels lower than has been established as clinically meaningful for this appraisal.

2.1.4 ERG summary of key issue 1

The ERG considers the revised S-K threshold for treatment of HK in patients with CKD of 6.0 mmol/L and of 5.5 mmol/L in patients with HF to be appropriate. The ERG questions the assertion that "*response*

to treatment is independent of whether the patient has CKD, HF or DM" and highlight potentially differential treatment effects.

2.2 Key Issue 2 – Comparative data to inform standard of care (SOC)

ACD comment (Section 3.7): *Trial evidence does not show whether sodium zirconium cyclosilicate is more clinically effective than current standard care in the NHS*

2.2.1 The evidence base for the clinical effectiveness of SOC

Within Section 3.7 of the ACD it is stated that the committee "*concluded that the comparators were calcium resonium and management of RAAS inhibitors in the emergency setting, and management of RAAS inhibitors in the outpatient treatment setting."* In Section 3.8 of the ACD, "*The Committee concluded that the company had not provided any data for the clinical effectiveness of treatments currently used in the NHS to correct hyperkalaemia and maintain normal serum potassium levels in the outpatient setting (that is, a low-potassium diet and management of RAAS inhibitors)."* Section 3.9 states that "*There was no control group for the correction period of the trial. This meant that it was unknown whether the proportion of patients whose potassium returned to the normal range was similar to what is seen with standard care*."

The ERG considers the most feasible comparators for SZC in the outpatient setting to be calcium resonium or a low potassium diet. The company state that few data exist to inform the decision problem on calcium resonium and diet as comparators to SZC and claim that due to patient non-compliance they are limited as comparators. The company cite an editorial written by clinicians who declare conflicts of interest due to funding received from manufacturers of phosphorus binders, nutritional supplements, or medications and items related to dialysis patients.[6]

The company responded that if a low-potassium diet were to be a background therapy independent of whether SZC was used that they would expect "*there would be a very low risk of this influencing clinical effectiveness results for SZC versus relevant comparators in the UK*". The company states that low-potassium diets would be considered as background therapy within the outpatient setting, although compliance is poor due to negative impact on patients' quality of life. Furthermore, the company states that the benefits of low potassium diets are difficult to disentangle given other medications prescribed concurrently.

The ERG also notes that as diet was not monitored in the clinical trials of SZC, it is still unclear whether patients can eat a high-potassium diet and expect the treatment response observed with SZC in the company's trials. Clinical advice to the ERG highlighted that patients who were not given dietary advice early on at the time of diagnosis of HK, will not welcome it later on.

Within the company's original submission,[7] the effectiveness of SOC in the correction phase was assumed equivalent to that of SZC; this potentially unfavourable assumption was made because open-label SZC was provided to all patients in the correction phase in ZS-004 and ZS-005. In response to the ACD, the company have used data from ZS-003,[8] which was a phase III, multicentre, prospective double-blind, placebo-controlled study. During the correction phase of ZS-003 patients were randomised to placebo or to one of four SZC doses (including 10g three times a day) for a period of 48 hours. Following the correction phase those who had received placebo were randomised to receive 1.25g or 2.5g once daily of SZC, whilst the remaining patients were randomised to receive either placebo or the same dose of SZC but once daily, rather than thrice daily. ZS-003 therefore provides a randomised comparison of SZC 10g thrice daily to placebo within a 48-hour correction phase. Within the course of the single technology appraisal the company and the ERG had previously concluded that ZS-003 was appropriately excluded from the CS meta-analysis due to the following reasons:

- The baseline S-K levels were not comparable between groups
- Only a small number of patients were treated in line with the licenced dose
- Only 15.4% of patients who received 10 g three times daily during the correction phase had a baseline S-K level >5.5 mmol/L

Therefore, the majority of the ZS-003 study population had a lower baseline S-K than would be regarded as clinically relevant in the correction or maintenance phase ([redacted] mmol/L in the 10 g SZC arm and [redacted] mmol/L in the placebo arm) compared with 5.6 mmol/L in ZS-004 and ZS-005. The ERG also note methodological heterogeneity for trial ZS-003 compared with trial ZS-004 and ZS-005. As S-K measurements are frequently spurious[9, 10] (known as pseudo-hyperkalaemia), trials ZS-004 and ZS-005 required two consecutive i-STAT potassium values, measured 60-minutes (± 15 minutes) apart to confirm S-K level. For trial ZS-003 however, only one i-STAT measurement was used to confirm S-K level; therefore, it is possible that some patients were inappropriately entered into ZS-003 and additionally that some of the endpoint measurements in trial ZS-003 were erroneous.

The company states that the S-K level at baseline was lower in ZS-003 than in ZS-004 and ZS-005 and due to this the company scaled the treatment effects observed in ZS-004 that related to the chosen S-K level categories. This was achieved by calculating that the relative increased reduction in S-K level in the correction phase of ZS-004 was [redacted] for the 5.5 mmol/L ≤ S-K level <6.0 mmol/L band and [redacted] for the S-K level ≥ 6.0 mmol/L band compared with a 5.1 mmol/L ≤ S-K level <5.5 mmol/L referent. The reduction in S-K levels in the correction phase for those on placebo estimated by the company when applying the relative decreases in S-K levels are [redacted] for those with a 5.1 mmol/L ≤ S-K level <5.5 mmol/L and [redacted] for those with an S-K level ≥ 6.0 mmol/L. The corresponding estimated values

for patients receiving 10g SZC thrice daily were [redacted] and [redacted]; the company compare these values to those observed in ZS-004, which were [redacted] and [redacted] respectively claiming that this provides "*confidence in the method used*".

2.2.2 ERG summary of key issue 2

The ERG has concerns with the approach taken by the company.

1) That the actual reductions observed, by S-K level band, in ZS-003 would provide a better indication of the reduction in S-K level than the adjusted data. Whilst the numbers are smaller there are [redacted] patients in the placebo arm with an S-K value ≥ 5.5 mmol/L and [redacted] patients in the SZC 10g thrice daily arm. The ERG believes that the actual reductions should be reported, and if considered to have face validity, used in preference to the adjusted data with an assumption of constant underlying S-K levels beyond the correction phase.
2) If it is necessary to use the adjusted data, it appears that the calculations made the company are incorrect as they apply the relative increase in change in S-K level compared to a 5.1 mmol/L ≤ S-K level <5.5 mmol/L referent to the change relative to the full intention to treat population. This will introduce inaccuracy in the calculation, although it is not clear how this will affect the ICER.
3) The ERG questions placebo as a valid representative of standard care and re-emphasise that this version of 'standard care' does not include a dietary intervention or calcium resonium.
4) The ZS-003 trial is not considered to be fully applicable. Baseline characteristics, apart from S-K levels, were not reported for the subgroup of patients used to estimate comparative efficacy in the correction phase. Furthermore, the use of only one i-STAT measurement reduces the reliability of the trial and may introduce inaccuracy in the comparative results. It is possible that the comparison is further confounded.

Although the ERG notes these limitations in the company's approach, the ERG does not have the necessary data to alter the methodology used.

2.3 Key Issue 3 – Evidence relating to S-K levels and long-term outcomes

ACD comment (Section 3.8): *Trial results show sodium zirconium cyclosilicate may lower serum potassium levels but the benefit of this to patients is unclear.*

Within Section 3.11 of the ACD the committee stated that the company had not provided a systematic review of the evidence relating to an association between S-K levels and mortality. Instead a single observational study was used that '*did not guarantee an independent association between high serum potassium levels and death, or provide evidence that lowering serum potassium extends life.*' To address this the company undertook a targeted literature review. The results are presented separately for patients

with CKD and patients with HF. The company state that the "*targeted literature review approach will be complemented with a systematic literature review of the evidence, however, outputs of this will not be available in advance of responding to the ACD*". The ERG have reviewed the search strategies and notes some limitations to the searches described in full in Appendix A. Briefly, whilst the ERG considers that the company's literature searches to have identified a number of relevant studies for this appraisal, the design of the search strategies would not be considered as best practice if they were used to inform a comprehensive systematic review on the topic. It is not possible to ascertain whether further relevant studies have been missed without redesigning and re-running the literature searches.

The company describe that [redacted] studies were identified as relevant from the targeted literature review. The ERG note that the two PRISMA diagrams provided in Figures 10 and 11 of the company's response to the ACD do not describe the study selection process that results in the [redacted] included studies.

2.3.1 The evidence base for patients with CKD

2.3.1.1 Mortality

[redacted] studies were considered potentially relevant by the company. One relevant study in terms of the association between S-K and mortality was that of Furuland *et al*.[11] which was a retrospective observational analysis of 191,964 patients with CKD contained in the Clinical Practice Research Datalink (CPRD) with a first record between 2006 and 2015. These patients had stage 3a to 5 CKD. The analyses controlled for covariates which included: age; sex; history of DM; cancer; major adverse cardiac event (MACE); dementia; time-updated estimated glomerular filtration rate (eGFR) levels; time-updated RAASi use; and six S-K categories, using 4.5 mmol/L ≤ S-K level <5.0 mmol/L as the referent. The risk equations were estimated using generalised estimating equations. S-K levels <4.0 mmol/L and ≥ 5.0 mmol/L were associated with statistically significant increases in the rates of mortality with incident rate ratios (IRR) of 1.60 (95% CI 1.52-1.68) for those with 5.5 mmol/L ≤ S-K level < 6.0 mmol/L and an IRR of 2.88 (2.61-3.18) for those with an S-K level ≥ 6.0 mmol/L. The IRR values for those with hypokalaemia were not reported in the paper but the midpoints appear to be approximately 2.5 for those with an S-K level < 3.5 mmol/L and 1.25 for those with 3.5 mmol/L ≤ S-K level < 4.0 mmol/L. Furuland *et al*.[11] report the similarity in IRRs to those published by Luo *et al*.,[12] which analysed data on 55,266 American patients and controlled for multiple relevant covariates, which were 1.60 (95% CI 1.37-1.88) and 3.31 (95% CI 2.52-4.34) respectively; corresponding values for those with an S-K level < 3.5mmol/L were 3.05 (2.53-3.68). Luo et al state that generalised additive models were used to analyse non-linear associations using Poisson / negative binomial links. Associations were estimated using mixed-effects Poisson models using both random intercept terms for individual patients and fixed-effects terms. In all instance the models S-K levels by eGFR interactions were estimated and removed where no interaction was observed.

The company provide additional supportive data from [redacted] trials to show an association between S-K levels and mortality in patients with CKD. The company used the values of Luo *et al*. in the base case in line with the original company submission,[7] and tested the use of Furuland *et al*. in a scenario analyses, alongside values provided by Collins *et al*.[13] and Nakhoul *et al*.[14] Further scenario analyses changed the values in Luo *et al*. by +/- 20%.

2.3.1.2 MACE

The Furuland *et al*.[11] and Luo *et al.*[12] papers were again identified as key sources of information. Data reported in Luo *et al.* indicate a U-shaped curve with IRR compared to a 4.5 mmol/L ≤ S-K level <4.9 mmol/L referent of 1.12 (95% CI 1.05 – 1.20) for patients with 5.5 mmol/L ≤ S-K level <5.9 mmol/L and 1.88 (95% CI 1.66 to 2.12) for patients with an S-K level ≥ 6.0 mmol/L. For those with hypokalaemia the midpoint values were 1.89 for patients with an S-K level < 3.5 mmol/L and 1.27 for patients with 3.5 mmol/L ≤ S-K level <4.0 mmol/L.

Data from Furuland *et al*. also exhibit a U-shaped curve, although the IRR was not statistically significant in the S-K level ≥ 6.0 mmol/L due to a wide confidence interval. The IRR values for those with hypokalaemia were not reported in the paper but the midpoints appear to be approximately 1.37 for those with an S-K level < 3.5 mmol/L and 1.12 for those with 3.5 mmol/L ≤ S-K level < 4.0 mmol/L. The company used the values of Luo *et al*. in the base case in line with the original company submission,[7] and tested the use of Furuland *et al*. in a scenario analyses. Further scenario analyses changed the values in Luo *et al*. by +/- 20%.

2.3.1.3 Hospitalisation

[redacted] studies were considered potentially relevant by the company. The most relevant in terms of the association between S-K and mortality was that of Luo *et al*.[12] and of Thomsen *et al*.(2017)[15] The data provided by Luo *et al*. was divided into eGFR and S-K levels and typically showed a U-shaped association, with the range in midpoint IRR dependent on eGFR level for patients with an S-K level ≥ 6.0 mmol/L being 1.07 – 3.65. For patients with an S-K level <3.5 mmol/L the range in midpoint IRR, dependent on eGFR level, was 1.77 to 2.64.

Thomsen *et al*.(2017)[15] estimate through a case-matched analysis (using multiple variables) of Danish patients with elevated S-K levels that the IRR for "*any hospital outpatient contact*" was 1.37, increasing to 2.11 for "*Any acute hospitalisation*". The company used the values of Luo *et al*. in the base case in line with the original company submission.[7] Scenario analyses changed the values in Luo *et al*. by +/- 20%.

2.3.1.4 Summary values

Figure 8 in the company response to the ACD[2] presents the relationships "*sourced from the literature*" between S-K levels and relative measures of mortality, MACE and hospitalisation. This figure has been reproduced as Figure 1. The ERG comments that it is not clear which studies were used to populate Figure 1.

Figure 1: The association between S-K levels and mortality, MACE, and hospitalisation in people with CKD

2.3.2 The evidence base for patients with HF.

2.3.2.1 Mortality

[redacted] studies were considered potentially relevant by the company. The most pertinent studies are summarised in this report.

Nunez *et al*.[16] prospectively collected data on 2164 consecutively discharged patients with HF and explicitly analysed changes within S-K levels and association with mortality. The study controlled for many variables including: age; blood pressure; heart rate; left ventricular ejection fraction; eGFR; New York Heart Association (NYHA) class; Charlson comorbidity Index; β-blockers; and potassium modifying treatments. The results showed that S-K levels > 5.0 mmol/L had a statistically significant greater risk of death than for people with a 3.5 mmol/L ≤ S-K level ≤5.0 mmol/L. Furthermore, this study showed that changing a person from being hyperkalaemic (defined as an S-K level >5.0 mmol/L)

to being normokalemic (3.5 mmol/L ≤ S-K level ≤5.0 mmol/L) resulted in a statistically significant reduction in the risk of all-cause mortality.

Desai *et al*.[17] used data from a phase III RCT (TOPCAT) which investigated the impact of treatment with spironolactone on clinical outcomes in patients with HF and preserved ejection fraction in patients in the Americas, Russia and Georgia. S-K levels were measured as one of 24 secondary outcomes. As a by-product of this study, analyses on the correlation between S-K levels and all-cause mortality could be conducted as spironolactone was associated with statistically significant increases in HK (HR 3.1 (2.46 to 4.20)) and severe hypokalaemia (HR 3.21 (1.94 to 5.08)). These analyses showed that in a multivariable-adjusted model (adjusted for variables including: age; sex; NYHA class; smoking status; DM; eGFR; relevant medication use; and blood pressure) both hypokalaemia and HK were associated with higher risks of all-cause mortality and cardiovascular mortality. Desai *et al*. report that the hazard ratio of mortality, compared with a referent of 3.5 mmol/L ≤ S-K level <5.5 mmol/L was: 1.47 for patients with an S-K level ≥ 5.0 mmol/L; 1.72 for patients with an S-K level ≥ 5.5 mmol/L; and 2.59 for patients with an S-K level ≥ 6.0.

Aldahl *et al*.[18] analysed a retrospective analysis of the 19,549 patients in a Danish registry who were diagnosed with HF. This study showed a statistically significant U-shaped association with mortality and controlled for multiple variables including: age; sex; DM; relevant concomitant therapies; acute myocardial infarction; and chronic obstructive pulmonary disease.

These previous studies are supported by additional studies, such as Collins *et al*.[13] which show a U-shaped curve comparing 50,203 patients with HF and 338,297 control patients.

The company used the values of Desai *et al*.[17] in the base case following the ACD. However, in the model construction the company have used the HR of 1.47 for the 5.0 mmol/L ≤ S-K level <5.5 mmol/L and used the HR of 1.72 for patients with 5.5 mmol/L ≤ S-K level <6.0 mmol/L; this is not the correct approach as the HR reported by Desai *et al*. include more severe patients. The company's method will therefore overestimate (to an unknown degree) the risk of mortality associated with high S-K levels in people with HF. A further complication is that the numbers reported by Desai for the patients with an S-K level ≥ 5.0 mmol/L group include people in the reference group; the ERG believes this couldn't be adjusted easily by the company. This limitation is likely to underestimate the mortality rate associated with high S-K levels in people with HF. Given that the two limitations work in opposite directions the ERG has assumed that the joint impact is negligible.

The company performed scenario analyses using data provided in Aldahl *et al*.[18] Collins *et al*.[13] Krogager *et al*.[19] Nunez *et al*.[16] and Polcwiartek *et al*.[20] Further scenario analyses changed the values in Desai *et al*. by +/- 20%.

2.3.2.2 MACE

The company did not identify any studies reporting the relationship between S-K levels and MACE in patients with HF. The company therefore did not model any relationship between S-K level and MACE in the HF population for S-K levels ≥ 4.5 mmol/L but did assume a relationship that values below < 4.5 mmol/L were related with increased risk of MACE. This relationship was assumed based on analysis of CPRD data (November 2017).

2.3.2.3 Hospitalisation

The company identified [redacted] observational studies reporting the relationship between S-K levels and hospitalisation in patients with HF. However, in the model the company state the IRR of hospitalisation based on S-K level band was taken from Desai *et al*.[17] which was not listed within the identified study; as such the ERG is unclear on the rationale for the selection of the Desai *et al*. study. The company, however, undertook scenario analyses changing the values in Desai *et al*. by +/- 20%.

2.3.2.4 Summary values

Figure 9 in the company response to the ACD[2] presents the relationships "*sourced from the literature*" between S-K levels and relative measures of mortality and hospitalisation. This figure has been reproduced as Figure 2. The ERG comments that it is not clear which studies were used to populate Figure 2.

Figure 2: The association between S-K levels and mortality and hospitalisation in people with HF

2.3.3 ERG summary of key issue 3

The ERG comments that whilst it a causal relationship between change in S-K levels and mortality, MACE, and hospitalisation in patients with CKD cannot definitively be asserted, these hypotheses are given weight due to the number of studies that have shown an association, having controlled for multiple variables, and in the clinical belief that reducing high S-K levels (for example with calcium resonium) is of benefit to the patient. The study by Nunez *et al*. using prospectively collected data indicated that moving a patient from a hyperkalaemic state to a normokalaemic state was associated with a significantly reduced risk of mortality. Nevertheless, there remains a possibility that there are unmeasured confounders. The ERG considers that high S-K levels are seen as a marker of potential renal insufficiency and are frequently predictive of cardiovascular events therefore clinical management of HK is commonly implemented even when asymptomatic. However, direct evidence to support the hypothesis that the U-shaped relationship between S-K levels and hard clinical endpoints is more than correlative, is limited. In an editorial, Fudim et al.[21] highlight a need to "*be careful to assert a general causal relationship between hyperkalaemia and clinical outcomes across the entire spectrum of hyperkalemia*". Fudim *et al*. also state the need to understand whether the use of potassium binders in a population with HF would allow 1) the use of RAASi or MRA; 2) increasing doses of RAASi or MRA; and 3) sustain the long-term benefits of RAASi and MRA use.

2.4 Key Issue 4 – Evidence relating to the impact of RAASi on long-term outcomes

ACD comment (Section 3.3): *The long-term benefit of continuing RAAS inhibitors on quality of life and survival in people with hyperkalaemia may vary from person to person.*

Within Section 3.4 of the ACD the committee concluded "*that factors affecting the harms and benefits of stopping RAAS inhibitors because of hyperkalaemia compared with using another antihypertensive (for people with high blood pressure) or with standard care (for people who would not normally be offered another blood pressure lowering drug) were affected by the: underlying condition, type of RAAS inhibitor, dose of RAAS inhibitor, number of RAAS inhibitors, reason for stopping RAAS inhibitor."* Furthermore, in Section 3.11 it was stated that "*It was unclear whether the benefits of starting RAAS inhibitors on survival and lower progression of chronic kidney disease (that had been assessed in the network meta-analyses of trials) were the same as the risks of stopping RAAS inhibitors to manage serum potassium levels. This was because patients may change to another antihypertensive drug."*

To provide further information the company undertook a targeted literature review to establish: (1) the evidence relating to the use of RAASi on mortality, MACE, and hospitalisation; and (2) the effects of RAASi on disease progression for people with CKD and for people with HF.

In order to assess the uncertainty in the impact of RAASi treatment in patients with CKD or patients with HF the company perform an unfavourable scenario analysis where it is assumed that discontinuation or down-titration of RAASi treatment has no impact on mortality, MACE or hospitalisations.

2.4.1 The evidence base for the relationship between RAASi and clinical outcomes for patients with CKD

The company's targeted literature review identified three studies reporting the impact of RAASi down-titration or discontinuation on clinical outcomes for patients with CKD. Analyses in Bennett *et al*.[22] using 144,388 patients with stage 3 or greater CKD, but not on dialysis, showed that the five-year mortality for people discontinuing RAASi treatment was increased by a factor of 2.3 compared with those who remained on treatment, although this appears to be published as an abstract only and thus the methodology cannot be critiqued and the covariates controlled for cannot be determined. The abstract did not provide details on the treatments patients may have received one RAASi treatment was discontinued.

A retrospective US-based observational study was performed by Epstein *et al*.[23] This study, which used records from 201,655 patients, of which over 30,000 had CKD without HF or DM, did not provide detailed descriptions of whether covariates were controlled for, although the paper stated that "p*atients*

on submaximum dose or who discontinued RAAS inhibitors died twice as frequently as patients on maximum dose irrespective of comorbidity status or patient age." The Epstein *et al.*[23] paper did not provide details on what treatment patients may have received as a replacement for RAASi when RAASi treatment was discontinued.

The third study reported was the systematic review and network meta-analyses (NMA) by Xie *et al*.(2016)[24] which was used in the company's initial submission. This was an NMA of angiotensin-converting enzyme inhibitor (ACEi) and angiotensin receptor blockers (ARB) using 119 randomised controlled trials (RCTs) of 64,768 patients with CKD who were initiated on treatment. This estimated an odds ratio (OR) of 0.87 (0.74 to 1.01) for all-cause mortality for ACEi vs placebo, and an OR of 0.82 (0.71 to 0.92) for ACEi vs placebo for cardiovascular events.

Following the targeted literature review the company state that "*the effect size of RAASi discontinuation on survival appears to be at least as large as the survival benefits of RAASi initiation, although the effect sizes are from different studies and therefore not directly comparable. Given the availability of more robust evidence on the benefits of RAASi initiation compared to the paucity of data on the effect of RAASi down-titration or discontinuation, it is appropriate to use data on RAASi initiation as proxy to model the effect of RAASi down-titration or discontinuation*." This led the company to maintain the approach used in the company submission, which was using the data of Xie *et al.*,(2016)[24] and assuming that the OR for suboptimal RAASi treatment was halfway between the OR for the maximum dose and 1. The company undertook scenario analyses using the ORs from Xie *et al.*(2016)[24] comparing ACEi and ARB against other active antihypertensives. Additionally, the company undertook scenario analyses changed the base case values taken from Xie *et al*.(2016)[24] by +/- 20%.

Within the company response to the ACD a scenario analysis is undertaken where it is assumed that RAASi have no benefit on mortality. The ERG believes that the approach taken by the company is reasonable.

2.4.2 The evidence base for the relationship between RAASi and clinical outcomes for patients with HF

The company's targeted literature review identified six studies relevant to this review question. These included the Bennett *et al*.[22] abstract, and the Epstein *et al*.[23] paper discussed in Section 2.4.1, a US-based retrospective observational study (Gilstrap *et al*.[25]), an NMA (Xie *et al*.(2016)[26]), and two meta-analyses (Thomsen *et al*. (2016)[27] and Miller *et al*.[28]). Multiple studies were identified in the targeted literature review that were not identified in the initial company submission.

The conclusion from the Epstein *et al*. study is the same as in Section 2.4.2, in that "p*atients on submaximum dose or who discontinued RAAS inhibitors died twice as frequently as patients on maximum dose irrespective of comorbidity status or patient age.*" This study recruited over 10,000 patients with HF but neither CKD nor DM, although there was limited reporting of controlling for covariates. The Bennett *et al*. study is reported to estimate that compared with patients who maintain RAASi treatment, the risk of five-year mortality in those who discontinued RAASi treatment was a factor of 3.3.

Gilstrap *et al*.[25] used multivariate Cox proportional hazards model to determine the relationship between ACEi and ARB and outcomes having controlled for covariates such as: age; sex; medical history; vital signs; and HF characteristics. The multivariate hazard ratio (HR) for mortality at one-year was 1.35 (1.13 to 1.61) for patients who discontinued RAASi compared with those patients who continued treatment. This study also produced a favourable point estimate relating to the HR of hospitalisation in those who continued RAASi treatment, although this was not statistically significant.

The NMA by Xie *et al*.(2016)[26] used 21 RCTs involving 69,229 patients. Compared with placebo ACEi had an OR of 0.80 (0.71-0.89) for all-cause mortality. The addition of an aldosterone receptor antagonist (ARA) to a background therapy of ACEi or ARB was associated with an OR for mortality of 0.73 (0.51 to 0.95) and an OR of 0.67 (0.47 to 0.87) for hospitalisation related to HF. These results were similar to those reported by Thomsen *et al*.(2016)[27] showing ACEi to have a relative risk ratio of 0.86 (0.81 to 0.91) for mortality and 0.71 (0.65 to 0.77) for hospitalisation related to HF.

The meta-analysis of Miller *et al*.[28] assessed the impact of NYHA class on treatment. For ACEi the relative risk for mortality was 0.90 (0.81 to 0.99) for NYHA classes I or II, and was 0.88 (0.78 to 1.00) for NHYA classes III or IV.

In the company's response to the ACD it is stated that "*patients who discontinued RAASi have worse outcomes in terms of mortality and HF hospitalisation compared to patients who continued on RAASi …. the effect size of RAASi discontinuation appears to be at least as large as the effect size of RAASi initiation, …. although these effect sizes are from different studies and therefore not directly comparable.*" Given this statement, the company maintain the data sources used in the initial company submission to model the impact on RAASi use on mortality and hospitalisation for patients with HF. For mortality this was the Seattle Heart Failure model (SHFM) that was derived from 1125 HF patients using a multivariate Cox model.[29] For hospitalisation this was data provided in Flather *et al*.[30] which used individual patient data from 5 RCTs incorporating 12,763 patients which produced an OR for mortality associated with the use of ACEi of 0.67 (0.61 to 0.74) with an assumption based on the Atlas study[31] that suboptimal therapy has only 36% of the efficacy of optimal therapy in preventing

hospitalisations. In generating this report, it appears that the risk of mortality due to HF is the same regardless of whether the patient is on optimal, or suboptimal RAASi treatment as the SHFM equation only has a binary value for ACEi and for ARB. This is a limitation within the model.

The company conducted a sensitivity analyses using an alternative source for hospitalisation, Xie *et al*.(2016)[26] weighting by type of RAASi using OR of 0.70 for those on maximum RAASi dose and 0,92 for those on a dose that has been down-titrated. Additionally, the company undertook scenario analyses changing the values of hospitalisation in Flather *et al*.[30] by +/- 20%.

Within the company response to the ACD a scenario analysis is undertaken where it is assumed that RAASi have no benefit on mortality. The ERG believes that the approach taken by the company is reasonable.

2.4.3 The evidence base for the relationship between RAASi and CKD and HF disease progression

From a targeted literature review the company stated that "*RAASi therapy is associated with a significant reduction in disease progression compared to other antihypertensive therapies … and as such, clinical benefits will be lost by replacing RAASi therapy with other antihypertensive treatments identified six studies.*"

For patients with CKD this statement was based primarily on the network meta-analysis of Xie *et al*.(2016)[24] which was described in Section 2.4.1, although the company provide supportive evidence of reduced proteinuria with RAASi treatment,[32] and that the delayed disease progression was dose-dependent.[33, 34]

For patients with HF this statement was based on a meta-analysis by Phelan *et al*.[35] which used 1575 patients from 14 RCTs exploring the use of aldesterone antagonists (AAs) which showed AA use was associated with statistically significant improvements in ejection fraction and improvement in NHYA class. Disease progression has also been shown to be delayed in HF patients by the use of ACEi.[36]

The company state that changing from a RAASi to an antihypertensive may not be possible as UK CPRD data (reference not provided) indicated that in patients with CKD and an S-K level ≥ 6.0 mmol/L. 35% were treated with calcium-channel blockers, 44% with diuretics and 31% with β-blockers. For patients with HF and an S-K level ≥ 6.0 mmol/L, the values were 26%, 78% and 58% respectively.

2.4.4 *ERG summary of key issue 4*

The targeted literature review identified several relevant studies which indicate RAASi treatment results in a significant benefit to clinical outcomes and to disease progression in patients with HF and CKD,

despite increased S-K levels. An editorial by Fudim *et al*. (2018)[21] discusses that HK associated with a medical treatment, such as RAASi might be more reflective of drug effect as opposed to evolving maladaptive cardiorenal interactions. This was observed in the EMPHASIS trial[37] where favourable effects of eplerenone on all-cause death were seen irrespective of the incidence of HK or worsening renal function. Fudim *et al*.[21] describe that elevated potassium level (<5.5 mmol/L) can be a surrogate of successfully implemented RAASi therapy and also posit that HK in HF is not consistently an ominous sign as evidenced in the TOPCAT trial[38] where the reduction in cardiovascular mortality from those randomized to spironolactone endured after accounting for post-randomisation variations in S-K levels. There is as yet no trial evidence to show that there is a differential effect on RAASI treatment due to the use of SZC, or evidence that using SZC does not impact on the effectiveness of RAASi treatment.

Given the comments within the ACD that alternatives to RAASi are available in the event of HK, the ERG believes that the Committee would prefer the values from Xie *et al*.(2016)[26] that compare with other active antihypertensive therapies rather than placebo. The ERG highlights that the midpoint OR associated with mortality for RAASi treatment is lower compared with active treatment than compared with placebo which may lack face validity.

2.5 Key Issue 5 – The potential use and efficacy of SZC in the emergency setting

ACD comment (Section 3.9): *The company submission is not relevant to how hyperkalaemia is treated in NHS as an emergency or in an outpatient setting.*

Within Section 3.10 of the ACD the committee noted "*that it had seen no data for people with life-threatening hyperkalaemia who would be treated in the emergency setting because this population was not included in the trial."*

The company have positioned SZC after the use of insulin dextrose which is a temporising agent where potential retreatment is common. The company highlights a subgroup of eight patients with S-K levels ≥ 6.5 mmol/L who received SZC in the correction phase of trial ZS-004. The average absolute reduction in S-K level was [redacted] with [redacted] of patients having an S-K level < 5.5 mmol/L at 48 hours. However, the comparative reduction associated with insulin dextrose is unknown. [redacted] However, one patient with baseline S-K 7.2 mmol/L did not complete the correction phase of the study and was therefore not included in the analysis. The average absolute reduction in S-K levels for patients with an S-K level ≥ 6.5 mmol/L ([redacted]) was greater than patients with a 5.5 mmol/L ≤ S-K level <6.0 mmol/L ([redacted]). Due to the low number of patients in this subgroup the ERG highlights considerably uncertainty within the results and comments that no interaction test was presented. The company also highlight the

speed of action of SZC, with a median time to an S-K level ≤5.0 mmol/L of 2.2 hours for an intention to treat population.

2.5.1 ERG summary of key issue 5

The ERG notes a key limitation with the data presented on the potential use of SZC in emergency care is the low number of patients in this subgroup who have S-K levels representative of patients seen in emergency care.

2.6 Key Issue 6 – Model Uncertainty

ACD comment (Section 1.2): *Because of the lack of relevant clinical-effectiveness evidence, the cost-effectiveness estimates for sodium zirconium cyclosilicate are not valid.*

The company have made multiple changes to the submitted economic model in order to address the decision problem and to remove the limitations raised by the committee in Section 3.11 of the ACD. The key changes to the model are detailed in the following section. A full description of the model inputs used in the company's revised base case is provided in Table 9 of the company's response to the ACD.[2] All of the amendments were changed in both the outpatient setting analyses and the emergency setting analyses.

2.6.1 The treatment thresholds for SZC use

The company have changed the threshold at which SZC would be used to an S-K level ≥ 6.0 mmol/L in patients with CKD, but have maintained the threshold to be an S-K level of ≥ 5.5 mmol/L in patients with HF. This has been discussed in Section 2.1.1

2.6.2 The assumed trajectories for patients receiving SZC and for patients receiving SOC

The company provided post-hoc analysis of subgroups of the pooled ZS-004 and ZS-005 data to estimate the average S-K levels for patients with an S-K level ≥ 6.0 mmol/L (for patients with CKD) and the average S-K levels for patients with an S-K level ≥ 5.5 mmol/L (for patients with HF) who were randomised to either 5g daily or 10g daily in the maintenance phase. These are average values and are also subject to a patient component, which is assumed fixed throughout the time horizon and an observation component, which is assumed to vary each cycle. Further details on this are contained in Section 3.2.8 of the ERG report.[39] The average values for each subgroup are shown in Table 3. Further details are provided in the company's response to the ACD. The ERG comments that using both CKD and HF patients to generate the values assumes that the effects of SZC are independent of underlying disease as discussed in Section 2.1.3 which may not be correct. [redacted]

[redacted]

Table 3: The average S-K level for subgroups of patients receiving SZC who were randomised to either 5g daily or 10g daily in the maintenance phases of ZS-004 and ZS-005

	Correction Phase	Maintenance phase		
Baseline S-K level	Day 0 (reduction per day for 3 days)	Day 4 to 14	Day 15 to 28	Day 29 and onwards
≥ 6.0 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]
≥ 5.5 mmol/L	[redacted]	[redacted]	[redacted]	[redacted]

For average S-K levels in the SOC arm, the company chose to use the adjusted values from ZS-003 which have been detailed in Section 2.2.1. As stated in that section, the ERG noted multiple limitations that are detailed in Section 2.2.2. The company states that as "*the S-K levels in the placebo arm of ZS-003 were generally stable during the maintenance treatment, the S-K trajectory during the maintenance phase was modelled to be constant*". The ERG comments that as the S-K levels increased in the control arm of ZS-004 the assumption of constancy may be unfavourable to SZC. The average S-K levels assumed by the company for the SOC arm are shown in Table 4.

Table 4: The average S-K level for subgroups of patients receiving SOC

	Correction Phase	Maintenance phase
Baseline S-K level	Day 0 (reduction per day for 3 days)	Day 4 onwards
≥ 6.0 mmol/L	[redacted]	[redacted]
≥ 5.5 mmol/L	[redacted]	[redacted]

A scenario analysis for the S-K level trajectory in the SOC arm was undertaken, assuming that the rate if decrease for 2 days observed in ZS-003 continued for a third day. This resulted in S-K levels of [redacted] for patients with a baseline S-K level ≥ 6.0 mmol/L and [redacted] for patients with a baseline S-K level ≥ 5.5 mmol/L. The ERG believe that the approach taken by the company in terms of S-K level reduction is reasonable but there may be considerable uncertainty in the reductions in S-K levels for patients receiving SOC.

2.6.3 Effect of RAASi down-titration or discontinuation on S-K levels

The company used the assumption made by the ERG within the ERG report to reduce the S-K level of patients who discontinue or down-titrate RAASi treatment. This was a reduction of 0.23 mmol/L in patients who discontinue RAASi treatment and a reduction of 0.115 mmol/L in patients who down-

titrate RAASi treatment. The company state that this is "*considered conservative in light of the evidence retrieved in the targeted literature review describing potential changes in S-K following RAASi discontinuation or down-titration*." The ERG believes that the approach taken by the company is reasonable.

2.6.4 The proportions of patients that discontinue or down-titrate RAASi treatment and the probability that patients resume RAASi treatment

The company assume that all patients with an S-K level ≥ 6.0 mmol/L will have RAASi treatment withdrawn. For these patients the company use differential rates of returning to RAASi treatment conditional on whether a patient is receiving SZC or SOC. For patients with an 5.5 mmol/L ≤ S-K level <6.0 mmol/L the probability of treatment withdrawal or down-titration was set to 0% in the SZC arm but in the SOC arm discontinuation was set to be 20% of patients with 80% of patients being assumed to down-titrate. These values are attributable to clinical expert opinion. The ERG have looked at the clinical responses in Appendix N of the company submission, and feel that the clinicians have stated that the use of SZC may prevent down-titration, but this could be because the S-K level is now lower, rather than stating that down-titration would not happen for patients on SZC but would for a patient on SOC despite both having the same S-K level. As such, the ERG has conducted exploratory analyses to assess the impact of setting discontinuation, and down-titration rates equal for SZC and SOC.

It is assumed that all patients receiving SZC will return to RAASi treatment within 12 weeks, whereas only 49.7% of patients in the SOC arm would return to RAASi treatment within 12 weeks. The company base the value of 49.7% on Luo *et al*.[12] with 12 weeks being informed by expert opinion. The ERG identified a comment in the company submission that in standard care "*Attempts are made to re-initiate, many or all stay at lower dose or are not re-initiated*", but did not see a supporting statement for the rate of differential level of initiation for SZC. The ERG believes it is plausible that the rates of re-initiation are equal for both arms and have conducted exploratory analyses to assess the impact of such an assumption.

2.6.5 The utility of patients with CKD

The company conducted a targeted literature review in order to populate the utility for patients with CKD. This identified two papers Eriksson *et al*.[40] and Wolfgram *et al.*[41] which reported EQ-5D data. The company stated that Eriksson *et al.* was preferred as this study recruited patients in Europe, whereas Wolfgram *et al*. was based in the USA.

The ERG has concerns with the implementation of data from Eriksson *et al.*[40] within the economic model. These are two-fold. 1) That the company used data for patients without anaemia only, whereas

the majority of the data collected, from consecutive patients, was in patients with anaemia; and 2) that the company have used the standard deviation, rather than the standard error when calculating the parameters of the Beta distribution used in probabilistic sensitivity analyses. The ERG have estimated alternative parameters assuming independence between anaemia and CKD stage and performing a weighted average due to the absence of granular data. These are shown alongside the company's estimates in

Table 5.

Table 5: Utility Values associated with people with CKD

CKD Stage	Company's estimates (standard deviation)	ERG estimates (standard error)
3a / 3b	0.85 (0.21)	0.80 (0.02)
4	0.81 (0.22)	0.74 (0.02)
5 (pre renal replacement therapy)	0.74 (0.29)	0.71 0.02)

2.6.6 The disutility and costs associated with emergency admissions

The company performed a scenario analysis where the impact of emergency admissions in terms of costs and disutility were considered. These values were estimated from data presented in Sullivan *et al*.[42] assuming that 50% of patients would present with sepsis and that 50% would present with pneumonia, and assuming that the patient disutility lasted for 14 days per emergency admission. Non-elective long stay costs were assigned to each admission. This resulted in an estimated cost of £2,390 and a disutility of 0.067.

2.6.7 Changes made to the model based on the ERG's changes in the ERG report

The company have adopted some changes made by the ERG within the company's revised base case. These are: reducing the time horizon in the emergency setting to 52 weeks rather than lifetime, which assumes that patients will transfer to chronic care after one year; assuming that changing RAASi dosage occurs in an outpatient rather than an inpatient setting; and assuming that RAASi treatment is withheld for 12 weeks for patients who have an S-K level > 6.0 mmol/L.

Other changes suggested by the ERG have been explored in scenario analyses. These are: assuming that there is a wastage equivalent to 2 sachets for every 30 sachets of SZC prescribed; that patients who have an emergency admission can restart RAASi treatment; and that there is no reduction in the length of hospital stay associated with RAASi treatment

The company believe that the wastage assumption explored by the ERG is highly pessimistic as "*sachets would be stored at home and prescribed again once they have been consumed*". The ERG concurs that it is likely to be pessimistic but would anticipate that for patients on lifetime treatment repeat prescriptions would be issued routinely and that in such circumstances unconsumed sachets would be effectively wasted. The absolute level of wastage that would occur in clinical practice is unknown.

3 The cost-effectiveness results presented by the company

3.1 The company's base case values

The base case results from the company have been provided in Table 6. The ERG identified one amendment made by the company that was not documented which related to the acquisition cost of SZC. The change made, which was unexplained, increased the acquisition cost from £64.63 to £90.08 within the correction phase and from £273.05 to £273.91 per four-week cycle in the maintenance phase.

Table 6: The base case results estimated by the company

	Δ Costs	Δ QALYs	Cost per QALY
Outpatient setting			
CKD	£8,249	0.708	£11,644
HF	£14,860	0.818	£18,158
Emergency Setting			
CKD	-£4,079	0.007	Dominates
HF	-£3,536	0.009	Dominates

The company present extensive sensitivity and scenario analyses in Tables 11 and 12 of their response to the ACD.[2] The majority had only a small influence on the ICER. The exceptions, which all relate to the outpatient setting, have been collated in Table 7.

Table 7: Selected sensitivity and scenario analyses conducted by the company in the outpatient setting

	Δ Costs	Δ QALYs	Cost per QALY
Base case results			
CKD	£8,249	0.708	£11,644
HF	£14,860	0.818	£18,158
Assuming that the rate of S-K decline associated with placebo over 2 days in ZS-003 is extrapolated to a 3-day period.			
CKD	£11,362	0.573	£19,815
HF	£13,928	0.641	£21,729
Assuming alternative sources for the incidence rate ratios between S-K levels and mortality in CKD			
CKD (Collins *et al*[13])	£13,623	0.843	£16,157
CKD (Nakhoul *et al*[14])	£2,689	0.570	£4,717
Altering the HRs of the association between S-K and mortality in HF by +/- 20%			
HF (+20%)	£14,412	0.866	£16,645
HF (-20%)	£14,893	0.704	£21,165
Assuming that RAASi treatment has no effect on outcomes.			
CKD	£7,054	0.631	£11,173
HF	£12,575	0.499	£25,208

4 Exploratory analyses undertaken by the ERG

4.1 The parameter values changed

The base case results from the company have been amended by the ERG in the following way.

1) Utilising the company's scenario analysis for S-K level decrease in the correction phase.

2) The ERG think it is more plausible that the rate of decrease in S-K levels observed in the placebo arm of ZS-003 over a 2-day period continues for a third day rather than there being no decrease on the third day. The alternative approach used by the company in scenario analyses has been incorporated in the ERG's base case.

3) Using the same withdrawal rates of RAASi treatments and re-initiation rates for both the SZC and the SOC arms. As detailed in Section 2.5 the ERG believe that it is more plausible that the levels of discontinuation and re-initiation would be based on the absolute S-K levels rather than whether a patient was on SZC or not. The ERG has amended the down-titration rates, conditional on S-K level, for SZC such that they equal the values for SOC. The re-initiation rate for SZC has also been set to the value for SOC.

4) Using the ORs for RAASi treatment compared with active treatment rather than placebo. This decision was guided by the comments in the ACD that patients may well change to another antihypertensive. This change would only apply to people with CKD.

5) Changed utility values for patients with CKD. As shown in
6) Table 5 the utility values preferred by the ERG were lower than those used by the company and included people with anaemia.

The ERG left the acquisition price of SZC as that in the revised company model, but no longer included wastage of SZC or assumed that the durations of hospitalisation were the same for patients receiving SZC or SOC, assuming that the joint impact of these two changes would be marginal. This allowed direct comparison with the company's results.

4.2 The ERG's base case results

The ERG's base case results for the outpatient setting is shown in Table 8 for patients with CKD. Corresponding results are presented in Table 9 for patients with HF in an outpatient setting, in Table 10 for patients with CKD in an emergency setting, and in Table 11 for patients with HF in an emergency setting. The results presented by the ERG are deterministic only, as the results produced by probabilistic analyses in the original submission were similar to the deterministic values.

Table 8: The ERG's base case results for patients with CKD in the outpatient setting

	Δ Costs	Δ QALYs	Cost per QALY
The company's base case results	£8,249	0.708	£11,644
Using the company's alternative approach for decrease in S-K levels for SOC in the correction phase (1)	£11,362	0.573	£19,815
Setting the discontinuation and down-titration rates relating to RAASi treatment for SZC to that of SOC (2)	£1,397	0.443	£3,155
Using the OR for RAASi compared with active treatment (3)	£10,302	0.786	£13,102
Amending the utility values for people with CKD (4)	£8,249	0.654	£12,605
Combining (1) to (4)	£5,282	0.307	£17,179

Table 9: The ERG's base case results for patients with HF in the outpatient setting

	Δ Costs	Δ QALYs	Cost per QALY
The company's base case results	£14,860	0.818	£18,158
Using the company's alternative approach for decrease in S-K levels for SOC in the correction phase (1)	£13,928	0.641	£21,729
Setting the discontinuation and down-titration rates relating to RAASi treatment for SZC to that of SOC (2)	£12,293	0.634	£19,385
Combining (1) and (2)	£11,531	0.475	£24,291

Table 10: The ERG's base case results for patients with CKD in the emergency setting

	Δ Costs	Δ QALYs	Cost per QALY
The company's base case results	-£4,079	0.007	Dominates
Using the company's alternative approach for decrease in S-K levels for SOC in the correction phase (1)	-£3,444	0.004	Dominates
Amending the utility values for people with CKD (2)	-£4,079	0.006	Dominates
Combining (1) and (2)	-£3,444	0.004	Dominates

Table 11: The ERG's base case results for patients with HF in the emergency setting

	Δ Costs	Δ QALYs	Cost per QALY
The company's base case results	-£3,536	0.009	Dominates
ERG base case: Using the company's alternative approach for decrease in S-K levels for SOC in the correction phase	-£3,184	0.007	Dominates

4.3 Discussion of the results produced by the company and the ERG

The base case results produced by the company are below £20,000 per QALY gained for both patients with CKD, and patients with HF in the outpatient setting. The base case results produced by the ERG are higher values, and are approximately £17,000 per QALY gained for patients with CKD and £24,000 per QALY gained for patients with HF. Within the emergency setting the estimated results by both the company and the ERG is that SZC dominates. These results assume that the reduction in S-K levels is independent of underlying disease; it is possible that the ICERs for CKD may be more favourable to patients with CKD and less favourable to patients with HF.

Whilst the ERG believes that the base case values in the chronic setting are a relatively unbiased estimate the ERG acknowledges considerable uncertainty within the decision problem. These uncertainties also exist in the emergency setting where there are further limitations in that no trials have been undertaken in this setting. The known uncertainties that prohibit the ERG forming a definitive ICER include:

1) That there is no trial to provide comparative data between SZC and current standard of care for HK in England in both the correction phase and the maintenance phase. The post-hoc subgroup analysis of patients with high S-K levels in ZS-003 used to compare SZC with placebo in the correction phase may not be robust due to the reasons presented in Section 2.2.2. Whilst the approach taken by the company to populate the model appears reasonable the relatively small numbers in some of the subgroups means that there is considerable uncertainty in the results.
2) That there is no trial to demonstrate the impact of SZC on hard clinical endpoints, as the clinical endpoints relate to the surrogate measure of S-K level. However, the ERG comments that many guidelines recognise that high S-K levels should be reduced by treating with insulin dextrose, calcium resonium and the discontinuation or down-titration of RAASi treatment (see Figure 1 of the company's response to the ACD) indicating that clinicians believe that high levels of S-K warrant clinical intervention.
3) That data presented for SZC suggest a potentially better treatment effect of SZC on S-K levels for patients with CKD in the maintenance phase than the average level. If correct, this would result in worse treatment effects in the HF group and DM groups (although the latter group is not modelled).
4) That despite evidence that RAASi result in benefits to patients with HF and CKD, there appears no evidence that use of SZC enables patients to initiate, re-initiate or increase the dosage RAASi therapy and maintain optimum S-K levels.
5) That there is no study of the comparative effect of SZC compared to SOC in an emergency setting. The standard of care used in an emergency setting is likely to differ from the outpatient setting due to the use of interventions such as insulin dextrose and calcium resonium.

6) That the number of patients with baseline S-K levels ≥ 6.5 mmol/L that potentially represent HK patients in the emergency setting are too low to provide reliable estimates of absolute reduction in S-K levels.

The ERG comments that many of these limitations could be resolved if a trial, or trials were conducted comparing SZC to an active control which represents standard care in emergency and outpatient settings in patients who would be treated for HK in UK clinical practice. Preferably this trial would be of sufficient duration to establish the effects on mortality and major adverse cardiac events that are potentially associated with reduced S-K levels and potentially improved management of RAASi therapy.

5. REFERENCES

1. National Institute for Health and Care Excellence. Sodium zirconium cyclosilicate for treating hyperkalaemia. ACD. 2018.
2. AstraZeneca. Response to ACD Document. 2018.
3. AstraZeneca. Sodium zirconium cyclosilicate for treating hyperkalaemia [ID1293] Response to Clarification Letter. 2018.
4. Kosiborod M, Rasmussen HS, Lavin P, Qunibi WY, Spinowitz B, Packham D*, et al.* Effect of Sodium Zirconium Cyclosilicate on Potassium Lowering for 28 Days Among Outpatients With Hyperkalemia. *JAMA* 2014;312:2223.
5. NCT02163499. Open-label Safety and Efficacy of Sodium Zirconium Cyclosilicate for up to 12 Months. *Journal* 2014. https://clinicaltrials.gov/show/NCT02163499
6. Kalantar-Zadeh K, Tortorici AR, Chen JL, Kamgar M, Lau WL, Moradi H*, et al.* Dietary restrictions in dialysis patients: is there anything left to eat? *Seminars in dialysis* 2015;28:159-68.
7. AstraZeneca UK Ltd. Sodium Zirconium Cyclosilicate for Hyperkalaemia [ID 1293]. Company evidence submission. 2018.
8. Packham DK, Rasmussen HS, Lavin PT, El-Shahawy MA, Roger SD, Block G*, et al.* Sodium Zirconium Cyclosilicate in Hyperkalemia. *New England Journal of Medicine* 2015;372:222-31.
9. Friedman PA, Scott CG, Bailey K, Baumann NA, Albert D, Attia ZI*, et al.* Errors of classification with potassium blood testing: the variability and repeatability of critical clinical tests. Mayo Clinic Proceedings, abstract no. 599, p. 566-72.
10. Dylewski JF, Linas S. Variability of Potassium Blood Testing: Imprecise Nature of Blood Testing or Normal Physiologic Changes? Mayo Clinic Proceedings, abstract no. 600, p. 551-4.
11. Furuland H, McEwan P, Evans M, Linde C, Ayoubkhani D, Bakhai A*, et al.* Serum potassium as a predictor of adverse clinical outcomes in patients with chronic kidney disease: new risk equations using the UK clinical practice research datalink. *BMC nephrology* 2018;19:211.
12. Luo J, Brunelli SM, Jensen DE, Yang A. Association between Serum Potassium and Outcomes in Patients with Reduced Kidney Function. *Clin J Am Soc Nephrol* 2016;11:90-100.
13. Collins AJ, Pitt B, Reaven N, Funk S, McGaughey K, Wilson D*, et al.* Association of Serum Potassium with All-Cause Mortality in Patients with and without Heart Failure, Chronic Kidney Disease, and/or Diabetes. *Am J Nephrol* 2017;46:213-21.
14. Nakhoul GN, Huang H, Arrigain S, Jolly SE, Schold JD, Nally JV, Jr.*, et al.* Serum Potassium, End-Stage Renal Disease and Mortality in Chronic Kidney Disease. *Am J Nephrol* 2015;41:456-63.
15. Thomsen RW, Nicolaisen SK, Kim K, Palaka E, Sorensen HT. P593Healthcare resource utilization associated with elevated potassium levels in patients with congestive heart failure. *European Heart Journal* 2017;38.
16. Nunez J, Bayes-Genis A, Zannad F, Rossignol P, Nunez E, Bodi V*, et al.* Long-Term Potassium Monitoring and Dynamics in Heart Failure and Risk of Mortality. *Circulation* 2018;137:1320-30.
17. Desai AS, Liu J, Pfeffer MA, Claggett B, Fleg J, Lewis EF*, et al.* Incident Hyperkalemia, Hypokalemia, and Clinical Outcomes During Spironolactone Treatment of Heart Failure With Preserved Ejection Fraction: Analysis of the TOPCAT Trial. *J Card Fail* 2018;24:313-20.
18. Aldahl M, Jensen AC, Davidsen L, Eriksen MA, Moller Hansen S, Nielsen BJ*, et al.* Associations of serum potassium levels with mortality in chronic heart failure patients. *Eur Heart J* 2017;38:2890-6.
19. Krogager ML, Torp-Pedersen C, Mortensen RN, Køber L, Gislason G, Søgaard P*, et al.* Short-term mortality risk of serum potassium levels in hypertension: a retrospective analysis of nationwide registry data. *European Heart Journal* 2016; 10.1093/eurheartj/ehw129:ehw129.
20. Polcwiartek C, Hansen SM, Kragholm K, Krogager ML, Aldahl M, Kober L*, et al.* Prognostic role of serum sodium levels across different serum potassium levels in heart failure patients: A Danish register-based cohort study. *Int J Cardiol* 2018;272:244-9.

21. Fudim M, Grodin J, Mentz R. Hyperkalemia in Heart Failure: Probably Not O"K". *Journal of the American Heart Association* 2018;7.
22. Bennett H, Ayoubkhani D, Evans M, McEwan P, Qin L, Grandy S*, et al.* Quantifying The Relationship Between Hyperkalaemia And Outcomes In Patients With Heart Failure Or Chronic Kidney Disease. *Value in Health* 2017;20:A682.
23. Epstein M, Reaven NL, Funk SE, McGaughey KJ, Oestreicher N, Knispel J. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. *The American journal of managed care* 2015;21:S212-20.
24. Xie X, Liu Y, Perkovic V, Li X, Ninomiya T, Hou W*, et al.* Renin-angiotensin system inhibitors and kidney and cardiovascular outcomes in patients with CKD: A Bayesian network meta-analysis of randomized clinical trials. *Am J Kidney Dis* 2016;67:728-41.
25. Gilstrap LG, Fonarow GC, Desai AS, Liang L, Matsouaka R, DeVore AD*, et al.* Initiation, Continuation, or Withdrawal of Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers and Outcomes in Patients Hospitalized With Heart Failure With Reduced Ejection Fraction. *J Am Heart Assoc* 2017;6.
26. Xie W, Zheng F, Song X, Zhong B, Yan L. Renin-angiotensin-aldosterone system blockers for heart failure with reduced ejection fraction or left ventricular dysfunction: Network meta-analysis. *Int J Cardiol* 2016;205:65-71.
27. Thomsen MM, Lewinter C, Kober L. Varying effects of recommended treatments for heart failure with reduced ejection fraction: meta-analysis of randomized controlled trials in the ESC and ACCF/AHA guidelines. *ESC heart failure* 2016;3:235-44.
28. Miller RJH, Howlett JG, Exner DV, Campbell PM, Grant ADM, Wilton SB. Baseline Functional Class and Therapeutic Efficacy of Common Heart Failure Interventions: A Systematic Review and Meta-analysis. *Canadian Journal of Cardiology* 2015;31:792-9.
29. Levy WC. The Seattle Heart Failure Model: Prediction of Survival in Heart Failure. *Circulation* 2006;113:1424-33.
30. Flather MD, Yusuf S, Kober L, Pfeffer M, Hall A, Murray G*, et al.* Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. *Lancet* 2000;355:1575-81.
31. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JGF, Horowitz JD, Massie BM*, et al.* Comparative Effects of Low and High Doses of the Angiotensin-Converting Enzyme Inhibitor, Lisinopril, on Morbidity and Mortality in Chronic Heart Failure. *Circulation* 1999;100:2312-8.
32. Kunz R, Friedrich C, Wolbers M, Mann JF. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. *Annals of internal medicine* 2008;148:30-48.
33. Aranda P, Segura J, Ruilope LM, Aranda FJ, Frutos MA, Lopez V*, et al.* Long-term renoprotective effects of standard versus high doses of telmisartan in hypertensive nondiabetic nephropathies. *Am J Kidney Dis* 2005;46:1074-9.
34. Burgess E, Muirhead N, Rene de Cotret P, Chiu A, Pichette V, Tobe S. Supramaximal dose of candesartan in proteinuric renal disease. *Journal of the American Society of Nephrology : JASN* 2009;20:893-900.
35. Phelan D, Thavendiranathan P, Collier P, Marwick TH. Aldosterone antagonists improve ejection fraction and functional capacity independently of functional class: a meta-analysis of randomised controlled trials. 2012;98:1693-700.
36. Kleber FX, Niemoller L. Long-term survival in the Munich Mild Heart Failure Trial (MHFT). *The American journal of cardiology* 1993;71:1237-9.
37. Rossignol P, Dobre D, McMurray JJ, Swedberg K, Krum H, van Veldhuisen DJ*, et al.* Incidence, determinants, and prognostic significance of hyperkalemia and worsening renal function in patients with heart failure receiving the mineralocorticoid receptor antagonist eplerenone or placebo in addition to optimal medical therapy: results from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). 2014;7:51-8.

38. Desai AS, Liu J, Pfeffer MA, Claggett B, Fleg J, Lewis EF*, et al.* Incident hyperkalemia, hypokalemia, and clinical outcomes during spironolactone treatment of heart failure with preserved ejection fraction: analysis of the TOPCAT Trial. *Journal of cardiac failure* 2018;24:313-20.
39. Stevenson M, Hamilton J, Uttley L, Rawdin A, Clowes M, Alfonso A. Sodium Zirconium Cyclosilicate for Hyperkalaemia: A Single Technology Appraisal. *School of Health and Related Research (ScHARR)* 2018.
40. Eriksson D, Goldsmith D, Teitsson S, Jackson J, van Nooten F. Cross-sectional survey in CKD patients across Europe describing the association between quality of life and anaemia. *BMC nephrology* 2016;17:97.
41. Wolfgram DF, Garcia K, Evans G, Zamanian S, Tang R, Wiegmann T*, et al.* Association of Albuminuria and Estimated Glomerular Filtration Rate with functional performance measures in older adults with chronic kidney disease. *American journal of nephrology* 2017;45:172-9.
42. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. *Med Decis Making* 2011;31:800-4.

Appendix 1: ERG critique of the searches presented in the company response to the ACD

In support of their response to the NICE ACD, the company conducted a new review to identify studies supporting their estimation of associations between HK and long-term events and of the effect of RAASi treatment on long-term clinical outcomes.[2]

Searches were conducted in two phases: i.) a search for studies published between 2002 and August 2018 (date of initial search is not reported) and ii.) an update search conducted in November 2018. Medline, EMBASE and CENTRAL databases were searched recommended by NICE including. The full search strategies are presented in Appendix A of the company's response to the ACD.[2]

The ERG considers the conceptualisation of the search to be unconventional as concepts for population and outcomes have been combined. In the absence of an intervention for the review question (Table 1 – PICOS eligibility criteria), it would be simpler, for example, to search for the population (CKD, T2DB, hypertension or HF) and the outcome of interest (HK or death or MACE or hospitalization), and then to apply a study filter.

However, boundaries are blurred between the population and outcome terms in conceptualising, with the inclusion of a search string (line 2 in the Medline search strategy in tables 3 and 7 of Appendix C) that combines terms drug terms (MRA, ACEI etc.) with terms for outcomes (death, hospitalisation etc.) with 'OR'. All of these were combined with the disease and HK terms with 'AND'. An additional search facet (not specified in the inclusion criteria) has subsequently been added which looks for terms regarding incidence/association/risk. So, the actual search is conceptualised as: (CKD, T2DB, hypertension or HF) AND (MRA or ACEI or RAASi or death or MACE or hospitalization etc.) AND (HK or serum potassium) AND (incidence or association or risk or prediction)

There is little formal guidance available for systematic reviews of association between a condition and its potential outcomes. Studies demonstrating such links are difficult to identify and there is no indication that the terms used by the company (incidence or risk factors or predictor*, etc.) are derived from any published filter which has been validated for this purpose. Therefore, there is a risk that other studies may exist which suggest an association but have not been retrieved simply because they do not use any of the terms specified by the company.

The ERG also notes that in the Medline searches (company response to ACD, Tables 3 and 7 of Appendix C), instead of using a search filter to include study types of interest (trials and observational studies) the company have chosen to exclude those outside their scope (letters, editorials, case reports

etc.). While this strategy would potentially be justifiable if it only used the "publication type" field, to do so using terms in titles and abstracts carries an additional risk because it would exclude studies reporting on a trial that mention a prior case study. Unusually for an STA submission, the company searched the entire Cochrane library (not just the CENTRAL database of randomized controlled trials) and it is presumably for this reason that they used this strategy once again to exclude unwanted material (company response to ACD, Tables 5 and 9 of Appendix C), though here its impact on the number of results was less significant. A different filter was used for the EMBASE search (Tables 4 and 8 of Appendix C), with the company simply including anything identified as a journal article.

It is not clear from the presentation of the searches at which point the date limit (excluding pre-2002 studies) was applied. It is not clear whether the numbers in the PRISMA chart include results excluded on the basis of date.

The November update searches follow the same format as those from August 2018, except this time applying a date limit (1/1/2018-). There is an error in the Cochrane search as the start and end date are both set to January 2018.

Without re-running the searches and conducting a new SLR it is difficult for the ERG to predict the whether the company's approach would have resulted in any missed studies. As a rapid approach to identifying relevant papers the searches are adequate.

Sodium Zirconium Cyclosilicate for Hyperkalaemia: A Single Technology Appraisal. An addendum to the ERG critique of the company's response to the Appraisal Consultation Document.

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK Andrew Rawdin, Research Assistant, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
Date completed	21st March 2019

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 18/54/08.

Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Stevenson M and Rawdin A. Sodium Zirconium Cyclosilicate for Hyperkalaemia: Sodium Zirconium Cyclosilicate for Hyperkalaemia: A Single Technology Appraisal. An addendum to the ERG critique of the company's response to the Appraisal Consultation Document. ScHARR 2019

During the pre-meeting briefing call with NICE on the 21st of March, 2019 the ERG were requested to undertake additional sensitivity analyses to provide further information to the Appraisal Committee. These additional analyses explored the impact of removing the influence of S-K levels on changes in the risks of adverse events (mortality, major adverse cardiac events, and hospitalisation), leaving the benefits of SZC treatment purely in the ability to maintain a proportion of patients on RAASi treatment. The changes made to the model are detailed in the Appendix. This document should be read in conjunction with the ERG critique of the company's response to the ACD.[1]

The requested analyses have a number of limitations which are highlighted by the ERG.

1) That logically, if high, or low, S-K levels are not associated with adverse outcomes then patients would not need to have their RAASi treatments stopped as is still assumed, and which is more prevalent in the SOC arm.
2) That in adjusting multivariate equations, such as those produced by the Seattle Heart Failure Model, to remove the influence of S-K level, the resultant statistical model would no longer fit the observed data; ideally a model would be refitted having removed the S-K components.
3) That there are multiple studies, which have attempted to adjust for confounders, that have shown an associated between high, and low, S-K levels and adverse events. As such, the analyses should be viewed as exploratory rather than representing a most plausible ICER.

In all instances the amendments made to the company's model to form the ERG's base case have been maintained with the only changes being those required for the removal of an association with S-K levels and adverse outcomes. Deterministic results only have been produced. The results are shown in Tables 1 to 4 for each combination of underlying disease (CKD, or HF) and of setting (outpatient or emergency).

Within the analyses the ICERs have increased in the outpatient setting, to over £38,000 in CKD patients and to over £110,000 for HF patients. In the emergency setting, it is still estimated that the use of SZC dominates SOC. However, these results are subject to the limitations of the analyses just described, and also to the factors described in the ERG critique of the company response to the ACD[1] which suggest that there is considerable uncertainty in determining a robust ICER.

[1] Stevenson M, Uttley L, Hamilton J, Rawdin A. Sodium Zirconium Cyclosilicate for Hyperkalaemia: A Single Technology Appraisal. A critique of AstraZeneca's response to the Appraisal Consultation Document. School of Health and Related Research (ScHARR), 2019

Table 1: The ERG's base case results for patients with CKD in the outpatient setting

	Δ Costs	Δ QALYs	Cost per QALY
The company's base case results	£8,249	0.708	£11,644
The ERG's base case results	£5,282	0.307	£17,179
The ERG's base case results removing the association between S-K levels and adverse events	£3,369	0.088	£38,287

Table 2: The ERG's base case results for patients with HF in the outpatient setting

	Δ Costs	Δ QALYs	Cost per QALY
The company's base case results	£14,860	0.818	£18,158
The ERG's base case results	£11,531	0.475	£24,291
The ERG's base case results removing the association between S-K levels and adverse events	£11,732	0.106	£111,035

Table 3: The ERG's base case results for patients with CKD in the emergency setting

	Δ Costs	Δ QALYs	Cost per QALY
The company's base case results	-£4,079	0.007	Dominates
The ERG's base case results	-£3,444	0.004	Dominates
The ERG's base case results removing the association between S-K levels and adverse events	-£3,387	0.000	Dominates

Table 4: The ERG's base case results for patients with HF in the emergency setting

	Δ Costs	Δ QALYs	Cost per QALY
The company's base case results	-£3,536	0.009	Dominates
The ERG's base case results	-£3,184	0.007	Dominates
The ERG's base case results removing the association between S-K levels and adverse events	-£3,311	0.001	Dominates

Appendix:

Table 5: Changes made to the model to run the sensitivity analysis requested by NICE

Worksheet	Cells	Set to value
Inputs 2	AA30:AA71	1
Inputs 2	AA111:AA116	1
Inputs 2	AA118:AA130	1
Inputs 2	AA132:AA137	1
Inputs 2	AA139:AA144	1
Inputs 2	AA146:AA151	1
Inputs 2	AA152:AA158	1
Inputs 2	AJ8:AJ10	0
Inputs 2	AJ47:AJ52	0
Inputs 2	AJ67:AJ72	0