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. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Pumping Marvellous Foundation
   - British Society for Heart Failure
   - Renal Association
     The Royal College of Physicians endorsed the Renal Association comments

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

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

5. **Evidence Review Group critique of company response** – prepared by the School of Health and Related Research

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

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Sodium zirconium cyclosilicate for treating hyperkalaemia

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee (company)	AstraZeneca	AstraZeneca welcome the positive draft recommendation by the Committee in the second appraisal consultation document (ACD2) to use sodium zirconium cyclosilicate (SZC) in adults in the emergency care setting for up to 28 days. In response to the ACD2, we would like to stress the high unmet need for patients with hyperkalaema in the outpatient setting (in addition to the emergency care setting) and the volume of evidence supporting the relationships between serum potassium (S-K) and adverse clinical outcomes in these patients. We would like to ask the committee to kindly consider the following key points:	Thank you for your comments. SZC has been recommended in both the outpatient and emergency care settings, please see section 1.1 of the final appraisal document.
2	Consultee (company)	AstraZeneca	**There is a significant need to provide an alternative treatment option to the down-titration and discontinuation of guideline recommended cardio-renal protective RAASi medication for the treatment of hyperkalaemia in the outpatient setting** Current treatment options for the management of hyperkalaemia in the outpatient setting are limited to down-titration or discontinuation of cardio-renal protective RAASi therapy. As such, hyperkalaemia is a barrier to prescribing and optimising RAASi therapies in CKD and HF patients, leading to worse prognosis and higher risk for adverse cardio-renal events due to suboptimal RAASi therapy. Therefore, in addition to the emergency care setting, there is also a high unmet need for alternative treatment options to manage hyperkalaemia in the outpatient setting to enable a sustained lowering of S-K whilst allowing patients to maintain cardio-renal protective RAASi therapy.	Comment noted. SZC has been recommended in both the outpatient and emergency care settings, please see section 1.1 of the final appraisal document.
3	Consultee (company)	AstraZeneca	**Systematically identified evidence, UK clinical practice, and NICE clinical guidelines all support a relationship between S-K and adverse clinical outcomes. It is therefore reasonable to apply this relationship for fair and balanced decision making** The evidence on the relationships between S-K and adverse clinical outcomes previously	Comment noted. The relationship between serum potassium levels and adverse clinical

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			submitted to the Committee were identified via a systematic literature review, and all studies consistently support the U-shaped relationships whereby S-K levels below and above normokalaemia are associated with higher risks of adverse clinical outcomes. The Committee has also acknowledged in the ACD2 that relationships between S-K and adverse clinical outcomes are biologically plausible. Additionally, the ERG has stated that weight should be given to the U-shaped S-K relationships with adverse clinical outcomes "*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."* Furthermore, the ERG has also clearly stated that the scenario analyses excluding the relationship between S-K and adverse clinical outcomes "*should be viewed as exploratory rather than representing a most plausible ICER*". As such, whilst AstraZeneca acknowledge that a degree of residual confounding may affect the reported association between S-K and adverse clinical outcomes, we maintain that the best use of available evidence would be to capture the relationships between S-K and adverse clinical outcomes in the base case cost-effectiveness analyses, and explore the uncertainty with potential alternative assumptions in scenario analyses. In the scenarios where the relationship between S-K and adverse clinical outcomes have been entirely removed, as requested by the Committee, there are substantial uncaptured benefits and therefore the ICERs would not represent the most plausible ICERs.	outcomes was considered by the committee. Please see sections 3.13 and 3.16 of the final appraisal document.
4	Consultee (company)	AstraZeneca	**AstraZeneca is providing a patient access scheme (PAS), consisting of a [redacted], to improve the cost-effectiveness of SZC in the outpatient setting** The confidential PAS price of [redacted], after a [redacted] discount, [redacted], the PAS would be available both to patients in the emergency care setting and in the outpatient setting.	Comment noted. No action required.
5	Consultee (company)	AstraZeneca	**With the [redacted] confidential PAS discount, SZC is cost-effective versus standard care, with ICERs of [redacted]/QALY and [redacted]/QALY in HF and CKD patients, respectively** The differences between the updated company ACD2 base cases and the ERG base cases are primarily driven by the confidential PAS discount and by the higher S-K treatment threshold in the HF population. The treatment threshold in the HF population has been increased to S-K ≥6.0 mmol/L to address the Committee's comment that some clinicians may wish to treat	Comment noted. SZC has been recommended in both the outpatient and emergency care settings, please see section 1.1 of the final

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			hyperkalaemia at higher S-K thresholds than previously modelled. The results from the probabilistic sensitivity analyses show that there is an [redacted] and [redacted] likelihood that SZC is cost-effective at ICER thresholds of £20,000–£30,000/QALY in the HF and CKD populations, respectively. Exploratory scenario analyses show that SZC is still cost-effective at ICERs of [redacted]/QALY and [redacted]/QALY for HF and CKD, respectively, even when the relationships between S-K and adverse clinical outcomes are reduced by 50%. In an extreme scenario with substantial uncaptured benefits, where the relationships between S-K and adverse clinical outcomes are entirely removed, the ICERs are [redacted]/QALY and [redacted]/QALY for HF and CKD patients, respectively. As advised by the NICE technical team, the ICER threshold for decision making should be towards the upper end of the £20,000-£30,000/QALY range when there are uncaptured benefits in the cost-effectiveness analysis. The base case analyses and the scenario analyses clearly demonstrate the cost-effectiveness of SZC, with the [redacted] confidential PAS discount, even when uncertainty in the relationships between S-K and adverse clinical outcomes has been accounted for. Based on the above points and the detailed response to the ACD2 provided below, AstraZeneca urge the Committee to consider the strong case for extending the positive draft recommendation for SZC to patients with hyperkalaemia in the outpatient setting, to ensure that clinicians and patients have access to cost-effective SZC treatment and to address the current high unmet need for an effective treatment option for these patients.	appraisal document. NICE advised the company that above a most plausible ICER of £20,000 per QALY gained, the committee is more likely to consider a technology to a be a cost effective use of NHS resources if the company is able to demonstrate that there are additional benefits not captured in the QALY calculation. However, the committee would also consider other factors such as the degree of certainty around the ICER. See section 6.3.3 of the Guide to the methods of technology appraisal.
6	Consultee (company)	AstraZeneca	**1. There is a significant need to provide an alternative treatment option to the down-titration and discontinuation of guideline recommended cardio-renal protective RAASi medication for the treatment of hyperkalaemia in the outpatient setting** • Renin-angiotensin-aldosterone system inhibitors (RAASi) are the mainstay treatment options for the optimal management of patients with heart failure (HF) and/or chronic kidney disease (CKD) due to their proven cardio-renal protective effects. However, RAASi therapy often cause RAASi-induced hyperkalaemia.[1-8] • Despite the increased risk of developing hyperkalaemia, RAASi therapy is recommended in HF and CKD patients by clinical guidelines/consensus statements, including those published by NICE, the European Society of Cardiology (ESC), and consensus statements by the ESC and Think Kidney, the Renal Association and the	Comment noted. SZC has been recommended in both the outpatient and emergency care settings, please see section 1.1 of the final appraisal document.

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			British Society for Heart Failure.[9-11] • Current treatment options for the management of hyperkalaemia are limited. In the outpatient setting, the same guidelines which recommend treatment with RAASi therapy typically recommend a combination of down-titration and/or discontinuation of RAASi therapy for the management of hyperkalaemia.[9-14] • Hyperkalaemia is often viewed as a barrier to prescribing and optimising RAASi therapies in CKD and HF patients,[15-18] and therefore despite being recommended for use, RAASi therapy is often not re-instated following an episode of hyperkalaemia at or following discharge.[19-22] This in turn further exacerbates the loss of cardio-renal protection from RAASi therapy.[12, 19, 23] • Therefore, in addition to the emergency care setting for the management of hyperkalaemia, there is also a need to improve longer term management in an outpatient setting to enable a sustained lowering of serum potassium (S-K) whilst allowing patients to maintain RAASi where it would otherwise be reduced or stopped due to hyperkalaemia; thereby reducing the morbidity and mortality risks of hyperkalaemia and enabling the simultaneous cardio-renal protective effects of RAASi therapy.	
7	Consultee (company)	AstraZeneca	**2. <u>AstraZeneca do not consider clinically relevant hyperkalaemia to be defined as a S-K >5.0 mmol/L</u>** • AstraZeneca consider the current wording used in the ACD to be inaccurate and misleading. AstraZeneca do not consider clinically relevant hyperkalaemia in the UK to be defined as a S-K >5.0 mmol/L, but instead recognise that treatment is likely to be initiated in HF and CKD patients with S-K ≥5.5 mmol/L and S-K ≥6.0 mmol/L, respectively. • Whilst the clinical trial programme enrolled patients with baseline S-K levels below the UK treatment thresholds, AstraZeneca have aligned the clinical and cost-effectiveness analyses to S-K thresholds relevant to UK clinical practice. • Therefore, it would be more appropriate to recognise that whilst the clinical trial programme included patients with a S-K above 5.0 mmol/L, AstraZeneca agree that patients in UK clinical practice are not treated until higher S-K levels of 5.5 or 6.0 mmol/L. • Furthermore, AstraZeneca note the Committee's comment from the second Committee meeting that some clinicians may treat HF patients at higher S-K thresholds than previously modelled. Therefore, the effect of increasing the treatment threshold to S-K	Comment noted. The text describing the proposed positioning of SZC has been amended. Please see section 3.6 of the final appraisal document.

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			≥6.0 mmol/L in the cost-effectiveness analysis has been included as part of the updated cost-effectiveness analysis (see Section 6).	
8	Consultee (company)	AstraZeneca	**3. <u>Systematically identified evidence, UK clinical practice, and NICE clinical guidelines all support a relationship between S-K and adverse clinical outcomes. It is therefore reasonable to apply this relationship for fair and balanced decision making</u>** • AstraZeneca previously addressed the Committee's concerns relating to the way in which evidence was identified to support the relationships between S-K and adverse clinical outcomes by conducting a systematic review of the evidence base. • The systematic literature review identified 59 potentially relevant studies, which consistently reported U-shaped associations between S-K and adverse clinical outcomes, irrespective of geographical location or comorbid status. • AstraZeneca have conducted a thorough review of the evidence to ensure that the most appropriate data sources have been used in the cost-effectiveness model to mitigate the risk of potential confounding, including time-dependent confounding (see Section 3.3). Therefore, AstraZeneca believe that a robust approach has been taken to ensure the relationships have been appropriately modelled to support decision making. • Despite the Committee recognising that the relationships between S-K and adverse clinical outcomes are biologically plausible, the Committee has asked to see a scenario where SZC is cost-effective in the complete absence of relationships between S-K and adverse clinical outcomes. This contradicts NICE clinical guideline CG182 which recommends the cautious initiation or complete discontinuation of RAASi therapy at high S-K levels to avoid hyperkalaemia. If there were no relationships, there would be no clinical rationale for this clinical recommendation. • Therefore, AstraZeneca believe that it is perverse and against the evidence submitted to NICE to assume that no relationships exists between S-K and adverse clinical outcomes and to use this as the basis for decision making.	Comment noted. The relationship between serum potassium levels and adverse clinical outcomes was considered by the committee. Please see sections 3.13 and 3.16 of the final appraisal document.
9	Consultee (company)	AstraZeneca	**4. <u>Post-hoc analyses show the risk of hypokalaemia to be low with SZC in patient sub-groups with baseline S-K levels relevant to UK clinical practice</u>** • To better reflect UK clinical practice and in response to the first ACD (ACD1), AstraZeneca amended the treatment threshold treatment to S-K ≥6.0 mmol/L for patients with CKD, whilst the treatment threshold was kept at S-K ≥5.5 mmol/L for patients with	Comment noted. The risk of hypokalaemia is discussed in section 3.11 of the final appraisal

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			HF. • Post-hoc analyses of patients with baseline S-K >5.5 mmol/L and >6.0 mmol/L from ZS-004 and ZS-005 studies were presented to show outcomes relevant to UK clinical practice. These post-hoc analyses demonstrated that rates of hypokalaemia were low, and that the majority of patients maintained clinically appropriate S-K values. Additionally, because the S-K treatment goal in the UK is higher than in the SZC trials, the risk of hypokalaemia is likely to be lower in UK clinical practice compared to in the trials	document.
10	Consultee (company)	AstraZeneca	**5. <u>AstraZeneca and independent professional bodies consider SZC to be innovative</u>** • Professional organisation submission forms submitted prior to the first committee meeting clearly indicated that SZC is considered to be an innovate therapy for the management of adults with hyperkalaemia. • In line with these submissions, AstraZeneca believe that SZC should be considered innovative, as other potassium binders, calcium resonium and SPS, are not commonly used due to their poor tolerance. Even when used, calcium resonium and SPS are only used for short periods of time. • As such, currently there are no alternative treatment options for patients with hyperkalaemia other than down-titrating or discontinuing cardio-renal protective RAASi medication and SZC would represent a step-change in the current management of hyperkalaemia.	Comment noted. Innovation is discussed in section 3.19 of the final appraisal document.
11	Consultee (company)	AstraZeneca	**6. <u>SZC is a cost-effective treatment option for the management of hyperkalaemia in the outpatient setting</u>** • The company cost-effectiveness base case has been updated to address the Committee's concerns in the second ACD (ACD2), including adopting the changes from the ERG that were favoured by the Committee. Additionally, the treatment threshold in the HF population has been increased to S-K ≥6.0 mmol/L in the updated company ACD2 base case to address the Committee's comment at the second Committee meeting that some clinicians may treat HF patients at higher S-K thresholds than previously modelled. Furthermore, a confidential PAS price reduction of [redacted] has been applied to improve the cost-effectiveness of SZC and to alleviate the Committee's concerns about uncertainty in the cost-effectiveness estimate, leading to ICERs of [redacted] and [redacted] for the HF and CKD populations, respectively. The PAS price [redacted]. • As exploratory scenario analyses to address the uncertainty expressed by the Committee of the relationships between S-K and adverse clinical outcomes, the U-	Comment noted. SZC has been recommended in both the outpatient and emergency care settings, please see section 1.1 of the final appraisal document.

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			shaped relationships between S-K and adverse clinical outcomes were reduced by 50% or removed entirely, despite the documented evidence supporting these relationships. Even in these highly pessimistic scenario analyses, with clear uncaptured benefits (particularly when no relationship was assumed), the ICERs remained cost-effective at [redacted] and [redacted] for HF and CKD, respectively, when 50% of the relationships were removed; and cost-effective at [redacted] and [redacted] for HF and CKD, respectively, when the S-K relationships were entirely removed. • The ICERs from the probabilistic sensitivity analyses (PSAs) of the base case in the HF population and the CKD population are comparable to the deterministic ICERs and the cost-effectiveness acceptability curves (CEACs) show that there is an [redacted] likelihood that SZC is cost-effective at ICER thresholds of £20,000–£30,000/QALY. • PSAs of the scenarios where the relationships between S-K and adverse clinical outcomes have been entirely removed also show the probabilistic ICERs to be comparable to the deterministic ICERs, with a [redacted] likelihood that SZC is cost-effective at ICER thresholds of £20,000–£30,000/QALY, where the ICER threshold should be towards the upper end of the £20,000–£30,000/QALY range due to uncaptured benefits in these overly pessimistic scenarios.	
12	Consultee (company)	AstraZeneca	**1 Current draft recommendation** The current draft NICE recommendation is for the treatment of hyperkalaemia in adults in the emergency care setting, and for up 28 days or stopped sooner if hyperkalaemia resolves. AstraZeneca would like to highlight that SZC is not licensed for mono-therapy of life-threatening hyperkalaemia in the emergency care setting, but should be used alongside current standard care, including insulin dextrose, in the emergency care setting. Therefore, AstraZeneca would like to ask NICE to amend the wording in the recommendation to reflect that SZC can be used as an adjunct to standard care in the emergency care setting.	Comment noted. The text has been amended, please see section 1.1 of the final appraisal document.
13	Consultee (company)	AstraZeneca	**2 Definition of hyperkalaemia** **ACD2 Section 3.1:** *"The company defined high serum potassium values as above 5.0 mmol/litre, (…) The committee concluded that the company's clinical definition of hyperkalaemia as serum potassium levels above 5.0 mmol/litre was not widely accepted. It also concluded that, unless they need emergency treatment, few patients in the NHS with serum potassium levels above 5.0 mmol/litre have treatment to lower potassium."*	Comment noted. The text has been amended, please see section 3.1 of the final appraisal document.

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			AstraZeneca understand the *clinical* definition of HK to be S-K >5.0 mmol/L and this was also the definition used in the SZC trials. However, the initial company submission used a higher treatment threshold of S-K ≥5.5 mmol/L to align with UK clinical practice (see Section B.1.3.1.1; para 1) and the treatment threshold was amended to S-K ≥6.0 mmol/L in patients with CKD, in response to ACD1 and following engagement with clinical experts. Furthermore, in response to the ACD1, AstraZeneca stated that *"AstraZeneca agree that patients with hyperkalaemia (HK) are not always treated when S-K levels are above 5.0 mmol/L".* Therefore, AstraZeneca consider the wording of the statement in ACD2 Section 3.1 to be inaccurate and misleading. It would be more appropriate to state that whilst the clinical trial programme included patients with baseline S-K >5.0 mmol/L, AstraZeneca agree that patients in UK clinical practice are not treated until higher S-K levels of 5.5 or 6.0 mmol/L for HF and CKD patients, respectively. Furthermore, in order to address the Committee's comment from the second Committee meeting that some clinicians may treat HF patients at higher S-K thresholds than previously modelled, the effect of increasing the treatment threshold to S-K ≥6.0 mmol/L for HF patients in the cost-effectiveness analysis has been included as part of the updated cost-effectiveness analysis (see Section 0).	
14	Consultee (company)	AstraZeneca	**3 Relationships between S-K and adverse clinical outcomes** **3.1 Systematically identified evidence, UK clinical practice, and NICE clinical guidelines all support a link between serum potassium and adverse clinical outcomes** **ACD2 Section 3.12:** *"The committee noted that the observational data did not guarantee an independent association between high serum potassium levels and death. It also noted that the observational data did not provide evidence that lowering serum potassium extends life. (…) The committee concluded that there was insufficient evidence to prove definitively that lowering serum potassium levels in the outpatient setting leads to improved outcomes.* **ACD2 Section 3.16:** *"Given the uncertainty, the committee concluded that it would like to have seen that sodium zirconium cyclosilicate was cost effective in the absence of an association between serum potassium and adverse outcomes, including death."* **ACD2 Section 3.22:** *"The committee recalled its conclusion that a link between lowering serum*	Comment noted. The relationship between serum potassium levels and adverse clinical outcomes was considered by the committee. Please see sections 3.13 and 3.16 of the final appraisal document.

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			potassium levels and improved long-term outcomes was plausible for some outcomes, but unproven (see section 3.16). It agreed that an ICER for decision making would lie near the ERG's scenario analysis removing the association between serum potassium levels and outcomes." To address the concerns raised by the Committee during the first committee meeting, AstraZeneca conducted a systematic literature review (SLR) using recommended methods to identify published literature documenting the relationship between S-K and adverse clinical outcomes.[24] The SLR identified 59 studies which were potentially relevant to the decision problem. The ERG's critique of the evidence stated that *"whilst 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"*.[25] Whilst AstraZeneca acknowledge that a degree of residual confounding may affect the reported association between S-K and adverse clinical outcomes, we disagree that the association should be entirely removed from the cost-effectiveness model and we disagree that this scenario should be used as a basis for decision making. The evidence consistently demonstrates a U-shaped association between S-K and adverse clinical outcomes, and clinicians routinely manage patients with hyperkalaemia in the outpatient setting by down-titrating and/or discontinuing proven cardio-renal protective therapy (RAASi) to avoid hyperkalaemia. In addition, the cardiologist clinical expert at the second committee meeting strongly supported a causal link between S-K and adverse clinical outcomes and stated that *chronically* elevated S-K can increase the risk of death which may present as sudden cardiac death. In comparison, *sudden and extreme* rises in S-K often lead to cardiac arrhythmias. Section 3.12 of the ACD states *"[The Committee] agreed that a relationship between lowering serum potassium to a normal range and fewer adverse outcomes was biologically plausible for a subset of endpoints"*, and Section 3.16 acknowledges that assuming no relationship between S-K and adverse clinical outcomes could be considered conservative. Furthermore, Section 3.11 of	

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			the ACD2 states that *"the committee understood that hypokalaemia, like hyperkalaemia, is associated with life-threatening arrhythmias*". Therefore, it would be inappropriate and biased to acknowledge a relationship between hypokalaemia and adverse clinical outcomes, and not consider the documented relationship between hyperkalaemia and adverse clinical outcomes. Therefore, AstraZeneca deem it to be inappropriate to base decision making on a scenario where the relationships between S-K and adverse clinical outcomes are entirely removed. AstraZeneca would also like to note that NICE clinical guideline CG182 highlights S-K as an important consideration when making treatment decisions in patients with CKD.[9] The guideline recommends the cautious initiation and complete discontinuation of RAASi therapy when S-K levels increase to ≥5.0 mmol/L and ≥6.0 mmol/L, respectively, thereby recognising the need to manage hyperkalaemia – even when S-K is ≥5.0 mmol/L. This is indicative that NICE and the wider clinical community inherently accept a clinical cause for concern when S-K is elevated, even at S-K levels that may not be treated in UK clinical practice. In detail, NICE CG182 makes the following recommendations: • **Section 1.4.7:** Offer dietary advice about potassium, phosphate, calorie and salt intake appropriate to the severity of CKD. [2008, amended 2014] • **Section 1.6.7:** In people with CKD, measure S-K concentrations and estimate the GFR before starting renin–angiotensin system antagonists. Repeat these measurements between 1 and 2 weeks after starting renin–angiotensin system antagonists and after each dose increase. [2008] • **Section 1.6.8:** Do not routinely offer a renin–angiotensin system antagonist to people with CKD if their pretreatment S-K concentration is greater than 5.0 mmol/litre. [2008, amended 2014] • **Section 1.6.9:** When hyperkalaemia precludes use of renin–angiotensin system antagonists, assessment, investigation and treatment of other factors known to promote hyperkalaemia should be undertaken and the S-K concentration rechecked. [2008] • **Section 1.6.11:** Stop renin-angiotensin system antagonists if the S-K concentration increases to 6.0 mmol/litre or more and other drugs known to promote hyperkalaemia	

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			have been discontinued. [2008] If there were no relationships between S-K and adverse clinical outcomes, there would be no clinical rationale for the need to alter RAASi therapy in response to elevated S-K levels as recommended in NICE CG182; particularly given the weight of evidence proving the cardio-renal protective properties of RAASi therapies. These recommendations have been published in NICE guidance for the three latest versions of this guideline. Whilst the Committee has stated that it would like to use the scenario where the relationships between S-K and adverse clinical outcomes are entirely removed as the basis for decision making, we would like to kindly ask the Committee to reconsider its conclusion. We would urge the Committee to consider the wealth of evidence which consistently reports associations between S-K and adverse clinical outcomes, the fact that NICE clinical guidelines use S-K as a basis for treatment decisions, the advice presented in the addendum to the ERG's critique of the company's ACD response which highlighted a number of limitations associated with the removal of the relationships between S-K and adverse clinical outcomes, and the recommendation by the ERG that "*this analyses should be viewed as exploratory rather than representing a most plausible ICER*".[26] Whilst a degree of residual confounding cannot be completely excluded, the volume and strength of the evidence demonstrating the relationships between S-K and adverse clinical outcomes is overwhelming. Therefore, it would be perverse and against the evidence made available to the Committee to assume that no relationships between S-K and adverse clinical outcomes exists. Such a scenario would have substantial uncaptured benefits and should be interpreted with significant caution. Instead, a cost-effectiveness analysis incorporating the relationships between S-K and adverse clinical outcomes based on the evidence available in the literature, including Luo et al. 2016 and Desai et al. 2018, would represent the best use of available evidence and should be considered as the best estimate of the most likely ICER.	
15	Consultee (company)	AstraZeneca	**3.2 Fudim et al., 2018 was not systematically identified and inappropriate conclusions have been drawn from the publication** **ERG's critique of the company's response to the ACD Section 2.3.3:** *"In an editorial, Fudim et al. highlight a need to "be careful to assert a general causal relationship between*	Comment noted. The committee concluded that Fudim et al. demonstrates some of the reasons why a causal

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			hyperkalaemia and clinical outcomes across the entire spectrum of hyperkalaemia". **ACD2 Section 3.12:** *"It also noted that the authors of a company-supported observational study used in the model cautioned against assuming a causal effect, and acknowledged the possibility of residual confounding."* The ERG refer to an editorial by Fudim et al. 2018 which cautions against asserting a general causal relationship between hyperkalaemia and adverse clinical outcomes across the entire spectrum of hyperkalaemia.[27] The editorial makes reference to 3 HF RCTs (RALES, EMPHASIS, and TOPCAT) and an analysis of real-world data published by Hoss et al.[28-31] RALES is a HF RCT which included a total of 1,663 patients with NYHA class III—IV and randomised patients to receive treatment with spironolactone (25 mg) or placebo.[28] The study concluded that MRA therapy provides a mortality benefit which is sustained in patients with S-K levels up to 5.5 mmol/L, above which the mortality benefit is reduced,[28] potentially due to MRA dose reductions in patients with S-K ≥5.5 mmol/L and/or due to the mortality effect of hyperkalaemia. Whilst the study demonstrated a mortality benefit compared with placebo, the study nonetheless reports a U-shaped association between S-K and adverse clinical outcomes. EMPHASIS is a HF RCT which included a total of 2,737 patients with NYHA class III—IV who received treatment with eplerenone (25/50 mg).[29] The study concluded that MRA therapy provides a mortality benefit irrespective of S-K levels and that there is a statistically significant increase in all-cause mortality in patients with S-K ≥5.5 mmol/L; thereby supporting the relationships between S-K and adverse clinical outcomes. TOPCAT is a HF RCT which included a total of 1,767 patients in the Americas with NYHA class II—IV and randomised patients to receive treatment with spironolactone (15—45 mg) or placebo.[30] Whilst treatment with spironolactone resulted in a mortality benefit when compared with those receiving placebo, a statistically significant U-shaped association was also observed between S-K and cardiovascular mortality, and all-cause mortality, further supporting the relationships between S-K and adverse clinical outcomes. In line with the three RCTs mentioned above, the real-world data analysis by Hoss et al. concluded that the treatment benefit of MRA therapy is sustained up-to a S-K level of 5.5 mmol/L, but that S-K levels ≥5.5 are associated with increased mortality as per the U-shaped	effect between serum potassium levels and long-term outcomes cannot be assumed, but not that it disproves such a relationship. No action required.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			relationships between S-K and adverse clinical outcomes observed in other studies.[31] Specifically, the real-world analysis by Hoss et al. reported hypokalaemia (defined as S-K <3.5 mmol/L) and severe hyperkalaemia (defined as S-K ≥6.0 mmol/L) to be associated with the lowest survival rates amongst all S-K groups in the study. Therefore, the evidence presented in the editorial by Fudim et al. does not disprove the relationships between S-K and adverse clinical outcomes, but simply supports a protective benefit of MRA therapy in HF patients up-to a S-K level of 5.5 mmol/L. Irrespective of MRA therapy, a U-shaped association was consistently observed in the studies mentioned in the Fudim et al. editorial; further supporting the relationships between S-K and mortality. As such, it is unlikely that the strong U-shaped relationship consistently observed across multiple studies (see Section 0) can be explained by the existence of any unknown confounders, which would need to be strongly associated with both S-K and adverse clinical outcomes. Given this, it is likely that the effect of any residual confounding on the U-shaped relationships between S-K and adverse clinical outcomes would be negligible.	
16	Consultee (company)	AstraZeneca	**3.3 Time-dependent variables** **ACD2 Section 3.19:** *"[The Committee] also noted that the studies may have been affected by time-dependent confounding, for example, because increasing serum potassium levels affects RAAS inhibitor use, which in turn affects subsequent serum potassium levels and long-term outcomes. Therefore, RAAS inhibitor use is a time-dependent confounder. The committee was aware that using standard regression adjustment is not appropriate when attempting to estimate causal effects from observational data affected by time-dependent confounding, and noted that the company was unable to show that alternative appropriate methods had been used."* The relationships between S-K and adverse clinical outcomes, including mortality, CV events and hospitalisation, were modelled based on systematically identified published incidence rate ratios (IRRs) and hazard ratios (HRs) by S-K intervals. For the CKD population, the IRRs reported by Luo et al. were used in the base case to inform the relationships between S-K and mortality, S-K and CV events, and S-K and hospitalisation. Luo et al. analysed time-updated data from 55,266 CKD patients to examine the relationships between S-K and mortality, S-K and hospitalisation and additional S-K and RAASi discontinuation. Generalised estimating equations with independent or exchangeable working	Comment noted. The potential for time-dependent confounding was considered by the committee. Please see sections 3.13 and 3.16 of the final appraisal document.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			correlation structures were used to analyse the non-linear relationships between S-K and adverse clinical outcomes. Poisson/negative binomial links were used on the basis of the empirical distribution of outcomes in the study cohort. Covariates that were imbalanced across categories of S-K, and covariates known or presumed to be associated with the outcomes studies were included in the analysis, including age, sex, race/ethnicity, diabetes, congestive heart failure, coronary artery disease, cerebrovascular disease, beta blocker use, RAASi use, nondihydropyridine calcium channel blocker use, thiazide diuretic use, loop diuretic use, and eGFR. S-K levels and covariates were updated at the time of each successive S-K measurement, to capture the time-dependent nature of the covariates. Additionally, for the CKD population, IRRs reported by Furuland et al. were used in scenario analyses to provide alternative values based on an analysis of a UK population (191,964 CKD patients from the CPRD). Patient-intervals were defined as the period between successive S-K measurements, and clinical events of interest were assigned to these patient-intervals based on the date on which they occurred. In addition to the base case analysis, a scenario analysis was also presented by Furuland et al. where the associations between S-K and adverse clinical outcomes based on patient intervals were restricted to the 30 days following each S-K measurement, mitigating the impact of time-dependent confounding from unobserved factors. This scenario analysis showed that associations between S-K and adverse clinical outcomes were broadly consistent with those estimated from unrestricted patient intervals (base case analysis). Generalised estimating equations with an exchangeable working correlation structure to account for intra-patient correlation were used to estimate risk equations for mortality, CV outcomes and RAASi discontinuation. Events were assumed to be Poisson distributed and a natural logarithm link function and an offset equal to the natural logarithm of patient-years (defined as the exposure time in each patient-interval) were used. Predicted incidence rates and IRRs were adjusted for covariates included as explanatory variables in the risk equations, which included time-updated RAASi use amongst other covariates. Each observation included in the analysis conducted by Luo et al. and Furuland et al. was a patient interval rather than a patient, and each patient would appear in the analysis as many times as they had intervals over the study period. Generalised estimating equations were used, where intra-patient correlation was accounted for by using a modified version of the estimation process to obtain model parameter point estimates and by estimating standard errors that are robust to the effects of clustering. Furuland et al. also assessed the sensitivity of results to the	

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			choice of modelling framework and found that associations were maintained when using a generalised linear mixed model, where intra-patient correlation is accounted for using patient specific random intercepts. Luo et al. considered generalised estimating equations to be the most appropriate model, as the primary study question was whether there were any differences in event rates with respect to S-K at a population level and as the sample size was sufficient to estimate the marginal effects. An assumption was made that data were missing at random, based on the authors experiences with previous studies using the same data sources. Both the Luo et al. and the Furuland et al. studies showed high S-K levels to be associated with RAASi discontinuation, with RAASi discontinuation having a direct effect on S-K levels and on adverse clinical outcomes. As such, RAASi use/discontinuation is a time-dependent confounder that needs to be adjusted for in the relationships between S-K and adverse clinical outcomes. The generalised estimating equations used in Luo et al. and Furuland et al. for estimating the relationships between S-K and adverse clinical outcomes include time-updated RAASi as a covariate, and therefore appropriately adjust for RAASi use as a confounder and isolate the effect of S-K on adverse clinical outcomes. The effect of RAASi on adverse clinical outcomes remain important in the cost-effectiveness analysis of SZC; this relationship is separately and explicitly modelled based on ORs of RAASi treatment effects on mortality, CV events and hospitalisation, as reported by Xie et al. (CKD), Levy et al. (HF), and Flather et al. (HF). This modelling approach allows the relationship between different risk-factors (S-K and RAASi use) to be explicitly modelled and independently adjusted, whilst avoiding double-counting of treatment effect (Figure 1 and Figure 2). For the HF population, the HRs reported by Desai et al.[30] were used to inform the relationships between S-K and mortality, and S-K and hospitalisation. Time-updated Cox models adjusted for significant predictors of incidence hypo- and hyperkalaemia were used to relate the most recent measured S-K value to the risk of mortality and hospitalisation. Hazard ratios were adjusted for region, age, gender, race, baseline eGFR, baseline S-K, baseline RAASi use, baseline beta blocker use, baseline loop diuretics and treatment arm in the TOPCAT trial. The relationship was not adjusted for time-updated RAASi use as patients in the TOPCAT trial continued to receive ACEi or ARB throughout the trial,[32] and therefore it is unlikely that time-updated use of ACEi or ABR would have significantly affected the HRs. In conclusion, the statistical models used to estimate the relationships between S-K and adverse	

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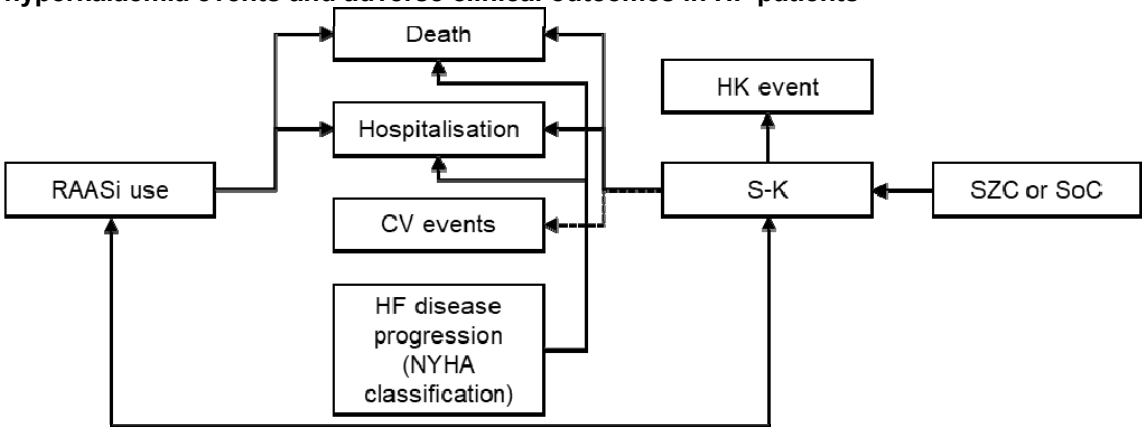
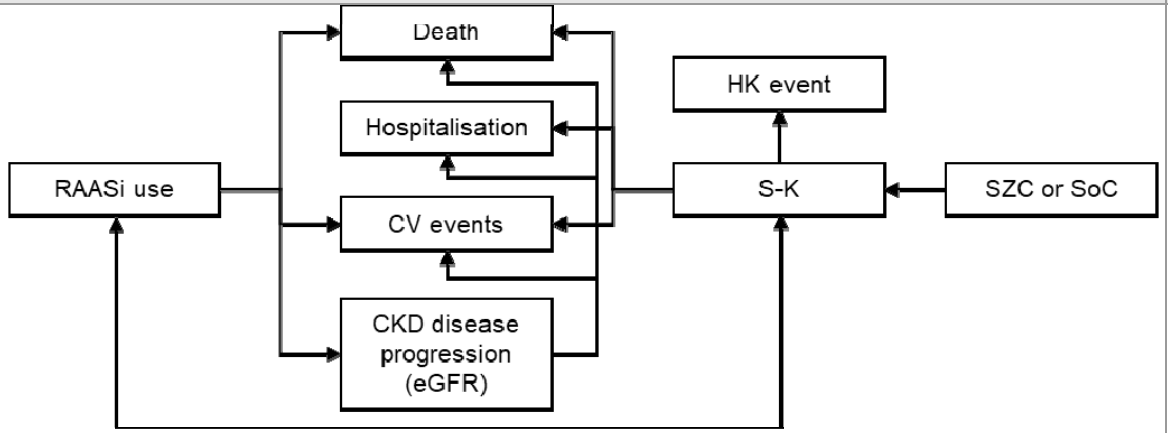
			clinical outcomes were carefully selected to ensure all known covariates were appropriately accounted for and to take the features of the data analysed into account. The published results from the literature were applied in the cost-effectiveness analysis to explicitly model the relationships between S-K and adverse clinical outcomes, alongside the relationships between RAASi and outcomes (also modelled explicitly, but separately to the S-K and adverse clinical outcomes relationship). **Figure 1. Relationships modelled between treatment, S-K levels, RAASi use, hyperkalaemia events and adverse clinical outcomes in HF patients**  **Key**: solid arrows, relationships modelled; dashed arrows, relationship did not reach statistical significance in CPRD analysis, but the relationship between hypokalaemia and CV events has been conservatively modelled in favour of SoC **Abbreviations**: CV, cardiovascular; HK, hyperkalaemia; NYHA, New York Heart Association; RAASi, renin angiotensin aldosterone system inhibitor; S-K, serum potassium; SoC, standard care; SZC, sodium zirconium cyclosilicate. **Figure 2. Relationships modelled between treatment, S-K levels, RAASi use, hyperkalaemia events and adverse clinical outcomes in CKD patients**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 **Key**: solid arrows, relationships modelled **Abbreviations**: CV, cardiovascular; eGFR, estimated glomerular filtration rate; HK, hyperkalaemia; RAASi, renin angiotensin aldosterone system inhibitor; S-K, serum potassium; SoC, standard care; SZC, sodium zirconium cyclosilicate.	
17	Consultee (company)	AstraZeneca	**4 Risk of hypokalaemia** **ACD2 Section 3.10:** *"Clinicians in the NHS may not always view a serum potassium level of below 5.0 mmol/litre as the target for treatment if serum potassium levels are reduced to non-life-threatening levels, depending on the serum potassium level that precipitated treatment."* **ACD2 Section 3.11:** *"The company presented data showing that treatment with sodium zirconium cyclosilicate was associated with hypokalaemia, that is low serum potassium. The committee understood that hypokalaemia, like hyperkalaemia, is associated with life-threatening arrhythmias."* AstraZeneca would like to re-emphasise the positioning of SZC with respect to the thresholds for intervention and the S-K treatment goal. To better reflect UK clinical practice and in response to the ACD1, AstraZeneca amended the threshold for treatment to S-K ≥6.0 mmol/L for CKD patients, whilst the threshold for HF patients was maintained at ≥5.5 mmol/L.[24]. AstraZeneca also recognised that clinicians may not always view the S-K treatment goal as <5.0 mmol/L in UK clinical practice and understand that clinicians would prefer to treat to prevent S-K levels ≥5.5	Comment noted. The risk of hypokalaemia is discussed in section 3.11 of the final appraisal document.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			mmol/L in HF patients and S-K ≥6.0 in CKD patients. Therefore, post-hoc analyses of patients with baseline S-K >5.5 mmol/L and >6.0 mmol/L from studies ZS-004 and ZS-005 were presented to show outcomes relevant to UK clinical practice: S-K >5.5 or >6.0 mmol/L at the end of the correction phase and during the maintenance phase S-K >4.0, ≤5.5 or S-K >4.0, ≤6.0 mmol/L at the end of the correction phase and during the maintenance phase S-K <4.0 mmol/L (the Committee's preferred definition of hypokalaemia) at the end of the correction phase and during the maintenance phase These post-hoc analyses demonstrate that the risk of hypokalaemia is low. In patients with baseline S-K >5.5 mmol/L, there were [redacted] and [redacted] patients with S-K <4.0 mmol/L at the end of the corrective phase of ZS-004 and ZS-005, respectively. At the end of the maintenance phase, [redacted] and [redacted] patients receiving 5 g and 10 g OD, respectively in ZS-004, and [redacted] patients in ZS-005 had S-K <4.0 mmol/L. In patients with baseline S-K >6.0 mmol/L, [redacted] patient in the corrective phase of ZS-005 reported S-K <4.0 mmol/L, and [redacted] patient receiving treatment with 10 g OD in the maintenance phase of ZS-004, and [redacted] patients in the maintenance phase of ZS-005 with had S-K <4.0 mmol/L. AstraZeneca would like to re-iterate that the dose of SZC should be up- or down-titrated as per the SmPC to maintain an appropriate S-K. If patients become hypokalaemic, therapy should be discontinued. As such, hypokalaemia is unlikely to be a frequent adverse event in UK clinical practice, given the low rate of hypokalaemia in the post-hoc analysis and the higher S-K treatment goal in UK clinical practice compared to the SZC trials. As stated in Section 0, in order to address the Committee's comment from the second Committee meeting that some clinicians may treat HF patients at higher S-K thresholds than previously modelled, the effect of increasing the treatment threshold to S-K ≥6.0 mmol/L for HF patients in the cost-effectiveness analysis has been included as part of the updated cost-effectiveness analysis (see Section 0).	
18	Consultee (company)	AstraZeneca	**5 Innovation** **ACD2 Section 3.23:** *"The company proposed several benefits of sodium zirconium cyclosilicate, including preventing the need to modify RAAS inhibitor treatment and avoiding a restrictive low-*	Comment noted. Innovation is discussed in section 3.19 of the final

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			potassium diet. The committee recalled that people would still need to avoid dietary potassium. The patient experts stated that, if the company had shown evidence for these benefits, then sodium zirconium cyclosilicate would be innovative. The committee was aware that other gastrointestinal potassium binders exist and, although these are not well tolerated, sodium zirconium cyclosilicate does not represent a step-change in treatment. The committee concluded, sodium zirconium cyclosilicate could not be considered innovative." AstraZeneca would like to kindly ask the committee to reconsider its conclusion that SZC should not be considered innovative. When asked if the technology is considered to be innovate, professional organisation submissions from The Renal Association and Royal College of Physicians, and The Royal College of Pathologists stated the following: *"This is a new area on management of patients with electrolyte disorders mainly as a consequence of medications and in part diet. This addition may transform our ability to effectively manage patients with chronic hyperkalaemia"* and *"It has potential to be innovative"* Furthermore, AstraZeneca believe that SZC should be considered innovative, as other potassium binders, calcium resonium and SPS, are not commonly used or only used for short periods of time due to their poor tolerance. Additionally, calcium resonium and SPS do not selectively bind potassium but also bind several other ions, leading to adverse events associated with electrolyte imbalances. As such, currently there are no significant alternative treatment options for patients with hyperkalaemia, other than down-titrating or discontinuing cardio-renal protective RAASi medication.	appraisal document.
19	Consultee (company)	AstraZeneca	**6 Cost-Effectiveness Analysis** **ACD2 Section 3.7**: *"The company proposed that sodium zirconium cyclosilicate would be started, and RAAS inhibitors stopped or reduced, in people with persistently high serum potassium levels of 5.5 mmol/litre and above (heart failure) or 6.0 mmol/litre and above (chronic kidney disease). The committee accepted that the levels proposed by the company were intended to align with clinical expert opinion (see section 3.1), but noted that some clinicians may wish to treat hyperkalaemia at alternative serum potassium thresholds."* **ACD2 Section 3.16:** *"Given the uncertainty, the committee concluded that it would like to have*	Comment noted. SZC has been recommended in both the outpatient and emergency care settings, please see section 1.1 of the final appraisal document.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			seen that sodium zirconium cyclosilicate was cost effective in the absence of an association between serum potassium and adverse outcomes, including death." **ACD2 Section 3.19**: *"The committee recalled that the company assumed that in the outpatient setting, patients would have treatment for up to 1 year, and then sodium zirconium cyclosilicate would be stopped (see section 3.15). It noted that this did not align with the expected use in clinical practice, where treatment would continue indefinitely if there was clinical benefit. It would have preferred to have seen a scenario analysis in which the costs and benefits of sodium zirconium cyclosilicate were modelled beyond 52 weeks."* **ACD2 Section 3.22**: *"The committee noted that the ERG's base case for chronic kidney disease used an odds ratio for RAAS inhibitor outcomes compared with active control (see section 3.20), and that removing this assumption in line with committee's preferences would likely reduce the incremental cost-effectiveness ratio (ICER) by around £1,500 per QALY gained."* **ACD2 Section 3.22**: *"The committee recalled its conclusion that a link between lowering serum potassium levels and improved long-term outcomes was plausible for some outcomes, but unproven (see section 3.16). It agreed that an ICER for decision making would lie near the ERG's scenario analysis removing the association between serum potassium levels and outcomes. The committee would have preferred to have seen evidence that sodium zirconium cyclosilicate was cost effective when this assumption was used."* **ACD2 Section 3.22**: *"It would also have liked to have seen cost-effectiveness scatter plots to help determine the effect of the uncertainty in the modelled parameters on the cost-effectiveness estimates."* **ACD2 Section 3.22**: *"The committee also recalled its conclusion that treatment with RAAS inhibitors would improve outcomes but noted that uncertainties around the assumptions of how many patients would down-titrate or restart RAAS inhibitors had not been fully addressed in the company's model (see section 3.17)."* **6.1 Updated company base case in the outpatient setting** The cost-effectiveness analyses for SZC in HF and CKD patients in the outpatient setting have been updated to align with the ERG base cases, and to address concerns raised in the ACD2 by making the changes outlined below for the revised company ACD2 base case (Table 1 and	

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			Table 2). The S-K reduction over the 2-day correction phase in the placebo arm of ZS-003 has been linearly extrapolated to modelled continued reductions in S-K over Day 3. This alternative S-K profile was preferred by the ERG, and it is conservative with respect to SZC as the rate of S-K reductions in the placebo arm is likely to lower on Day 3 compared to Day 1 and Day 2. The proportion of patients who down-titrate and discontinue conditional on S-K levels, and the proportion of patients who reinitiate RAASi therapy in the SZC arm have been set to that of the SoC arm, as per the ERG base cases. This assumption addresses the Committee's concern regarding the uncertainty around the assumption of how many patients would down-titrate or restart RAASi (ACD2 Section 3.22). In clinical practice, clinicians with experience of SZC are likely to allow patients to maintain RAASi whilst being treated with SZC – the assumption of equal RAASi down-titration, discontinuation and re-initiation in the SZC and SoC arms is therefore conservative with respect to SZC. The treatment duration of SZC has been increased to life-time treatment to provide "*a scenario analysis in which the costs and benefits of sodium zirconium cyclosilicate were modelled beyond 52 weeks"* as requested by the Committee in ACD2 Section 3.19. The treatment threshold in the HF population has been increased to S-K ≥6.0 mmol/L to address the Committee's comment in ACD2 Section 3.3 and 3.7 that some clinicians may wish to treat hyperkalaemia at higher S-K thresholds than previously modelled. The Committee chair also expressed interest in the cost-effectiveness of SZC at this higher threshold at the second Committee meeting. (HF only) The effect of RAASi on mortality and CV events has been changed back to the ORs based on the comparison of RAASi with placebo, to align with the Committee's preference stated in the ACD2 Section 3.22. (CKD only) The health state utility values for CKD patients have been updated according to the ERG base case. (CKD only) A confidential PAS discount has been applied [redacted] to improve cost-effectiveness. The PAS price is [redacted] (equivalent to a [redacted] discount) and would be available for patients in both the emergency care setting and the outpatient setting. The price	

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			[redacted].	

The updated company ACD2 base case combines all the changes listed above and results in ICERs of [redacted] and [redacted] for HF and CKD patients, respectively. The differences between the updated company ACD2 base cases and the ERG base cases are primarily driven by the confidential PAS discount and by the higher S-K treatment threshold in the HF population.

Table 1. Updated company ACD2 base case for HF patients

#	Scenario	ΔCosts	ΔQALYs	ICER
1	Company base case submitted in the ACD1 response	£14,860	0.818	£18,158
2	Company ACD1 base case + applying a 3-day S-K reduction in the correction phase *(as per the ERG base case)*	£13,928	0.641	£21,729
3	Company ACD1 base case + setting the RAASi discontinuation, down-titration and re-initiation rates in SZC to that of SoC *(as per the ERG base case)*	£12,293	0.634	£19,385
4	Company ACD1 base case + life-time SZC treatment *(as per Committee's preference, ACD2 Section 3.19)*	£17,003	0.938	£18,125
5	Company ACD1 base case + threshold for treatment changed to S-K ≥6.0 mmol/L *(as per Committee's preference, ACD2 Section 3.7 and discussions at second Committee meeting)*	£7,883	0.965	£8,172
6	Company ACD1 base case + [redacted] confidential PAS discount [redacted]	[redacted]	[redacted]	[redacted]
7	Combining 1+2+3+4+6 above (i.e. threshold for treatment maintained at S-K ≥5.5 mmol/L)	[redacted]	[redacted]	[redacted]
8	**Updated company ACD2 base case (combining 1+2+3+4+5+6 above)** (i.e. threshold for treatment changed to S-K ≥6.0 mmol/L)	[redacted]	[redacted]	[redacted]
9	ERG base case in critique of company response to ACD1 (note this scenario retains treatment threshold at S-K ≥5.5 mmol/L)	£11,531	0.475	£24,291

Abbreviations: ACD1, first appraisal consultation document; ACD2, second appraisal consultation

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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>document; ERG, evidence review group; HF, heart failure; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SoC, standard care; SZC, sodium zirconium cyclosilicate; ΔCosts, incremental costs; ΔQALYs, incremental QALYs.

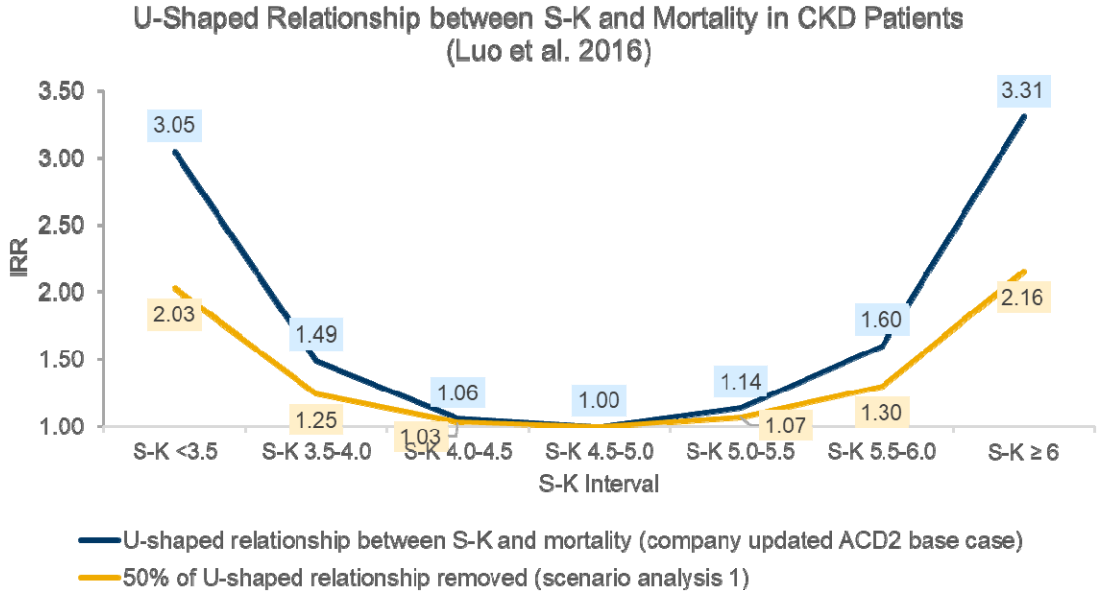
Table 2. Updated company ACD2 base case for CKD patients
<table>
<tr><th>#</th><th>Scenario</th><th>ΔCosts</th><th>ΔQALYs</th><th>ICER</th></tr>
<tr><td>1</td><td>Company base case submitted in the ACD1 response</td><td>£8,249</td><td>0.708</td><td>£11,644</td></tr>
<tr><td>2</td><td>Company ACD1 base case + applying a 3-day S-K reduction in the correction phase (as per the ERG base case)</td><td>£11,362</td><td>0.573</td><td>£19,815</td></tr>
<tr><td>3</td><td>Company ACD1 base case + setting the RAASi discontinuation, down-titration and re-initiation rates in SZC to that of SoC (as per the ERG base case)</td><td>£1,397</td><td>0.443</td><td>£3,155</td></tr>
<tr><td>4</td><td>Company ACD1 base case + life-time SZC treatment (as per Committee’s preference, ACD2 Section 3.19)</td><td>£9,225</td><td>0.879</td><td>£10,491</td></tr>
<tr><td>5</td><td>Company ACD1 base case + using OR for RAASi compared to placebo (as per Committee’s preference, ACD2 Section 3.22)</td><td>£8,249</td><td>0.708</td><td>£11,644</td></tr>
<tr><td>6</td><td>Company ACD1 base case + amending the utility values for people with CKD (as per the ERG base case)</td><td>£8,249</td><td>0.654</td><td>£12,605</td></tr>
<tr><td>7</td><td>Company ACD1 base case + [redacted] confidential PAS discount [redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>8</td><td>Updated company ACD2 base case (combining 1+2+3+4+5+6+7 above)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>9</td><td>ERG base case in critique of company response to ACD1</td><td>£5,282</td><td>0.307</td><td>£17,179</td></tr>
</table>
Abbreviations: ACD1, first appraisal consultation document; ACD2, second appraisal consultation document; CKD, chronic kidney disease; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; RAASi, renin-angiotensin-aldosterone system inhibitor; PAS, patient access scheme; S-K, serum potassium; SoC, standard care; SZC, sodium zirconium cyclosilicate; ΔCosts, incremental costs; ΔQALYs, incremental quality adjusted life-years.</td><td></td></tr>
<tr><td>20</td><td>Consultee (company)</td><td>AstraZeneca</td><td>6.2 Scenario analyses in the outpatient setting

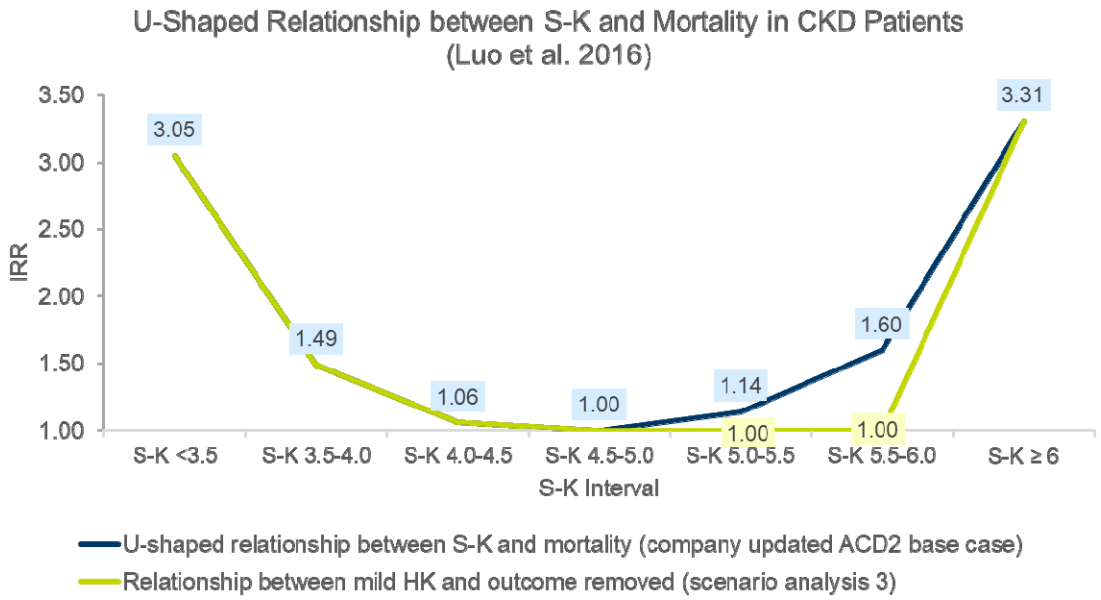
Additional scenario analyses have been conducted to address potential residual uncertainties,</td><td>Comment noted.

SZC has been</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			as outlined below and as summarised in Table 3 and Table 4. **6.2.1 Removal of relationships between S-K and adverse clinical outcomes (scenario 2)** The Committee has requested to see a scenario where no relationships between S-K and adverse clinical outcomes are modelled. AstraZeneca strongly believe that this scenario is overly pessimistic, given the abundance of systematically identified evidence from the literature demonstrating this relationship across geographies and comorbid populations, and given clinical guidelines that recommend high S-K levels to be managed through RAASi down-titration/discontinuation and low potassium diet (e.g. NICE CG182). The ERG has also highlighted this scenario is unlikely to reflect clinical reality, and the Committee has itself acknowledged that *"a relationship between lowering S-K to normal range and fewer adverse outcomes was biologically plausible for a subset of endpoints"*. As such, this scenario analysis should be viewed as exploratory and at most represent an extreme upper limit of the ICER, and should not to be used as the basis for decision making. When 100% of the relationships between S-K and adverse clinical outcomes are removed (scenario 2), the ICERs increase by ~£15,000 and ~£9,300 compared to the updated company ACD2 base case for HF and CKD patients, respectively (Table 3 and Table 4 #2). This scenario is exploratory and is likely to grossly underestimate the benefits of SZC, as benefits from reduced clinical events (mortality, CV events and hospitalisation) mediated through the lowering of S-K levels are not captured at all. As advised by the NICE technical team, the ICER threshold for decision making should be towards the upper end of the £20,000-£30,000/QALY range when there are uncaptured benefits in the cost-effectiveness analysis, as in this case. **6.2.2 Reduction of the relationships between S-K and adverse clinical outcomes by 50% (scenario 1)** Despite the documented evidence supporting a strong relationship between hyperkalaemia and long-term adverse clinical outcomes, and the approaches taken to account for time-dependant confounding (see Section 0) an alternative scenario is provided with 50% of the relationships between S-K and adverse clinical outcomes removed (scenario 1). This alternative scenario should be considered to be more reflective of UK clinical practice compared with assuming no relationship, given the wealth of evidence supporting the relationships between S-K and adverse clinical outcomes, and the biological plausibility for this relationship as acknowledged by the	recommended in both the outpatient and emergency care settings, please see section 1.1 of the final appraisal document. The relationship between serum potassium levels and adverse clinical outcomes was considered by the committee. Please see sections 3.13 and 3.16 of the final appraisal document.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Committee. This alternative scenario analysis was conducted by scaling the IRRs associated with hypo- and hyperkalaemia for mortality and hospitalisation in HF patients, and the IRRs for mortality, CV events and hospitalisation in CKD patients, so that the risk of events in patients with hypo- and hyperkalaemia reduced compared with the base case (see Figure 3 for the relationship between S-K and mortality as an example). When 50% of the relationships between S-K and adverse clinical outcomes are removed (scenario 1), the ICER increases by ~£1,500 and ~£2,000 compared to the updated company ACD2 base case for HF and CKD, respectively (Table 3 and Table 4, #1). AstraZeneca consider this scenario to be more relevant for decision making, as some of the relationships between S-K and adverse clinical outcomes have been retained, even though a large proportion of the relationship has been conservatively removed. The ICERs in this scenario remain well below [redacted] in both the HF and CKD population, and as such SZC should be considered as a cost-effective treatment option for hyperkalaemia in the outpatient setting. **Figure 3. U-shaped relationship between S-K and mortality modelled in the base case (blue line) and in scenario 1 where 50% of the relationships between S-K and adverse clinical outcomes have been removed (orange line)**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 The relationships between S-K and other adverse clinical outcomes for HF and CKD patients were also similarly adjusted as in Figure 3. **Abbreviations**: ACD2, second appraisal consultation document; IRR, incidence rate ratio; S-K, serum potassium. **6.2.3 Removal of the relationships between mild hyperkalaemia and adverse clinical outcomes (scenario 3)** Based on the Committee's understanding that severe hyperkalaemia in the emergency care setting is associated with life-threatening arrhythmias, a scenario analysis (scenario 3) has been conducted where the U-shaped relationships between S-K and adverse clinical outcomes have been modulated to remove the relationships between mild hyperkalaemia and adverse clinical outcomes, whilst the relationships between severe hyperkalaemia and adverse clinical outcomes have been retained. As a conservative assumption, the full relationships between hypokalaemia (regardless of severity of hypokalaemia) and adverse clinical outcomes have been retained, in line with the Committee's comment about the adverse effects of hypokalaemia in ACD2 Section 3.11 (see Figure 4 for the relationship between S-K and mortality as an example).	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Scenario 3 shows that the ICERs for both the HF and CKD populations remain below [redacted], at [redacted] and [redacted], respectively, even when the relationships between mild hyperkalaemia and adverse clinical outcomes (death, CV events, hospitalisation) were removed, whilst the full relationships between hypokalaemia and adverse clinical outcomes were fully retained (Table 3 and Table 4, #3). **Figure 4. U-shaped relationship between S-K and mortality modelled in the base case (blue line) and in scenario 3 where the relationships between mild hyperkalaemia and adverse clinical outcomes have been removed (green line)**  The relationships between S-K and other adverse clinical outcomes for HF and CKD patients were also similarly adjusted as in Figure 4. **Abbreviations**: ACD2, second appraisal consultation document; IRR, incidence rate ratio; S-K, serum potassium. **6.2.4 Dose distribution (scenarios 4 and 5)**	

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			In the base case analysis as submitted by the company in the ACD1 response, the daily cost of SZC maintenance therapy was calculated as the weighted average cost based on the actual SZC doses received by patients during the maintenance phase of the ZS-005 trial. In the maintenance phase of ZS-005, the starting dose was SZC 5 g OD. Thereafter, the dose was maintained, or increased to a maximum of 15 g OD or decreased to a minimum of 5 g once every other day if potassium increased to >5.5 mmol/L or decreased to between 3.0 and 3.4 mmol/L, respectively. Because the S-K treatment goal is less stringent in UK clinical practice (S-K <5.5 mmol/L and <6.0 mmol/L for HF and CKD patients, respectively) compared with those in the ZS-005 trial, it is likely that a smaller proportion of patients in UK clinical practice require dose up-titration in order to achieve normokalaemia as defined in the UK clinical practice. Therefore, scenario analyses were carried out where the proportion of patients who require the 10 g daily dose was reduced to 10% and 20%, compared with 37.4% in the base case. Due to a lower weighted average daily cost, the ICER in these scenarios were £1,000–£2,200 lower than the updated company ACD2 base case (Table 3 and Table 4, #4 and #5). **6.2.5 Relationships between S-K and adverse clinical outcomes modelled based on Furuland et al. 2018 (scenario 6, CKD only)** During the second Committee meeting, the Committee criticised the use of Luo et al. 2016 to inform the relationships between S-K and adverse clinical outcomes in CKD patients, due to the non-UK data in this study. To address this, a scenario analysis based on the relationships between S-K and adverse clinical outcomes reported by Furuland et al. 2018 has been conducted. Furuland et al. 2018 was a study of 191,964 UK CKD patients listed in the Clinical Practice Research Datalink (CPRD) and is therefore likely to be representative of UK clinical practice. Details of the statistical model used by Furuland et al. 2018 to account for time-dependent covariates are also provided in Section 3.3. The ICER in the scenario analysis with Furuland et al. is ~£1,300 lower than the updated company ACD2 base case (Table 4, #6). **Table 3. Additional scenarios based on the company ACD2 base case for HF patients** **# | Scenario | ΔCosts | ΔQALYs | ICER** **- | Updated company ACD2 base case | [redacted] | [redacted] | [redacted]**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

	Relationships between S-K and adverse clinical outcomes modelled as per Desai et al. 2018 Dose distribution modelled as 5 g one every other day/5 g once daily/10 g once daily: 0.9%/61.7%/37.4%			
1	Updated company ACD2 base case + remove 50% of relationships between S-K and adverse clinical outcomes	[redacted]	[redacted]	[redacted]
2	Updated company ACD2 base case + remove 100% of relationships between S-K and adverse clinical outcomes	[redacted]	[redacted]	[redacted]
3	Updated company ACD2 base case + remove relationships between *mild* S-K and adverse clinical outcomes	[redacted]	[redacted]	[redacted]
4	Updated company ACD2 base case + alternative dose distribution (5 g one every other day/5 g once daily/10 g once daily: 0.9%/79.1%/20%)	[redacted]	[redacted]	[redacted]
5	Updated company ACD2 base case + alternative dose distribution (5 g one every other day/5 g once daily/10 g once daily: 0.9%/89.1%/10%)	[redacted]	[redacted]	[redacted]

Abbreviations: ACD2, second appraisal consultation document; HF, heart failure; ICER, incremental cost-effectiveness ratio; S-K, serum potassium; ΔCosts, incremental costs; ΔQALYs, incremental QALYs.

Table 4. Additional scenarios based on the company ACD2 base case for CKD patients

#	Scenario	ΔCosts	ΔQALYs	ICER
-	**Updated company ACD2 base case** Relationships between S-K and adverse clinical outcomes modelled as per Luo et al. 2018 Dose distribution modelled as 5 g one every other day/5 g once daily/10 g once daily: 0.9%/61.7%/37.4%	[redacted]	[redacted]	[redacted]
1	Updated company ACD2 base case + remove 50% of relationships between S-K and adverse clinical outcomes	[redacted]	[redacted]	[redacted]
2	Updated company ACD2 base case + remove 100% of relationships between S-K and adverse clinical outcomes	[redacted]	[redacted]	[redacted]
3	Updated company ACD2 base case + remove	[redacted]	[redacted]	[redacted]

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			relationship between mild S-K and adverse clinical outcomes 4 Updated company ACD2 base case + alternative dose distribution (5 g one every other day/5 g once daily/10 g once daily: 0.9%/79.1%/20%) [redacted] 5 Updated company ACD2 base case + alternative dose distribution (5 g one every other day/5 g once daily/10 g once daily: 0.9%/89.1%/10%) [redacted] 6 Updated company ACD2 base case + relationships between S-K and adverse clinical outcomes modelled based on Furuland et al. 2018 *(as per Committee's preference to use UK data)* [redacted] **Abbreviations**: ACD2, second appraisal consultation document; CKD, chronic kidney disease; ICER, incremental cost-effectiveness ratio; S-K, serum potassium; ΔCosts, incremental costs; ΔQALYs, incremental quality adjusted life-years.	
21	Consultee (company)	AstraZeneca	**6.3 Probabilistic sensitivity analyses in the outpatient setting** **6.3.1 Updated company ACD2 base cases** The cost-effectiveness plane from the PSA of the updated company ACD2 base case for HF is presented in **Error! Reference source not found.** and the CEAC is presented in **Error! Reference source not found.**. The probabilistic ICERs in the HF population of [redacted] is similar to the determinist ICER of [redacted] (see Section 0). The PSA shows that there is a [redacted] likelihood for SZC to be cost-effective at willingness to pay (WTP) thresholds of £20,000–£30,000/QALY in the HF population. The cost-effectiveness plane from the PSA of the updated company ACD2 base case for CKD is presented in **Error! Reference source not found.** and the cost-effectiveness acceptability curve is presented in **Error! Reference source not found.**. The probabilistic ICERs in the CKD population of [redacted] is similar to the determinist ICER of [redacted] (see Section 0). The PSA shows that there is an [redacted] likelihood for SZC to be cost-effective at WTP thresholds of £20,000–£30,000/QALY in the CKD population. **Error! Reference source not found.** and **Error! Reference source not found.** show that a	Comment noted. SZC has been recommended in both the outpatient and emergency care settings, please see section 1.1 of the final appraisal document.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			sufficient number of simulations have been conducted for the ICERs to converge in the PSAs for the HF population and CKD population, respectively. [Figures 5–10 contain confidential in confidence information and have been redacted]	
22	Consultee (company)	AstraZeneca	**6.3.2 Scenario analyses where the relationships between S-K and adverse clinical outcomes have been entirely removed** The cost-effectiveness plane from the PSA of the scenario analyses in HF patients where the relationships between S-K and adverse clinical outcomes have been entirely removed is presented in **Error! Reference source not found.** and the cost-effectiveness acceptability curve is presented in **Error! Reference source not found.**. The probabilistic ICERs in the HF population of [redacted] is similar to the determinist ICER of [redacted] (see Section 0). The PSA shows that there is a [redacted] likelihood for SZC to be cost-effective at WTP thresholds of £20,000–£30,000/QALY in the HF population. The cost-effectiveness plane from the PSA of the scenario analyses in CKD patients where the relationships between S-K and adverse clinical outcomes have been entirely removed is presented in **Error! Reference source not found.** and the cost-effectiveness acceptability curve is presented in **Error! Reference source not found.**. The probabilistic ICERs in the CKD population of [redacted] is similar to the determinist ICER of [redacted] (see Section 0). The PSA shows that there is a [redacted] likelihood for SZC to be cost-effective at WTP thresholds of £20,000–£30,000/QALY in the CKD population. Given the substantial uncaptured benefits in these scenarios, the ICER threshold (WTP threshold) should be towards the upper end of the £20,000-£30,000/QALY range, as advised by the NICE technical team. Therefore, there is a high likelihood for SZC to be cost-effective even in these overly pessimistic scenarios. **Error! Reference source not found.** and **Error! Reference source not found.** show that a sufficient number of simulations have been conducted for the ICERs to converge in the PSAs for the HF population and CKD population, respectively. [Figures 11–16 contain confidential in confidence information and have been redacted]	The relationship between serum potassium levels and adverse clinical outcomes was considered by the committee. Please see sections 3.13 and 3.16 of the final appraisal document.
23	Consultee (company)	AstraZeneca	**7 Factual inaccuracies identified in the ACD** **Table 5: Factual inaccuracies identified in the ACD2** **Section** | **ACD2 statement** | **Comments/Corrections**	Comments noted.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row			NICE Response Please respond to each comment
			Section 3.1, page 5	• The company defined high serum potassium values as above 5.0 mmol/litre, […] • The committee concluded that the company's clinical definition of hyperkalaemia as serum potassium levels above 5.0 mmol/litre was not widely accepted. It also concluded that, unless they need emergency treatment, few patients in the NHS with serum potassium levels above 5.0 mmol/litre have treatment to lower potassium.	• These statements in the ACD2 are misleading, as the company defined clinically relevant hyperkalaemia as S-K ≥5.5 mmol/L in HF patients and S-K ≥6.0 mmol/L in CKD patients in response to the ACD1. • The treatment threshold in the SZC trials were set at S-K ≥5.1 mmol/L. If the statement in the ACD2 referred to the S-K threshold used in the SZC trials, then this should be clarified to avoid misunderstanding.	The text has been amended please see section 3.1 of the final appraisal document.
			Section 3.4, page 9	• The committee was aware that an NIHR-funded trial is evaluating the potential benefit of withdrawing ACE inhibitors and ARBs in people with stage 4 or 5 chronic kidney disease.	• As responded to by Dr McCafferty at the second Committee meeting, this NIHR-funded trial aims to test the hypothesis that RAASi induced reduction in GFR could adversely influence outcomes and management e.g. earlier instigation of dialysis. This study has not reported and therefore implications are currently unknown and are of no importance to a decision on hyperkalaemia management. • The positioning of SZC is to support RAASi where RAASi is clinically indicated.	This study was highlighted to emphasise that the balance of benefits and risks of RAAS inhibitors should be considered. It is no longer referred to in the final appraisal document.
			Section 3.4, page 9	• The British Society for Heart Failure's response to consultation and a clinical expert present at the second meeting both noted that RAAS inhibitors may be of greater benefit in people with heart failure with reduced ejection fraction compared with people with preserved ejection fraction.	• AstraZeneca would like to clarify that RAASi therapy is not indicated in HFpEF patients, and that we are positioning SZC as a treatment option where RAASi therapy is proven to give mortality and disease modification benefits such as HFrEF.	The text has been amended. Please see section 3.4 of the final appraisal document.
			Section	• The clinical experts explained that	• Based on clinical expert	

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			3.5, page 10	they consider the diet worth trying, that it is recommended by NICE, and that it lowers serum potassium compared with an unrestricted diet.	engagement, dietitian-supported low potassium diets are only used by patients with later stage CKD in UK clinical practice. For HF patients, only high-level advice on low potassium diets are provided which is of no proven benefit.	No action required.
			Section 3.5, page 10	• The committee concluded that sodium zirconium cyclosilicate is unlikely to replace a low-potassium diet.	• SZC is not positioned to replace a low potassium diet. • SZC is positioned to be used alongside low potassium diet where clinically appropriate, when a strict low potassium diet is not possible, or when low potassium diet does not work. • SZC may allow patients to have a less restrictive low potassium diet.	The text has been amended. Please see section 3.7 of the final appraisal document.
			Section 3.7, page 11	• The company proposed that sodium zirconium cyclosilicate would be used: o In an outpatient setting, as an alternative to stopping RAAS inhibitors and a strict low-potassium diet to manage chronic hyperkalaemia and prevent it developing into life-threatening hyperkalaemia • In people with hyperkalaemia identified through routine monitoring; the clinical and patient experts did not expect sodium zirconium cyclosilicate to replace the need for a low-potassium diet (see section 3.5).		
			Section 3.11, page 16	• The committee also noted the wording from the European Medicines Agency that the risk of intestinal perforation is currently unknown but has been reported with polymers that act in the gastrointestinal tract. The committee concluded that sodium zirconium cyclosilicate is associated with adverse effects.	• Intestinal perforation is a complication associated with polymers/sorbitol and has therefore been added to the SmPC as a precaution. There is no biological rationale for this complication to occur with SZC, and clinical trials show that gastrointestinal side effects are not seen more commonly with SZC (ZS-004: 6.7% [5 g OD] and 2.0% [10 g OD] of patients in the	This text has been removed. Please see section 3.11 of the final appraisal document.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row			NICE Response Please respond to each comment
					maintenance phase) compared to placebo (ZS-004: 14.1% of patients during the maintenance phase).We would also like to clarify that SZC is not a polymer, unlike calcium resonium. • The SmPC states: *"The risk for intestinal perforation with the use of Lokelma is currently unknown. No events of intestinal perforation have been reported with Lokelma. Since intestinal perforation has been reported 4 with polymers that act in the gastrointestinal tract, specific attention should be paid to signs and symptoms related to intestinal perforation."*	The text has been amended. Please see section 3.19 of the final appraisal document.
			Section 3.23, page 28	• The patient experts stated that, if the company had shown evidence for these benefits, then sodium zirconium cyclosilicate would be innovative.	• This sentence is misleading as it does not represent our understanding of the views expressed by the patient expert at the first and second Committee meetings. This patient expert should be specifically asked the question about innovation to ensure ACD accurately represents their views.	
24	Consultee (company)	AstraZeneca	**8 References** 1. Montford JR, Linas S. How Dangerous Is Hyperkalemia? *J Am Soc Nephrol*. 2017;28(11):3155-65. 2. Einhorn LM, Zhan M, Hsu VD, Walker LD, Moen MF, Seliger SL, et al. The Frequency of Hyperkalemia and Its Significance in Chronic Kidney Disease. *Arch Intern Med*. 2009;169(12):1156-62. 3. Thomsen RW, Nicolaisen SK, Hasvold P, Garcia-Sanchez R, Pedersen L, Adelborg K, 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). 4. Horne L, Ashfaq A, MacLachlan S, Sinsakul M, Qin L, Locasale R. MP370 Incidence of			Comment noted.

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			and Risk Factor for Hyperkalemia in Adults in the UK (Poster). *Nephrol Dial Transplant*. 2017;32(Suppl 3):iii563. 5. Thomsen RW, Nicolaisen SK, Hasvold P, Sanchez RG, Pedersen L, Adelborg K, 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. Nilsson E, Gasparini A, Arnlov J, Xu H, Henriksson KM, Coresh J, et al. Incidence and determinants of hyperkalemia and hypokalemia in a large healthcare system. *Int J Cardiol*. 2017. 7. Thomsen R, Nicolaisen S, Adelborg K, Svensson E, Hasvold P, Palaka E, et al. Hyperkalaemia in people with diabetes: occurrence, risk factors and outcomes in a Danish population-based cohort study. *Diabetic Medicine*. 2018. 8. Dunn JD, benton WW, Orozco-Torrenter E, Adamson RT. The Burden of Hyperkalemia in Patients with Cardiovascular and Renal Disease. *The American Journal of Managed Care*. 2015;21(15):S307-S15. 9. National Institute of Clinical and Care Excellence (NICE). Chronic kidney disease in adults: assessment and management [CG182] 2015 [Available from: https://www.nice.org.uk/guidance/cg182 Accessed March 2019]. 10. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, 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):2129-200. 11. 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. 12. Rosano GMC, Tamargo J, Kjeldsen KP, Lainscak M, Agewall S, Anker SD, 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):180-8. 13. 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. 14. Alfonzo A, Soar J, MacTier R, Fox J, Shillday I, Nolan J, et al. Clinical Practice Guidelines, Treatment of Acute Hyperkalaemia in Adults, UK Renal Association 2014 [Available from: https://renal.org/wp-content/uploads/2017/06/hyperkalaemia-guideline-1.pdf Accessed March 2019]. 15. Maggioni AP, Dahlstrom U, Filippatos G, Chioncel O, Crespo Leiro M, Drozdz J, et al. EURObservational Research Programme: regional differences and 1-year follow-up results of	

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			the Heart Failure Pilot Survey (ESC-HF Pilot). *European journal of heart failure*. 2013;15(7):808-17. 16. Gheorghiade M, Albert NM, Curtis AB, Thomas Heywood J, McBride ML, Inge PJ, 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. 17. Shirazian S, Grant CD, Mujeeb S, Sharif S, Kumari P, Bhagat M, 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):510-5. 18. Molnar MZ, Kalantar-Zadeh K, Lott EH, Lu JL, Malakauskas SM, Ma JZ, 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):650-8. 19. 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. 20. Jun M, Jardine MJ, Perkovic V, Pilard Q, Billot L, Rodgers A, et al. Hyperkalemia and renin-angiotensin aldosterone system inhibitor therapy in chronic kidney disease: A general practice-based, observational study. *PloS one*. 2019;14(3):e0213192. 21. 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):S212-20. 22. Qin L, McEwan P, Evans M, Horne L, Grandy S. TH-PO1102 Relationship Between Serum Potassium and Dose Modification and Discontinuation of Renin-Angiotensin-System Inhibitors in UK Patients with Heart Failure (Poster). American Society of Nephrology2017. 23. 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 Cardiology2017. 24. AstraZeneca. 2018. Response to ACD Document. 25. 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. 26. 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. 27. Fudim M, Grodin JL, Mentz RJ. Hyperkalemia in Heart Failure: Probably Not O"K". *J Am Heart Assoc*. 2018;7(11). 28. Vardeny O, Claggett B, Anand I, Rossignol P, Desai AS, Zannad F, et al. Incidence,	

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			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):573-9. 29. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *New England Journal of Medicine*. 2011;364(1):11-21. 30. 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(5):313-20. 31. 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):1868-74. 32. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, et al. Spironolactone for heart failure with preserved ejection fraction. *New England Journal of Medicine*. 2014;370(15):1383-92.	
25	Consultee (professional organisation)	British Society for Heart Failure (BSH)	The BSH agrees with the recommendation to make sodium zirconium cyclosilicate available for the treatment of hyperkalaemia in the emergency setting.The BSH recognises the paucity of information from clinical trials available to inform the potential for wider use of this agent	Thank you for your comments. Comment noted.
26	Consultee (professional organisation)	BSH	Recommendation 1.1: The BSH agrees with the NICE TA Committee that there is clinical need for effective treatment of hyperkalaemia.	Comment noted.
27	Consultee (professional organisation)	BSH	3.1 Treatment of hyperkalaemia: The BSH agrees with the comment that treatment of elevated K^+ is often instigated at lower levels in patients with heart failure compared to patients with chronic kidney disease.	Comment noted.
28	Consultee (professional organisation)	BSH	3.3 / 3.4 People with chronic hyperkalaemia would welcome an alternative to stopping RAAS inhibitor The BSH agrees strongly that maintenance of RAASi agents is preferable in patients with heart failure (with reduced left ventricular function), given the disease-modifying properties of these agents in this setting.	Comment noted.
29	Consultee (professional organisation)	BSH	3.4 The BSH is concerned that this section has the potential to be misleading. There are multiple placebo-controlled, clinical trials demonstrating the prognostic benefit of RAASi agents in patients with reduced left ventricular function, and none showing efficacy in patients with heart failure with preserved left ventricular function. As it stands at the moment (RAAS inhibitors may	Comment noted. The text has been amended. Please see

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			be of greater benefit in people with heart failure with reduced ejection fraction compared with people with preserved ejection fraction.”…..”) the ACD implies there is some doubt regarding this differentiation.	section 3.4 of the final appraisal document.
30	Consultee (professional organisation)	BSH	3.10 It is not clear whether lowering serum potassium is beneficial in chronic hyperkalaemia. The BSH recognises the paucity of trials-based evidence around this question. The BSH wishes to comment that reduction / withdrawal of RAASi agents due to elevated K^+ in patients with heart failure is a major factor limiting the use of these agents in clinical practice, thus denying the prognostic benefits of these agents to patients.	Comment noted.
31	Consultee (professional organisation)	BSH	3. Stopping RAAS inhibitors likely increases the risk of death, hospitalisation and disease progression: The BSH agrees with this comment with regard to patients with heart failure with reduced left ventricular ejection function, and that all attempts should be made to maintain treatment with these agents in this patient group.	Comment noted.
32	Consultee (professional organisation)	Renal Association (endorsed by Royal College of Physicians [RCP])	We strongly support the revised use of sodium zirconium cyclosilicate for treating hyperkalaemia in those patients with Chronic Kidney Disease and a Potassium or greater than 6.0 mmol/L and those patients with heart failure with a potassium of >5.5 mmol/L with a view of reducing the potassium as a adjunct to current available therapies in the first 72 hours acutely and to a maximum of 28 days. The publication of the recent NHS improvement Patient safety alert in August 2018 from the National reporting and learning System to all NHS Trusts in the UK, highlighted that there was approximately 1 death per month as a result of hyperkalaemia in the last 3 years reviewed (Patients Safety improvement.nhs.uk/resources/patient-safety-alerts). It mandated that urgent action is required by all NHS organisations to deal with this unnecessary level of deaths. This is particularity pertinent given that patients with known or indeed unknown chronic kidney disease and hyperkalaemia have a 10 fold increased risk of mortality in the next 24 hours (Einhorn LM *et al. Arch Intern Med* 2009;169:1156–62). Therefore this additional therapy offers a viable solution.	Thank you for your comments. Comment noted.
33	Consultee (professional organisation)	Renal Association (endorsed by RCP)	This recommended area of use represents an area lacking in any new therapeutic option that is tolerable – the 10g dose used in a suspension of water fulfils this requirement. We recommend its introduction in the NHS.	Comment noted.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
34	Consultee (professional organisation)	Renal Association (endorsed by RCP)	We agree that indefinite use is not appropriate given that currently the data on potassium and mortality is based on observational data, however with up to 40% of patients with chronic kidney disease (1); 50% with chronic heart failure (2); 15% with diabetes (3) and 10% with resistant hypertension (4) developing hyperkalaemia with will require careful thought to reduce the burden of disease and impact on health care by a preventative approach which we would anticipate would lead to benefits in the longer term on minimising proteinuria; delaying renal progression from optimal ACEI use, at least in those with CKD stages 3b or better and in diabetics in line with both NICE and KDIGO recommendations on the use of ACEi/ARB therapy (5, 6). 1. Kovesday CP. *Nat Rev Nephrol.* 2014;10:653–662; 2. Vardeny O, et al. *Circ Heart Fail.* 2014;7:573–579; 3. Jarman PR, et al. *Postgrad Med J.* 1995;839:551–552; 4. Chang AR, et al. *J Am Heart Assoc.* 2016;67:1181–1188 5. NICE. *Chronic kidney disease in adults: assessment and management* [online] 2014. Available at: https://www.nice.org.uk/guidance/cg182. 6. KDIGO. *Kidney Int Suppl.* 2013;3:5–14	Comment noted. SZC has been recommended in both the outpatient and emergency care settings, please see section 1.1 of the final appraisal document.
35	Consultee (professional organisation)	Renal Association (endorsed by RCP)	Although the latest recommendation is to discontinue the potassium binder after 28 days, we feel that it will be very important to collect data on (a) Recurrent requirements to issue 28 day prescriptions of the potassium binder (b) Further hospitalisations for hyperkalaemia (health economics very important here) (c) Whether ACE-I, ARB or MRA are re-introduced or not after the episode of hyperkalaemia has been addressed The latter point is of importance in nephrology as there is good evidence that these agents are of benefit in terms of CKD progression and cardiovascular events. However, we recognise that the importance of continued use of these agents may be even more greatly emphasised in cardiology, especially in post-MI and heart failure patients.	Comment noted. SZC has been recommended in both the outpatient and emergency care settings, please see section 1.1 of the final appraisal document. The committee has made research recommendations which recognise the importance on collecting further data on SZC. Please see

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				section 5 of the final appraisal document.
36	Web comment (NHS professional)	N/A	**Answers to questions from NICE** Has all of the relevant evidence been taken into account? — Yes in so far as it is available or likely to become available Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? — Yes in so far as data that is currently available Are the recommendations sound and a suitable basis for guidance to the NHS? — Please see my comments on the recommendations as I do not believe that they are sound	Thank you for your comments. Comment noted.
37	Web comment (NHS professional)	N/A	I wish to make a submission as part of your consultation on your recommendations for the use of sodium zirconium cyclosilicate (SZC) for treating hyperkalaemia. I make this submission as a practising nephrologist who has an interest in the management of diabetes (of whom a the vast majority of the patients I care for also have heart failure). I am also a member of the editorial board of the Renal Association and Association of British Clinical Diabetologists joint writing group on guidelines for the management of diabetes. I am pleased that you are approving SZC for the management of hyperkalaemia in emergency settings although recognise units will need to have clear guidelines as to how this agent is utilised. I am however concerned by the current recommendation in relation to the chronic use of this agent and most particularly in patients with heart failure and/or chronic kidney disease in the context of diabetes in whom the presence of hyperkalaemia restricts the ability to provide an effective dose of an inhibitor of the renin angiotensin system. The presence of hyperkalaemia in these patients is not rare and there are a significant number of these patients who are unable to tolerate inhibitors of the renin angiotensin system due to hyperkalaemia. Even in our clinic where we take steps to ameliorate hyperkalaemia using low	Comment noted. SZC has been recommended in both the outpatient and emergency care settings, please see section 1.1 of the final appraisal document. The committee has made research recommendations which recognise the importance on collecting further data on SZC. Please see section 5 of the final appraisal document.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			potassium diet's and management of bicarbonate we have found that there are still approximately 20% of our patients who are either not on a renin angiotensin system inhibitor or on sub-optimal doses of these agents. We have also recently been amalgamating our guidelines with our colleagues in cardiology and have appreciated the even more robust stance in relation to the use of inhibitors of the renin angiotensin system in heart failure because of the clear benefits in relation to life expectancy and quality of life. You are correct to point out that there is no outcome data on the use of SZC in patients with heart failure or kidney disease but I believe it is an entirely inappropriate demand to suggest that a decision would depend on a study in this context. This would require a study of equivalent to the original studies undertaken on ramipril in heart failure and angiotensin 2 inhibitors in diabetic kidney disease but having to recruit from a smaller base. It is almost certainly that such data would be impossible to obtain or take very many years to complete such a study. What we do know is the data on the benefits of inhibitors of the renin angiotensin system and the lack of any recognisable adverse events in patients appropriately treated with SZC or indeed any theoretical significant adverse event that might reverse the beneficial effects of the renin angiotensin system inhibitors. I therefore urge you to consider how we might provide the potential benefits of this agent to our patients as early as possible rather than leave them on sub-optimal treatment and at an increased risk of both progression of kidney disease and death from heart failure. What we need are guidelines that inform primary and secondary care about when to use these agents in the context of low potassium diets and management of bicarbonate levels and how we use these drugs safely and effectively in the longer term.	
38	Web comment (NHS professional)	N/A	Has all of the relevant evidence been taken into account? — yes Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? — yes, but see my comment on calcium resonium	Thank you for your comments. Comment noted.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Are the recommendations sound and a suitable basis for guidance to the NHS? — see my comment on 1.1 suggesting new wording of setting for use Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? — no	
39	Web comment (NHS professional)	N/A	Recommendation 1.1 I suggest review of the phrase ""emergency care setting."" It may be taken to restrict use to A&E and related settings. I think ZSC should be available for hyperkalaemia requiring urgent treatment in any setting where it will be of benefit. Examples would include inpatient hyperkalaemia, pre inter-hospital transfer for or with hyperkalaemia, being admitted from clinic for treatment of hyperkalaemia etc. Suggest the phrase "Urgent treatment of hyperkalaemia in a secondary care setting." Section 3.11 Not all polymers are the same chemistry and so the link of certain polymers to GI tract perforation is not strictly evidence for an adverse effect of SZC. I think the current wording of 3.11 invites a false belief that there is such evidence. I would agree that careful monitoring and reporting of AE in patients given SZC is essential and there should be a particular focus on GI events. It is premature and maybe incorrect to describe SZC as causing adverse GI tract events. Sections 3.12 to 3.14 I agree that we have to be very careful not to deduce cause and effect from observational data	Comment noted. SZC has been recommended in both the outpatient and emergency care settings, please see section 1.1 of the final appraisal document. This text has been removed. Please see section 3.11 of the final appraisal document. The committee has made research

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			showing associations. I also agree that there is no prospective controlled study showing patient benefit from outpatient treatment with SZC. I think we urgently need clarity on this as the possible benefits of SZC are great especially in providing more access to optimum RAAS therapy where it is evidence based. I suggest the company should as a priority address this with clinical studies. A well conducted study showing that SZC does allow more patients to receive optimum RAAS would be of great value and should not be too hard to deliver. It would go a long way to convince clinicians of the value of SZC. A larger study looking at patient outcomes directly remains ethical in my view and should also be completed. Section 3.22 I agree that the current evidence does not allow reliable estimates of the cost per QUALY to be generated. A good way forward would be to generate prospective evidence about the size of the effect or SZC on optimum RAAS use. This can then be put in the model with some confidence. The QUALY cost result can then be tested for sensitivity to different assumptions about the underlying causal link between serum K and outcomes (including a worst case of no link). Section 3.23 I agree that the criteria for innovation my not have been met. However I think we need to remind ourselves of the lack of confidence in current oral treatments. The text refers to calcium resonium on many occasions. This is a really unpleasant and ineffective measure as anyone who has used it will attest. An effective oral agent would perhaps not be called innovative but it would be of huge benefit."	recommendations which recognise the importance on collecting further data on SZC. Please see section 5 of the final appraisal document. The relationship between serum potassium levels and adverse clinical outcomes was considered by the committee. Please see sections 3.13 and 3.16 of the final appraisal document.
40	Web comment (NHS professional)	N/A	Has all of the relevant evidence been taken into account? — The relevant evidences have been taken into account from reviewing the literature. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? — Partially. Are the recommendations sound and a suitable basis for guidance to the NHS? — Within reason and requires some modifications and review. Please refer to open comments	Thank you for your comments. Comment noted.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? No	
41	Web comment (NHS professional)	N/A	Dear Committee Team I would like to introduce myself as a Pharmacist Advanced Clinical Practitioner with a specialist interest in cardio-metabolic medicine in primary care. I am delighted to hear that the committee are recommending Sodium zirconium cyclosilicate for the treatment of hyperkalaemia in adult patients in an emergency setting. From reviewing the literature, there should be a recommendation in place for long term maintenance treatment of Sodium zirconium cyclosilicate in those patients where RASS inhibitor therapy has resulted in previous or new onset hyperkalaemia. This is particularly important for the management of underlying heart failure and/or chronic kidney disease. The current recommendation stipulates either stopping or reducing the dose of these agents. From reviewing real world data, in many cases these therapy agents are stopped due to the clinical complications associated with hyperkalaemia. The evidence for usage of RAAS inhibitor therapy is fundamental in the management of heart failure with reduced ejection fraction. Usage of Sodium zirconium cyclosilicate for episodic management of hyperkalaemia limits the clinicians ability to further up titrate RAAS inhibitor therapy where deemed clinically appropriate. This is because there would always remain concerns about the patient having re-occurring hyperkalaemia and poses even higher risk of developing life threatening arrhythmias in this patient population. With the ability to consider on-going maintenance therapy, it provides clinicians the opportunity to consider up titration and inhibit the neurohumoral response which is fundamental in heart failure management to improve	Comment noted. SZC has been recommended in both the outpatient and emergency care settings, please see section 1.1 of the final appraisal document. The committee has made research recommendations which recognise the importance on collecting further data on SZC. Please see section 5 of the final appraisal document.

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			quality of life, prevent hospital admissions and reduce mortality. I hope this has provided you with some insight from a primary care point of view and the potential benefits Sodium zirconium cyclosilicate can offer to those patients who benefit from RAAS inhibitor therapy agents and various other clinical scenarios which have been mentioned in your consultation.	

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 20 May 2019 **email:** TACommB@nice.org.uk

	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):	Pumping Marvellous Foundation
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**
Name of commentator person completing form:	[redacted]

Comment number	Comments
	Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	With respect, I am concerned that the committee still hasn't understood the enormity and grasped the challenges of managing the effects of prognostically beneficial triple therapy drugs that can cause increases in potassium levels.
2	The patient population is not large but to those that are affected this technology could help better management of RASI drugs which are the mainstay of HF guideline therapy. It is imperative to ensure that where possible the optimum dosage of RASI drugs is maintained or if down titrated in an emergency situation brought up to optimum levels as appropriately as soon as possible.
3	I agree that it will be useful in an emergency room situation and if the evidence suggests that the correct clinical decision to stop the technology is no more than 28 days then I agree with that. I don't however agree that it is just an emergency administered technology. As integrated teams are now promoted heavily (NHS Long Term Plan) the prescribing of the technology could be tightly managed by specialist MDT members, especially in heart failure who manage the most at risk patients, those on triple therapy. This would reduce the cost of a hospital admission or day care treatment. There is significant evidence of heart failure specialist nurses managing patients well and reducing unplanned hospital admissions.
4	As one of the experts indicated in the 2nd committee meeting this gives him an option, at the moment he has none.
5	I don't understand why the recommendation is just about treating at the point of emergency. Aren't we trying to keep people out hospital and managing peoples conditions better in the community with specialist MDT's
6	

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.
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- 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.

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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.

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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]

Comment number	Comments Insert each comment in a new row.

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	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	The BSH agrees with the recommendation to make sodium zirconium cyclosilicate available for the treatment of hyperkalaemia in the emergency setting.The BSH recognises the paucity of information from clinical trials available to inform the potential for wider use of this agent.
2	Recommendation 1.1: The BSH agrees with the NICE TA Committee that there is clinical need for effective treatment of hyperkalaemia.
3	3.1 Treatment of hyperkalaemia: The BSH agrees with the comment that treatment of elevated K^+ is often instigated at lower levels in patients with heart failure compared to patients with chronic kidney disease.
4	3.3 / 3.4 People with chronic hyperkalaemia would welcome an alternative to stopping RAAS inhibitor The BSH agrees strongly that maintenance of RAASi agents is preferable in patients with heart failure (with reduced left ventricular function), given the disease-modifying properties of these agents in this setting.
5	3.4 The BSH is concerned that this section has the potential to be misleading. There are multiple placebo-controlled, clinical trials demonstrating the prognostic benefit of RAASi agents in patients with reduced left ventricular function, and none showing efficacy in patients with heart failure with preserved left ventricular function. As it stands at the moment (RAAS inhibitors may be of greater benefit in people with heart failure with reduced ejection fraction compared with people with preserved ejection fraction.”…..”) the ACD implies there is some doubt regarding this differentiation.
6	3.10 It is not clear whether lowering serum potassium is beneficial in chronic hyperkalaemia. The BSH recognises the paucity of trials-based evidence around this question. The BSH wishes to comment that reduction / withdrawal of RAASi agents due to elevated K^+ in patients with heart failure is a major factor limiting the use of these agents in clinical practice, thus denying the prognostic benefits of these agents to patients.
7	3. Stopping RAAS inhibitors likely increases the risk of death, hospitalisation and disease progression: The BSH agrees with this comment with regard to patients with heart failure with reduced left ventricular ejection function, and that all attempts should be made to maintain treatment with these agents in this patient group.

Insert extra rows as needed

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
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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.	[Received funding to attend educational meetings and an investigator in the DIALYZE clinical STUDY in dialysis patients using set drug under evaluation]
Name of commentator person completing form:	[redacted]

Comment number	Comments
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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We strongly support the revised use of sodium zirconium cyclosilicate for treating hyperkalaemia in those patients with Chronic Kidney Disease and a Potassium or greater than 6.0 mmol/L and those patients with heart failure with a potassium of >5.5 mmol/L with a view of reducing the potassium as a adjunct to current available therapies in the first 72 hours acutely and to a maximum of 28 days. The publication of the recent NHS improvement Patient safety alert in August 2018 from the National reporting and learning System to all NHS Trusts in the UK, highlighted that there was approximately 1 death per month as a result of hyperkalaemia in the last 3 years reviewed (Patients Safety improvement.nhs.uk/resources/patient-safety-alerts). It mandated that urgent action is required by all NHS organisations to deal with this unnecessary level of deaths. This is particularity pertinent given that patients with known or indeed unknown chronic kidney disease and hyperkalaemia have a 10 fold increased risk of mortality in the next 24 hours (Einhorn LM *et al. Arch Intern Med* 2009;169:1156–62). Therefore this additional therapy offers a viable solution.
2	This recommended area of use represents an area lacking in any new therapeutic option that is tolerable – the 10g dose used in a suspension of water fulfils this requirement. We recommend its introduction in the NHS.
3	We agree that indefinite use is not appropriate given that currently the data on potassium and mortality is based on observational data, however with up to 40% of patients with chronic kidney disease (1); 50% with chronic heart failure (2); 15% with diabetes (3) and 10% with resistant hypertension (4) developing hyperkalaemia with will require careful thought to reduce the burden of disease and impact on health care by a preventative approach which we would anticipate would lead to benefits in the longer term on minimising proteinuria; delaying renal progression from optimal ACEI use, at least in those with CKD stages 3b or better and in diabetics in line with both NICE and KDIGO recommendations on the use of ACEi/ARB therapy (5, 6). 1. Kovesday CP. *Nat Rev Nephrol.* 2014;10:653–662; 2. Vardeny O, et al. *Circ Heart Fail.* 2014;7:573–579; 3. Jarman PR, et al. *Postgrad Med J.* 1995;839:551–552; 4. Chang AR, et al. *J Am Heart Assoc.* 2016;67:1181–1188 5. NICE. *Chronic kidney disease in adults: assessment and management* [online] 2014. Available at: https://www.nice.org.uk/guidance/cg182. 6. KDIGO. *Kidney Int Suppl.* 2013;3:5–14
4	Although the latest recommendation is to discontinue the potassium binder after 28 days, we feel that it will be very important to collect data on (a) Recurrent requirements to issue 28 day prescriptions of the potassium binder (b) Further hospitalisations for hyperkalaemia (health economics very important here) (c) Whether ACE-I, ARB or MRA are re-introduced or not after the episode of hyperkalaemia has been addressed The latter point is of importance in nephrology as there is good evidence that these agents are of benefit in terms of CKD progression and cardiovascular events. However, we recognise that the importance of continued use of these agents may be even more greatly emphasised in cardiology, especially in post-MI and heart failure patients.
5	

Insert extra rows as needed

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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 20 May 2019 **email:** TACommB@nice.org.uk

- 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.

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Comments on the ACD submitted through the NICE website

Name	[redacted]
Represents and organisation?	no

Answers to questions from NICE

Has all of the relevant evidence been taken into account?	Yes in so far as it is available or likely to become available
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?	Yes in so far as data that is currently available
Are the recommendations sound and a suitable basis for guidance to the NHS?	Please see my comments on the recommendations as I do not believe that they are sound

Comments

I wish to make a submission as part of your consultation on your recommendations for the use of sodium zirconium cyclosilicate (SZC) for treating hyperkalaemia. I make this submission as a practising nephrologist who has an interest in the management of diabetes (of whom a the vast majority of the patients I care for also have heart failure). I am also a member of the editorial board of the Renal Association and Association of British Clinical Diabetologists joint writing group on guidelines for the management of diabetes.

I am pleased that you are approving SZC for the management of hyperkalaemia in emergency settings although recognise units will need to have clear guidelines as to how this agent is utilised.

I am however concerned by the current recommendation in relation to the chronic use of this agent and most particularly in patients with heart failure and/or chronic kidney disease in the context of diabetes in whom the presence of hyperkalaemia restricts the ability to provide an effective dose of an inhibitor of the renin angiotensin system.

The presence of hyperkalaemia in these patients is not rare and there are a significant number of these patients who are unable to tolerate inhibitors of the renin angiotensin system due to hyperkalaemia. Even in our clinic where we take steps to ameliorate hyperkalaemia using low potassium diet's and management of bicarbonate we have found that there are still approximately 20% of our patients who are either not on a renin angiotensin system inhibitor or on sub-optimal doses of these agents. We have also recently been amalgamating our guidelines with our colleagues in cardiology and have appreciated the even more robust stance in relation to the use of inhibitors of the renin angiotensin system in heart failure because of the clear benefits in relation to life expectancy and quality of life.

You are correct to point out that there is no outcome data on the use of SZC in patients with heart failure or kidney disease but I believe it is an entirely inappropriate demand to suggest that a decision would depend on a study in this context. This would require a study of equivalent to the original studies undertaken on ramipril in heart failure and angiotensin 2 inhibitors in diabetic kidney disease but having to recruit from a smaller base. It is almost certainly that such data would be impossible to obtain or take very many years to complete such a study. What we do know is the data on the benefits of inhibitors of the renin angiotensin system and the lack of any recognisable adverse events in patients appropriately treated with SZC or indeed any theoretical significant adverse event that might reverse the beneficial effects of the renin angiotensin system inhibitors.

I therefore urge you to consider how we might provide the potential benefits of this agent to our patients as early as possible rather than leave them on sub-optimal treatment and at an increased risk of both progression of kidney disease and death from heart failure.

What we need are guidelines that inform primary and secondary care about when to use these agents in the context of low potassium diets and management of bicarbonate levels and how we use these drugs safely and effectively in the longer term."

Name	[redacted]
Represents and organisation?	no

Answers to questions from NICE

Has all of the relevant evidence been taken into account?	yes
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?	yes, but see my comment on calcium resonium
Are the recommendations sound and a suitable basis for guidance to the NHS?	see my comment on 1.1 suggesting new wording of setting for use
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	no

Comments

Recommendation 1.1
I suggest review of the phrase ""emergency care setting."" It may be taken to restrict use to A&E and related settings. I think ZSC should be available for hyperkalaemia requiring urgent treatment in any setting where it will be of benefit. Examples would include inpatient hyperkalaemia, pre inter-hospital transfer for or with hyperkalaemia, being admitted from clinic for treatment of hyperkalaemia etc. Suggest the phrase
"Urgent treatment of hyperkalaemia in a secondary care setting."

Section 3.11
Not all polymers are the same chemistry and so the link of certain polymers to GI tract perforation is not strictly evidence for an adverse effect of SZC. I think the current wording of 3.11 invites a false belief that there is such evidence. I would agree that careful monitoring and reporting of AE in patients given SZC is essential and there should be a particular focus on GI events. It is premature and maybe incorrect to describe SZC as causing adverse GI tract events.

Sections 3.12 to 3.14
I agree that we have to be very careful not to deduce cause and effect from observational data showing associations. I also agree that there is no prospective controlled study showing patient benefit from outpatient treatment with SZC. I think we urgently need clarity on this as the possible benefits of SZC are great especially in providing more access to optimum RAAS therapy where it is evidence based. I suggest the company should as a priority address this with clinical studies. A well conducted study showing that SZC does allow more patients to receive optimum RAAS would be of great value and should not be too hard to deliver. It would go a long way to convince clinicians of the value of SZC. A larger study looking at patient outcomes directly remains ethical in my view and should also be completed.

Section 3.22
I agree that the current evidence does not allow reliable estimates of the cost per QUALY to be generated. A good way forward would be to generate prospective evidence about the size of the effect or SZC on optimum RAAS use. This can then be put in the model with some confidence. The QUALY cost result can then be tested for sensitivity to different assumptions about the underlying causal link between serum K and outcomes (including a worst case of no link).

Section 3.23
I agree that the criteria for innovation my not have been met. However I think we need to remind ourselves of the lack of confidence in current oral treatments. The text refers to calcium resonium on many occasions. This is a really unpleasant and ineffective measure as anyone who has used it will attest. An effective oral agent would perhaps not be called innovative but it would be of huge benefit."

Name	[redacted]
Represents and organisation?	no

Answers to questions from NICE

Has all of the relevant evidence been taken into account?	The relevant evidences have been taken into account from reviewing the literature.
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?	Partially.
Are the recommendations sound and a suitable basis for guidance to the NHS?	Within reason and requires some modifications and review. Please refer to open comments
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	No

Comments

Dear Committee Team

I would like to introduce myself as a Pharmacist Advanced Clinical Practitioner with a specialist interest in cardio-metabolic medicine in primary care. I am delighted to hear that the committee are recommending Sodium zirconium cyclosilicate for the treatment of hyperkalaemia in adult patients in an emergency setting.

From reviewing the literature, there should be a recommendation in place for long term maintenance treatment of Sodium zirconium cyclosilicate in those patients where RASS inhibitor therapy has resulted in previous or new onset hyperkalaemia. This is particularly important for the management of underlying heart failure and/or chronic kidney disease. The current recommendation stipulates either stopping or reducing the dose of these agents. From reviewing real world data, in many cases these therapy agents are stopped due to the clinical complications associated with hyperkalaemia.

The evidence for usage of RAAS inhibitor therapy is fundamental in the management of heart failure with reduced ejection fraction. Usage of Sodium zirconium cyclosilicate for episodic management of hyperkalaemia limits the clinicians ability to further up titrate RAAS inhibitor therapy where deemed clinically appropriate. This is because there would always remain concerns about the patient having re-occurring hyperkalaemia and poses even higher risk of developing life threatening arrhythmias in this patient population. With the ability to consider on-going maintenance therapy, it provides clinicians the opportunity to consider up titration and inhibit the neurohumoral response which is fundamental in heart

failure management to improve quality of life, prevent hospital admissions and reduce mortality.

I hope this has provided you with some insight from a primary care point of view and the potential benefits Sodium zirconium cyclosilicate can offer to those patients who benefit from RAAS inhibitor therapy agents and various other clinical scenarios which have been mentioned in your consultation. Should you require any further information please do not hesitate to contact me via e-mail: [redacted].

Kind Regards
[redacted]
Pharmacist Advanced Clinical Practitioner
Medicines Management, Primary Care
[redacted]

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	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 welcome the positive draft recommendation by the Committee in the second appraisal consultation document (ACD2) to use sodium zirconium cyclosilicate (SZC) in adults in the emergency care setting for up to 28 days. In response to the ACD2, we would like to stress the high unmet need for patients with hyperkalaema in the outpatient setting (in addition to the emergency care setting) and the volume of evidence supporting the relationships between serum potassium (S-K) and adverse clinical outcomes in these patients. We would like to ask the committee to kindly consider the following key points:

1. **There is a significant need to provide an alternative treatment option to the down-titration and discontinuation of guideline recommended cardio-renal protective RAASi medication for the treatment of hyperkalaemia in the outpatient setting**

   Current treatment options for the management of hyperkalaemia in the outpatient setting are limited to down-titration or discontinuation of cardio-renal protective RAASi therapy. As such, hyperkalaemia is a barrier to prescribing and optimising RAASi therapies in CKD and HF patients, leading to worse prognosis and higher risk for adverse cardio-renal events due to suboptimal RAASi therapy. Therefore, in addition to the emergency care setting, there is also a high unmet need for alternative treatment options to manage hyperkalaemia in the outpatient setting to enable a sustained lowering of S-K whilst allowing patients to maintain cardio-renal protective RAASi therapy.

2. **Systematically identified evidence, UK clinical practice, and NICE clinical guidelines all support a relationship between S-K and adverse clinical outcomes. It is therefore reasonable to apply this relationship for fair and balanced decision making**

   The evidence on the relationships between S-K and adverse clinical outcomes previously submitted to the Committee were identified via a systematic literature review, and all studies consistently support the U-shaped relationships whereby S-K levels below and above normokalaemia are associated with higher risks of adverse clinical outcomes. The Committee has also acknowledged in the ACD2 that relationships between S-K and adverse clinical outcomes are biologically plausible. Additionally, the ERG has stated that weight should be given to the U-shaped S-K relationships with adverse clinical outcomes "*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."* Furthermore, the ERG has also clearly stated that the scenario analyses excluding the relationship between S-K and adverse clinical outcomes "*should be viewed as exploratory rather than representing a most plausible ICER*". As such, whilst AstraZeneca acknowledge that a degree of residual confounding may affect the reported association between S-K and adverse clinical outcomes, we maintain that the best use of available evidence would be to capture the relationships between S-K and adverse clinical outcomes in the base case cost-effectiveness analyses, and explore the uncertainty with potential alternative assumptions in scenario analyses. In the scenarios where the relationship between S-K and adverse clinical outcomes have been entirely removed, as requested by the Committee, there are substantial <u>uncaptured</u> benefits and therefore the ICERs would not represent the most plausible ICERs.

3. **AstraZeneca is providing a patient access scheme (PAS), consisting of a [redacted] confidential discount to the list price of the 10 g dose, to improve the cost-effectiveness of SZC in the outpatient setting**

   The confidential PAS price of [redacted], after a [redacted] discount, for the 10 g dose will only be available if SZC is recommended in the outpatient setting, in addition to the emergency care setting, as SZC has already been deemed to be cost-effective in the emergency care setting at the current price (current draft recommendation). If SZC is recommended in the outpatient

setting, the PAS would be available both to patients in the emergency care setting and in the outpatient setting.

4. **With the [redacted] confidential PAS discount, SZC is cost-effective versus standard care, with ICERs of [redacted]/QALY and [redacted]/QALY in HF and CKD patients, respectively**

   The differences between the updated company ACD2 base cases and the ERG base cases are primarily driven by the confidential PAS discount and by the higher S-K treatment threshold in the HF population. The treatment threshold in the HF population has been increased to S-K ≥6.0 mmol/L to address the Committee's comment that some clinicians may wish to treat hyperkalaemia at higher S-K thresholds than previously modelled. The results from the probabilistic sensitivity analyses show that there is an [redacted] and [redacted] likelihood that SZC is cost-effective at ICER thresholds of £20,000–£30,000/QALY in the HF and CKD populations, respectively. Exploratory scenario analyses show that SZC is still cost-effective at ICERs of [redacted]/QALY and [redacted]/QALY for HF and CKD, respectively, even when the relationships between S-K and adverse clinical outcomes are reduced by 50%. In an extreme scenario with substantial uncaptured benefits, where the relationships between S-K and adverse clinical outcomes are entirely removed, the ICERs are [redacted]/QALY and [redacted]/QALY for HF and CKD patients, respectively. As advised by the NICE technical team, the ICER threshold for decision making should be towards the upper end of the £20,000-£30,000/QALY range when there are uncaptured benefits in the cost-effectiveness analysis. The base case analyses and the scenario analyses clearly demonstrate the cost-effectiveness of SZC, with the [redacted] confidential PAS discount, even when uncertainty in the relationships between S-K and adverse clinical outcomes has been accounted for.

Based on the above points and the detailed response to the ACD2 provided below, AstraZeneca urge the Committee to consider the strong case for extending the positive draft recommendation for SZC to patients with hyperkalaemia in the outpatient setting, to ensure that clinicians and patients have access to cost-effective SZC treatment and to address the current high unmet need for an effective treatment option for these patients.

Yours sincerely,

Elena Tricca
Market Access & Government Affairs Director

Executive summary

1. **There is a significant need to provide an alternative treatment option to the down-titration and discontinuation of guideline recommended cardio-renal protective RAASi medication for the treatment of hyperkalaemia in the outpatient setting**

   - Renin-angiotensin-aldosterone system inhibitors (RAASi) are the mainstay treatment options for the optimal management of patients with heart failure (HF) and/or chronic kidney disease (CKD) due to their proven cardio-renal protective effects. However, RAASi therapy often cause RAASi-induced hyperkalaemia.[1-8]
   - Despite the increased risk of developing hyperkalaemia, RAASi therapy is recommended in HF and CKD patients by clinical guidelines/consensus statements, including those published by NICE, 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.[9-11]
   - Current treatment options for the management of hyperkalaemia are limited. In the outpatient setting, the same guidelines which recommend treatment with RAASi therapy typically recommend a combination of down-titration and/or discontinuation of RAASi therapy for the management of hyperkalaemia.[9-14]
   - Hyperkalaemia is often viewed as a barrier to prescribing and optimising RAASi therapies in CKD and HF patients,[15-18] and therefore despite being recommended for use, RAASi therapy is often not re-instated following an episode of hyperkalaemia at or following discharge.[19-22] This in turn further exacerbates the loss of cardio-renal protection from RAASi therapy.[12, 19, 23]
   - Therefore, in addition to the emergency care setting for the management of hyperkalaemia, there is also a need to improve longer term management in an outpatient setting to enable a sustained lowering of serum potassium (S-K) whilst allowing patients to maintain RAASi where it would otherwise be reduced or stopped due to hyperkalaemia; thereby reducing the morbidity and mortality risks of hyperkalaemia and enabling the simultaneous cardio-renal protective effects of RAASi therapy.

2. **AstraZeneca do not consider clinically relevant hyperkalaemia to be defined as a S-K >5.0 mmol/L**

   - AstraZeneca consider the current wording used in the ACD to be inaccurate and misleading. AstraZeneca do not consider clinically relevant hyperkalaemia in the UK to be defined as a S-K >5.0 mmol/L, but instead recognise that treatment is likely to be initiated in HF and CKD patients with S-K ≥5.5 mmol/L and S-K ≥6.0 mmol/L, respectively.
   - Whilst the clinical trial programme enrolled patients with baseline S-K levels below the UK treatment thresholds, AstraZeneca have aligned the clinical and cost-effectiveness analyses to S-K thresholds relevant to UK clinical practice.
   - Therefore, it would be more appropriate to recognise that whilst the clinical trial programme included patients with a S-K above 5.0 mmol/L, AstraZeneca agree that patients in UK clinical practice are not treated until higher S-K levels of 5.5 or 6.0 mmol/L.
   - Furthermore, AstraZeneca note the Committee's comment from the second Committee meeting that some clinicians may treat HF patients at higher S-K thresholds than previously modelled. Therefore, the effect of increasing the treatment threshold to S-K ≥6.0 mmol/L in the cost-effectiveness analysis has been included as part of the updated cost-effectiveness analysis (see Section 6).

3. **Systematically identified evidence, UK clinical practice, and NICE clinical guidelines all support a relationship between S-K and adverse clinical outcomes. It is therefore reasonable to apply this relationship for fair and balanced decision making**

   - AstraZeneca previously addressed the Committee's concerns relating to the way in which evidence was identified to support the relationships between S-K and adverse clinical outcomes by conducting a systematic review of the evidence base.
   - The systematic literature review identified 59 potentially relevant studies, which consistently reported U-shaped associations between S-K and adverse clinical outcomes, irrespective of geographical location or comorbid status.

- AstraZeneca have conducted a thorough review of the evidence to ensure that the most appropriate data sources have been used in the cost-effectiveness model to mitigate the risk of potential confounding, including time-dependent confounding (see Section 3.3). Therefore, AstraZeneca believe that a robust approach has been taken to ensure the relationships have been appropriately modelled to support decision making.
- Despite the Committee recognising that the relationships between S-K and adverse clinical outcomes are biologically plausible, the Committee has asked to see a scenario where SZC is cost-effective in the complete absence of relationships between S-K and adverse clinical outcomes. This contradicts NICE clinical guideline CG182 which recommends the cautious initiation or complete discontinuation of RAASi therapy at high S-K levels to avoid hyperkalaemia. If there were no relationships, there would be no clinical rationale for this clinical recommendation.
- Therefore, AstraZeneca believe that it is perverse and against the evidence submitted to NICE to assume that no relationships exists between S-K and adverse clinical outcomes and to use this as the basis for decision making.

4. **Post-hoc analyses show the risk of hypokalaemia to be low with SZC in patient sub-groups with baseline S-K levels relevant to UK clinical practice**

- To better reflect UK clinical practice and in response to the first ACD (ACD1), AstraZeneca amended the treatment threshold treatment to S-K ≥6.0 mmol/L for patients with CKD, whilst the treatment threshold was kept at S-K ≥5.5 mmol/L for patients with HF.
- Post-hoc analyses of patients with baseline S-K >5.5 mmol/L and >6.0 mmol/L from ZS-004 and ZS-005 studies were presented to show outcomes relevant to UK clinical practice. These post-hoc analyses demonstrated that rates of hypokalaemia were low, and that the majority of patients maintained clinically appropriate S-K values. Additionally, because the S-K treatment goal in the UK is higher than in the SZC trials, the risk of hypokalaemia is likely to be lower in UK clinical practice compared to in the trials.

5. **AstraZeneca and independent professional bodies consider SZC to be innovative**

- Professional organisation submission forms submitted prior to the first committee meeting clearly indicated that SZC is considered to be an innovate therapy for the management of adults with hyperkalaemia.
- In line with these submissions, AstraZeneca believe that SZC should be considered innovative, as other potassium binders, calcium resonium and SPS, are not commonly used due to their poor tolerance. Even when used, calcium resonium and SPS are only used for short periods of time.
- As such, currently there are no alternative treatment options for patients with hyperkalaemia other than down-titrating or discontinuing cardio-renal protective RAASi medication and SZC would represent a step-change in the current management of hyperkalaemia.

6. **SZC is a cost-effective treatment option for the management of hyperkalaemia in the outpatient setting**

- The company cost-effectiveness base case has been updated to address the Committee's concerns in the second ACD (ACD2), including adopting the changes from the ERG that were favoured by the Committee. Additionally, the treatment threshold in the HF population has been increased to S-K ≥6.0 mmol/L in the updated company ACD2 base case to address the Committee's comment at the second Committee meeting that some clinicians may treat HF patients at higher S-K thresholds than previously modelled. Furthermore, a confidential PAS price reduction of [redacted] to the SZC 10 g dose has been applied to improve the cost-effectiveness of SZC and to alleviate the Committee's concerns about uncertainty in the cost-effectiveness estimate, leading to ICERs of [redacted] and [redacted] for the HF and CKD populations, respectively. The PAS price will only be available if SZC is recommended in the outpatient setting, in addition to the emergency care setting.
- As exploratory scenario analyses to address the uncertainty expressed by the Committee of the relationships between S-K and adverse clinical outcomes, the U-shaped relationships between S-K and adverse clinical outcomes were reduced by 50% or removed entirely, despite the documented evidence supporting these relationships. Even in these highly pessimistic scenario analyses, with clear uncaptured benefits (particularly

when no relationship was assumed), the ICERs remained cost-effective at [redacted] and [redacted] for HF and CKD, respectively, when 50% of the relationships were removed; and cost-effective at [redacted] and [redacted] for HF and CKD, respectively, when the S-K relationships were entirely removed.

- The ICERs from the probabilistic sensitivity analyses (PSAs) of the base case in the HF population and the CKD population are comparable to the deterministic ICERs and the cost-effectiveness acceptability curves (CEACs) show that there is an [redacted] likelihood that SZC is cost-effective at ICER thresholds of £20,000–£30,000/QALY.
- PSAs of the scenarios where the relationships between S-K and adverse clinical outcomes have been entirely removed also show the probabilistic ICERs to be comparable to the deterministic ICERs, with a [redacted] likelihood that SZC is cost-effective at ICER thresholds of £20,000–£30,000/QALY, where the ICER threshold should be towards the upper end of the £20,000–£30,000/QALY range due to uncaptured benefits in these overly pessimistic scenarios.

1 Current draft recommendation

The current draft NICE recommendation is for the treatment of hyperkalaemia in adults in the emergency care setting, and for up 28 days or stopped sooner if hyperkalaemia resolves.

AstraZeneca would like to highlight that SZC is not licensed for mono-therapy of life-threatening hyperkalaemia in the emergency care setting, but should be used alongside current standard care, including insulin dextrose, in the emergency care setting. Therefore, AstraZeneca would like to ask NICE to amend the wording in the recommendation to reflect that SZC can be used as an adjunct to standard care in the emergency care setting.

2 Definition of hyperkalaemia

ACD2 Section 3.1: *"The company defined high serum potassium values as above 5.0 mmol/litre, (…) The committee concluded that the company's clinical definition of hyperkalaemia as serum potassium levels above 5.0 mmol/litre was not widely accepted. It also concluded that, unless they need emergency treatment, few patients in the NHS with serum potassium levels above 5.0 mmol/litre have treatment to lower potassium."*

AstraZeneca understand the *clinical* definition of HK to be S-K >5.0 mmol/L and this was also the definition used in the SZC trials. However, the initial company submission used a higher treatment threshold of S-K ≥5.5 mmol/L to align with UK clinical practice (see Section B.1.3.1.1; para 1) and the treatment threshold was amended to S-K ≥6.0 mmol/L in patients with CKD, in response to ACD1 and following engagement with clinical experts. Furthermore, in response to the ACD1, AstraZeneca stated that *"AstraZeneca agree that patients with hyperkalaemia (HK) are not always treated when S-K levels are above 5.0 mmol/L".*

Therefore, AstraZeneca consider the wording of the statement in ACD2 Section 3.1 to be inaccurate and misleading. It would be more appropriate to state that whilst the clinical trial programme included patients with baseline S-K >5.0 mmol/L, AstraZeneca agree that patients in UK clinical practice are not treated until higher S-K levels of 5.5 or 6.0 mmol/L for HF and CKD patients, respectively.

Furthermore, in order to address the Committee's comment from the second Committee meeting that some clinicians may treat HF patients at higher S-K thresholds than previously modelled, the effect of increasing the treatment threshold to S-K ≥6.0 mmol/L for HF patients in the cost-effectiveness analysis has been included as part of the updated cost-effectiveness analysis (see Section 6).

3 Relationships between S-K and adverse clinical outcomes

3.1 Systematically identified evidence, UK clinical practice, and NICE clinical guidelines all support a link between serum potassium and adverse clinical outcomes

ACD2 Section 3.12: *"The committee noted that the observational data did not guarantee an independent association between high serum potassium levels and death. It also noted that the observational data did not provide evidence that lowering serum potassium extends life. (…) The committee concluded that there was insufficient evidence to prove definitively that lowering serum potassium levels in the outpatient setting leads to improved outcomes.*

ACD2 Section 3.16: *"Given the uncertainty, the committee concluded that it would like to have seen that sodium zirconium cyclosilicate was cost effective in the absence of an association between serum potassium and adverse outcomes, including death."*

ACD2 Section 3.22: *"The committee recalled its conclusion that a link between lowering serum potassium levels and improved long-term outcomes was plausible for some outcomes, but unproven*

(see section 3.16). It agreed that an ICER for decision making would lie near the ERG's scenario analysis removing the association between serum potassium levels and outcomes."

To address the concerns raised by the Committee during the first committee meeting, AstraZeneca conducted a systematic literature review (SLR) using recommended methods to identify published literature documenting the relationship between S-K and adverse clinical outcomes.[24] The SLR identified 59 studies which were potentially relevant to the decision problem. The ERG's critique of the evidence stated that *"whilst 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"*.[25]

Whilst AstraZeneca acknowledge that a degree of residual confounding may affect the reported association between S-K and adverse clinical outcomes, we disagree that the association should be entirely removed from the cost-effectiveness model and we disagree that this scenario should be used as a basis for decision making. The evidence consistently demonstrates a U-shaped association between S-K and adverse clinical outcomes, and clinicians routinely manage patients with hyperkalaemia in the outpatient setting by down-titrating and/or discontinuing proven cardio-renal protective therapy (RAASi) to avoid hyperkalaemia. In addition, the cardiologist clinical expert at the second committee meeting strongly supported a causal link between S-K and adverse clinical outcomes and stated that *chronically* elevated S-K can increase the risk of death which may present as sudden cardiac death. In comparison, *sudden and extreme* rises in S-K often lead to cardiac arrhythmias.

Section 3.12 of the ACD states *"[The Committee] agreed that a relationship between lowering serum potassium to a normal range and fewer adverse outcomes was biologically plausible for a subset of endpoints"*, and Section 3.16 acknowledges that assuming no relationship between S-K and adverse clinical outcomes could be considered conservative. Furthermore, Section 3.11 of the ACD2 states that *"the committee understood that hypokalaemia, like hyperkalaemia, is associated with life-threatening arrhythmias*". Therefore, it would be inappropriate and biased to acknowledge a relationship between hypokalaemia and adverse clinical outcomes, and not consider the documented relationship between hyperkalaemia and adverse clinical outcomes. Therefore, AstraZeneca deem it to be inappropriate to base decision making on a scenario where the relationships between S-K and adverse clinical outcomes are entirely removed.

AstraZeneca would also like to note that NICE clinical guideline CG182 highlights S-K as an important consideration when making treatment decisions in patients with CKD.[9] The guideline recommends the cautious initiation and complete discontinuation of RAASi therapy when S-K levels increase to ≥5.0 mmol/L and ≥6.0 mmol/L, respectively, thereby recognising the need to manage hyperkalaemia – even when S-K is ≥5.0 mmol/L. This is indicative that NICE and the wider clinical community inherently accept a clinical cause for concern when S-K is elevated, even at S-K levels that may not be treated in UK clinical practice. In detail, NICE CG182 makes the following recommendations:

- **Section 1.4.7:** Offer dietary advice about potassium, phosphate, calorie and salt intake appropriate to the severity of CKD. [2008, amended 2014]
- **Section 1.6.7:** In people with CKD, measure S-K concentrations and estimate the GFR before starting renin–angiotensin system antagonists. Repeat these measurements between 1 and 2 weeks after starting renin–angiotensin system antagonists and after each dose increase. [2008]
- **Section 1.6.8:** Do not routinely offer a renin–angiotensin system antagonist to people with CKD if their pretreatment S-K concentration is greater than 5.0 mmol/litre. [2008, amended 2014]

- **Section 1.6.9:** When hyperkalaemia precludes use of renin–angiotensin system antagonists, assessment, investigation and treatment of other factors known to promote hyperkalaemia should be undertaken and the S-K concentration rechecked. [2008]
- **Section 1.6.11:** Stop renin-angiotensin system antagonists if the S-K concentration increases to 6.0 mmol/litre or more and other drugs known to promote hyperkalaemia have been discontinued. [2008]

If there were no relationships between S-K and adverse clinical outcomes, there would be no clinical rationale for the need to alter RAASi therapy in response to elevated S-K levels as recommended in NICE CG182; particularly given the weight of evidence proving the cardio-renal protective properties of RAASi therapies. These recommendations have been published in NICE guidance for the three latest versions of this guideline.

Whilst the Committee has stated that it would like to use the scenario where the relationships between S-K and adverse clinical outcomes are entirely removed as the basis for decision making, we would like to kindly ask the Committee to reconsider its conclusion. We would urge the Committee to consider the wealth of evidence which consistently reports associations between S-K and adverse clinical outcomes, the fact that NICE clinical guidelines use S-K as a basis for treatment decisions, the advice presented in the addendum to the ERG's critique of the company's ACD response which highlighted a number of limitations associated with the removal of the relationships between S-K and adverse clinical outcomes, and the recommendation by the ERG that "*this analyses should be viewed as exploratory rather than representing a most plausible ICER*".[26]

Whilst a degree of residual confounding cannot be completely excluded, the volume and strength of the evidence demonstrating the relationships between S-K and adverse clinical outcomes is overwhelming. Therefore, it would be perverse and against the evidence made available to the Committee to assume that no relationships between S-K and adverse clinical outcomes exists. Such a scenario would have substantial <u>uncaptured benefits</u> and should be interpreted with significant caution. Instead, a cost-effectiveness analysis incorporating the relationships between S-K and adverse clinical outcomes based on the evidence available in the literature, including Luo et al. 2016 and Desai et al. 2018, would represent the best use of available evidence and should be considered as the best estimate of the most likely ICER.

3.2 Fudim et al., 2018 was not systematically identified and inappropriate conclusions have been drawn from the publication

ERG's critique of the company's response to the ACD Section 2.3.3: *"In an editorial, Fudim et al. highlight a need to "be careful to assert a general causal relationship between hyperkalaemia and clinical outcomes across the entire spectrum of hyperkalaemia".*

ACD2 Section 3.12: *"It also noted that the authors of a company-supported observational study used in the model cautioned against assuming a causal effect, and acknowledged the possibility of residual confounding."*

The ERG refer to an editorial by Fudim et al. 2018 which cautions against asserting a general causal relationship between hyperkalaemia and adverse clinical outcomes across the entire spectrum of hyperkalaemia.[27] The editorial makes reference to 3 HF RCTs (RALES, EMPHASIS, and TOPCAT) and an analysis of real-world data published by Hoss et al.[28-31]

RALES is a HF RCT which included a total of 1,663 patients with NYHA class III—IV and randomised patients to receive treatment with spironolactone (25 mg) or placebo.[28] The study concluded that MRA therapy provides a mortality benefit which is sustained in patients with S-K levels up to 5.5 mmol/L, above which the mortality benefit is reduced,[28] potentially due to MRA dose reductions in patients with S-K ≥5.5 mmol/L and/or due to the mortality effect of hyperkalaemia. Whilst the study demonstrated a mortality benefit compared with placebo, the study nonetheless reports a U-shaped association between S-K and adverse clinical outcomes.

EMPHASIS is a HF RCT which included a total of 2,737 patients with NYHA class III—IV who received treatment with eplerenone (25/50 mg).[29] The study concluded that MRA therapy provides a

mortality benefit irrespective of S-K levels and that there is a statistically significant increase in all-cause mortality in patients with S-K ≥5.5 mmol/L; thereby supporting the relationships between S-K and adverse clinical outcomes.

TOPCAT is a HF RCT which included a total of 1,767 patients in the Americas with NYHA class II—IV and randomised patients to receive treatment with spironolactone (15—45 mg) or placebo.[30] Whilst treatment with spironolactone resulted in a mortality benefit when compared with those receiving placebo, a statistically significant U-shaped association was also observed between S-K and cardiovascular mortality, and all-cause mortality, further supporting the relationships between S-K and adverse clinical outcomes.

In line with the three RCTs mentioned above, the real-world data analysis by Hoss et al. concluded that the treatment benefit of MRA therapy is sustained up-to a S-K level of 5.5 mmol/L, but that S-K levels ≥5.5 are associated with increased mortality as per the U-shaped relationships between S-K and adverse clinical outcomes observed in other studies.[31] Specifically, the real-world analysis by Hoss et al. reported hypokalaemia (defined as S-K <3.5 mmol/L) and severe hyperkalaemia (defined as S-K ≥6.0 mmol/L) to be associated with the lowest survival rates amongst all S-K groups in the study.

Therefore, the evidence presented in the editorial by Fudim et al. does not disprove the relationships between S-K and adverse clinical outcomes, but simply supports a protective benefit of MRA therapy in HF patients up-to a S-K level of 5.5 mmol/L. Irrespective of MRA therapy, a U-shaped association was consistently observed in the studies mentioned in the Fudim et al. editorial; further supporting the relationships between S-K and mortality. As such, it is unlikely that the strong U-shaped relationship consistently observed across multiple studies (see Section 3.1) can be explained by the existence of any unknown confounders, which would need to be strongly associated with both S-K and adverse clinical outcomes. Given this, it is likely that the effect of any residual confounding on the U-shaped relationships between S-K and adverse clinical outcomes would be negligible.

3.3 Time-dependent variables

ACD2 Section 3.19: *"[The Committee] also noted that the studies may have been affected by time-dependent confounding, for example, because increasing serum potassium levels affects RAAS inhibitor use, which in turn affects subsequent serum potassium levels and long-term outcomes. Therefore, RAAS inhibitor use is a time-dependent confounder. The committee was aware that using standard regression adjustment is not appropriate when attempting to estimate causal effects from observational data affected by time-dependent confounding, and noted that the company was unable to show that alternative appropriate methods had been used.*"

The relationships between S-K and adverse clinical outcomes, including mortality, CV events and hospitalisation, were modelled based on systematically identified published incidence rate ratios (IRRs) and hazard ratios (HRs) by S-K intervals.

For the CKD population, the IRRs reported by Luo et al. were used in the base case to inform the relationships between S-K and mortality, S-K and CV events, and S-K and hospitalisation. Luo et al. analysed time-updated data from 55,266 CKD patients to examine the relationships between S-K and mortality, S-K and hospitalisation and additional S-K and RAASi discontinuation. Generalised estimating equations with independent or exchangeable working correlation structures were used to analyse the non-linear relationships between S-K and adverse clinical outcomes. Poisson/negative binomial links were used on the basis of the empirical distribution of outcomes in the study cohort. Covariates that were imbalanced across categories of S-K, and covariates known or presumed to be associated with the outcomes studies were included in the analysis, including age, sex, race/ethnicity, diabetes, congestive heart failure, coronary artery disease, cerebrovascular disease, beta blocker use, RAASi use, nondihydropyridine calcium channel blocker use, thiazide diuretic use, loop diuretic use, and eGFR. S-K levels and covariates were updated at the time of each successive S-K measurement, to capture the time-dependent nature of the covariates.

Additionally, for the CKD population, IRRs reported by Furuland et al. were used in scenario analyses to provide alternative values based on an analysis of a UK population (191,964 CKD patients from the

CPRD). Patient-intervals were defined as the period between successive S-K measurements, and clinical events of interest were assigned to these patient-intervals based on the date on which they occurred. In addition to the base case analysis, a scenario analysis was also presented by Furuland et al. where the associations between S-K and adverse clinical outcomes based on patient intervals were restricted to the 30 days following each S-K measurement, mitigating the impact of time-dependent confounding from unobserved factors. This scenario analysis showed that associations between S-K and adverse clinical outcomes were broadly consistent with those estimated from unrestricted patient intervals (base case analysis). Generalised estimating equations with an exchangeable working correlation structure to account for intra-patient correlation were used to estimate risk equations for mortality, CV outcomes and RAASi discontinuation. Events were assumed to be Poisson distributed and a natural logarithm link function and an offset equal to the natural logarithm of patient-years (defined as the exposure time in each patient-interval) were used. Predicted incidence rates and IRRs were adjusted for covariates included as explanatory variables in the risk equations, which included time-updated RAASi use amongst other covariates.

Each observation included in the analysis conducted by Luo et al. and Furuland et al. was a patient interval rather than a patient, and each patient would appear in the analysis as many times as they had intervals over the study period. Generalised estimating equations were used, where intra-patient correlation was accounted for by using a modified version of the estimation process to obtain model parameter point estimates and by estimating standard errors that are robust to the effects of clustering. Furuland et al. also assessed the sensitivity of results to the choice of modelling framework and found that associations were maintained when using a generalised linear mixed model, where intra-patient correlation is accounted for using patient specific random intercepts. Luo et al. considered generalised estimating equations to be the most appropriate model, as the primary study question was whether there were any differences in event rates with respect to S-K at a population level and as the sample size was sufficient to estimate the marginal effects. An assumption was made that data were missing at random, based on the authors experiences with previous studies using the same data sources.

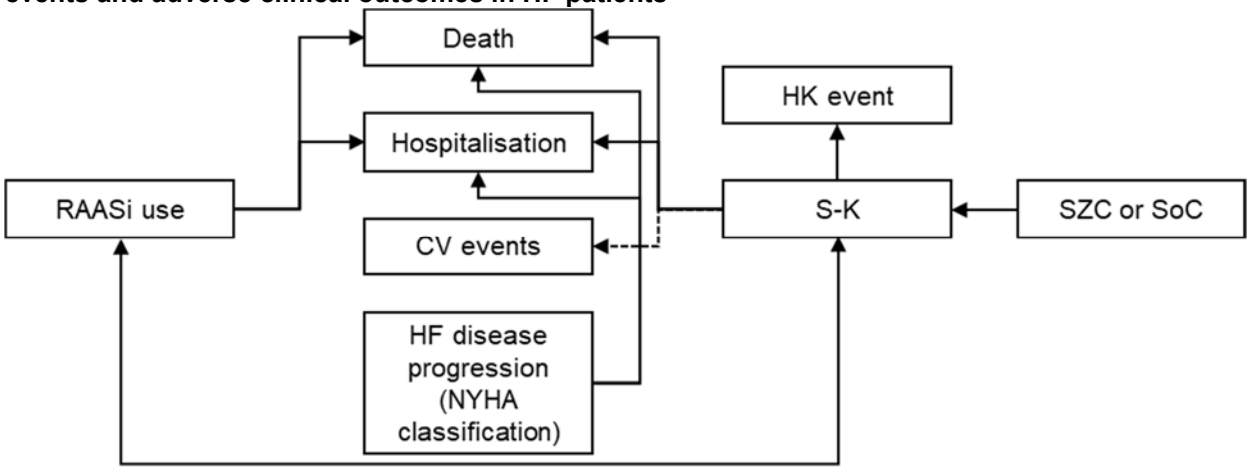
Both the Luo et al. and the Furuland et al. studies showed high S-K levels to be associated with RAASi discontinuation, with RAASi discontinuation having a direct effect on S-K levels and on adverse clinical outcomes. As such, RAASi use/discontinuation is a time-dependent confounder that needs to be adjusted for in the relationships between S-K and adverse clinical outcomes. The generalised estimating equations used in Luo et al. and Furuland et al. for estimating the relationships between S-K and adverse clinical outcomes include time-updated RAASi as a covariate, and therefore appropriately adjust for RAASi use as a confounder and isolate the effect of S-K on adverse clinical outcomes. The effect of RAASi on adverse clinical outcomes remain important in the cost-effectiveness analysis of SZC; this relationship is separately and explicitly modelled based on ORs of RAASi treatment effects on mortality, CV events and hospitalisation, as reported by Xie et al. (CKD), Levy et al. (HF), and Flather et al. (HF). This modelling approach allows the relationship between different risk-factors (S-K and RAASi use) to be explicitly modelled and independently adjusted, whilst avoiding double-counting of treatment effect (Figure 1 and Figure 2).

For the HF population, the HRs reported by Desai et al.[30] were used to inform the relationships between S-K and mortality, and S-K and hospitalisation. Time-updated Cox models adjusted for significant predictors of incidence hypo- and hyperkalaemia were used to relate the most recent measured S-K value to the risk of mortality and hospitalisation. Hazard ratios were adjusted for region, age, gender, race, baseline eGFR, baseline S-K, baseline RAASi use, baseline beta blocker use, baseline loop diuretics and treatment arm in the TOPCAT trial. The relationship was not adjusted for time-updated RAASi use as patients in the TOPCAT trial continued to receive ACEi or ARB throughout the trial,[32] and therefore it is unlikely that time-updated use of ACEi or ABR would have significantly affected the HRs.

In conclusion, the statistical models used to estimate the relationships between S-K and adverse clinical outcomes were carefully selected to ensure all known covariates were appropriately accounted for and to take the features of the data analysed into account. The published results from the literature were applied in the cost-effectiveness analysis to explicitly model the relationships

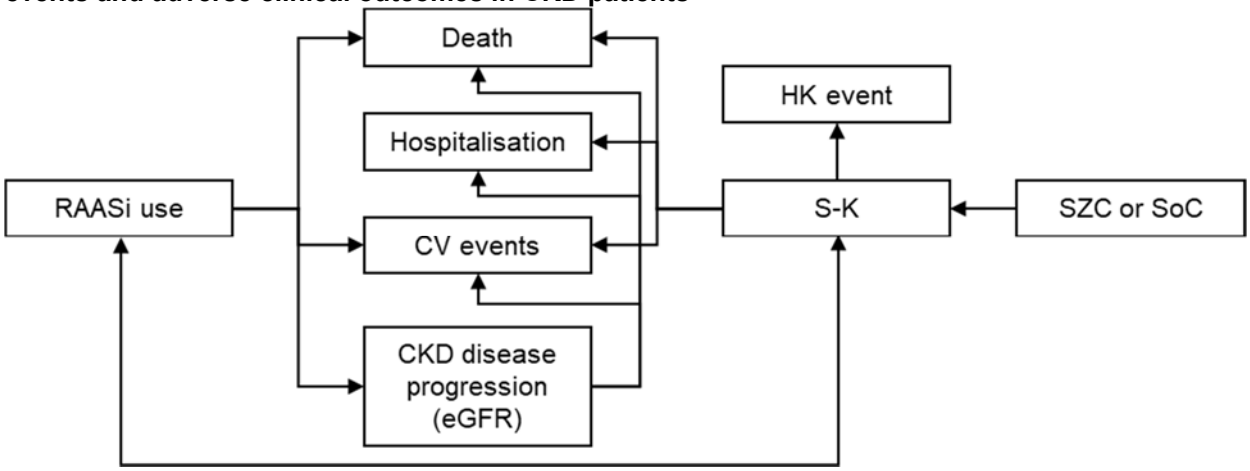
between S-K and adverse clinical outcomes, alongside the relationships between RAASi and outcomes (also modelled explicitly, but separately to the S-K and adverse clinical outcomes relationship).

Figure 1. Relationships modelled between treatment, S-K levels, RAASi use, hyperkalaemia events and adverse clinical outcomes in HF patients



Key: solid arrows, relationships modelled; dashed arrows, relationship did not reach statistical significance in CPRD analysis, but the relationship between hypokalaemia and CV events has been conservatively modelled in favour of SoC
Abbreviations: CV, cardiovascular; HK, hyperkalaemia; NYHA, New York Heart Association; RAASi, renin angiotensin aldosterone system inhibitor; S-K, serum potassium; SoC, standard care; SZC, sodium zirconium cyclosilicate.

Figure 2. Relationships modelled between treatment, S-K levels, RAASi use, hyperkalaemia events and adverse clinical outcomes in CKD patients



Key: solid arrows, relationships modelled
Abbreviations: CV, cardiovascular; eGFR, estimated glomerular filtration rate; HK, hyperkalaemia; RAASi, renin angiotensin aldosterone system inhibitor; S-K, serum potassium; SoC, standard care; SZC, sodium zirconium cyclosilicate.

4 Risk of hypokalaemia

ACD2 Section 3.10: *"Clinicians in the NHS may not always view a serum potassium level of below 5.0 mmol/litre as the target for treatment if serum potassium levels are reduced to non-life-threatening levels, depending on the serum potassium level that precipitated treatment."*

ACD2 Section 3.11: *"The company presented data showing that treatment with sodium zirconium cyclosilicate was associated with hypokalaemia, that is low serum potassium. The committee understood that hypokalaemia, like hyperkalaemia, is associated with life-threatening arrhythmias."*

AstraZeneca would like to re-emphasise the positioning of SZC with respect to the thresholds for intervention and the S-K treatment goal. To better reflect UK clinical practice and in response to the ACD1, AstraZeneca amended the threshold for treatment to S-K ≥6.0 mmol/L for CKD patients, whilst the threshold for HF patients was maintained at ≥5.5 mmol/L.[24]. AstraZeneca also recognised that clinicians may not always view the S-K treatment goal as <5.0 mmol/L in UK clinical practice and understand that clinicians would prefer to treat to prevent S-K levels ≥5.5 mmol/L in HF patients and S-K ≥6.0 in CKD patients. Therefore, post-hoc analyses of patients with baseline S-K >5.5 mmol/L and >6.0 mmol/L from studies ZS-004 and ZS-005 were presented to show outcomes relevant to UK clinical practice:

- S-K >5.5 or >6.0 mmol/L at the end of the correction phase and during the maintenance phase
- S-K >4.0, ≤5.5 or S-K >4.0, ≤6.0 mmol/L at the end of the correction phase and during the maintenance phase
- S-K <4.0 mmol/L (the Committee's preferred definition of hypokalaemia) at the end of the correction phase and during the maintenance phase

These post-hoc analyses demonstrate that the risk of hypokalaemia is low. In patients with baseline S-K >5.5 mmol/L, there were [redacted] and [redacted] patients with S-K <4.0 mmol/L at the end of the corrective phase of ZS-004 and ZS-005, respectively. At the end of the maintenance phase, [redacted] and [redacted] patients receiving 5 g and 10 g OD, respectively in ZS-004, and [redacted] patients in ZS-005 had S-K <4.0 mmol/L. In patients with baseline S-K >6.0 mmol/L, [redacted] patient in the corrective phase of ZS-005 reported S-K <4.0 mmol/L, and [redacted] patient receiving treatment with 10 g OD in the maintenance phase of ZS-004, and [redacted] patients in the maintenance phase of ZS-005 with had S-K <4.0 mmol/L. AstraZeneca would like to re-iterate that the dose of SZC should be up- or down-titrated as per the SmPC to maintain an appropriate S-K. If patients become hypokalaemic, therapy should be discontinued. As such, hypokalaemia is unlikely to be a frequent adverse event in UK clinical practice, given the low rate of hypokalaemia in the post-hoc analysis and the higher S-K treatment goal in UK clinical practice compared to the SZC trials.

As stated in Section 2, in order to address the Committee's comment from the second Committee meeting that some clinicians may treat HF patients at higher S-K thresholds than previously modelled, the effect of increasing the treatment threshold to S-K ≥6.0 mmol/L for HF patients in the cost-effectiveness analysis has been included as part of the updated cost-effectiveness analysis (see Section 6).

5 Innovation

ACD2 Section 3.23: *"The company proposed several benefits of sodium zirconium cyclosilicate, including preventing the need to modify RAAS inhibitor treatment and avoiding a restrictive low-potassium diet. The committee recalled that people would still need to avoid dietary potassium. The patient experts stated that, if the company had shown evidence for these benefits, then sodium zirconium cyclosilicate would be innovative. The committee was aware that other gastrointestinal potassium binders exist and, although these are not well tolerated, sodium zirconium cyclosilicate does not represent a step-change in treatment. The committee concluded, sodium zirconium cyclosilicate could not be considered innovative."*

AstraZeneca would like to kindly ask the committee to reconsider its conclusion that SZC should not be considered innovative. When asked if the technology is considered to be innovate, professional organisation submissions from The Renal Association and Royal College of Physicians, and The Royal College of Pathologists stated the following:

- *"This is a new area on management of patients with electrolyte disorders mainly as a consequence of medications and in part diet. This addition may transform our ability to effectively manage patients with chronic hyperkalaemia"* and
- *"It has potential to be innovative"*

Furthermore, AstraZeneca believe that SZC should be considered innovative, as other potassium binders, calcium resonium and SPS, are not commonly used or only used for short periods of time due to their poor tolerance. Additionally, calcium resonium and SPS do not selectively bind potassium but also bind several other ions, leading to adverse events associated with electrolyte imbalances. As such, currently there are no significant alternative treatment options for patients with hyperkalaemia, other than down-titrating or discontinuing cardio-renal protective RAASi medication.

6 Cost-Effectiveness Analysis

ACD2 Section 3.7: *"The company proposed that sodium zirconium cyclosilicate would be started, and RAAS inhibitors stopped or reduced, in people with persistently high serum potassium levels of 5.5 mmol/litre and above (heart failure) or 6.0 mmol/litre and above (chronic kidney disease). The committee accepted that the levels proposed by the company were intended to align with clinical expert opinion (see section 3.1), but noted that some clinicians may wish to treat hyperkalaemia at alternative serum potassium thresholds."*

ACD2 Section 3.16: *"Given the uncertainty, the committee concluded that it would like to have seen that sodium zirconium cyclosilicate was cost effective in the absence of an association between serum potassium and adverse outcomes, including death."*

ACD2 Section 3.19: *"The committee recalled that the company assumed that in the outpatient setting, patients would have treatment for up to 1 year, and then sodium zirconium cyclosilicate would be stopped (see section 3.15). It noted that this did not align with the expected use in clinical practice, where treatment would continue indefinitely if there was clinical benefit. It would have preferred to have seen a scenario analysis in which the costs and benefits of sodium zirconium cyclosilicate were modelled beyond 52 weeks."*

ACD2 Section 3.22: *"The committee noted that the ERG's base case for chronic kidney disease used an odds ratio for RAAS inhibitor outcomes compared with active control (see section 3.20), and that removing this assumption in line with committee's preferences would likely reduce the incremental cost-effectiveness ratio (ICER) by around £1,500 per QALY gained."*

ACD2 Section 3.22: *"The committee recalled its conclusion that a link between lowering serum potassium levels and improved long-term outcomes was plausible for some outcomes, but unproven (see section 3.16). It agreed that an ICER for decision making would lie near the ERG's scenario analysis removing the association between serum potassium levels and outcomes. The committee would have preferred to have seen evidence that sodium zirconium cyclosilicate was cost effective when this assumption was used."*

ACD2 Section 3.22: *"It would also have liked to have seen cost-effectiveness scatter plots to help determine the effect of the uncertainty in the modelled parameters on the cost-effectiveness estimates."*

ACD2 Section 3.22: *"The committee also recalled its conclusion that treatment with RAAS inhibitors would improve outcomes but noted that uncertainties around the assumptions of how many patients would down-titrate or restart RAAS inhibitors had not been fully addressed in the company's model (see section 3.17)."*

6.1 Updated company base case in the outpatient setting

The cost-effectiveness analyses for SZC in HF and CKD patients in the outpatient setting have been updated to align with the ERG base cases, and to address concerns raised in the ACD2 by making the changes outlined below for the revised company ACD2 base case (Table 1 and Table 2).

- The S-K reduction over the 2-day correction phase in the placebo arm of ZS-003 has been linearly extrapolated to modelled continued reductions in S-K over Day 3. This alternative S-K profile was preferred by the ERG, and it is conservative with respect to SZC as the rate of S-K reductions in the placebo arm is likely to lower on Day 3 compared to Day 1 and Day 2.

- The proportion of patients who down-titrate and discontinue conditional on S-K levels, and the proportion of patients who reinitiate RAASi therapy in the SZC arm have been set to that of the SoC arm, as per the ERG base cases. This assumption addresses the Committee's concern regarding the uncertainty around the assumption of how many patients would down-titrate or restart RAASi (ACD2 Section 3.22). In clinical practice, clinicians with experience of SZC are likely to allow patients to maintain RAASi whilst being treated with SZC – the assumption of equal RAASi down-titration, discontinuation and re-initiation in the SZC and SoC arms is therefore conservative with respect to SZC.
- The treatment duration of SZC has been increased to life-time treatment to provide "*a scenario analysis in which the costs and benefits of sodium zirconium cyclosilicate were modelled beyond 52 weeks"* as requested by the Committee in ACD2 Section 3.19.
- The treatment threshold in the HF population has been increased to S-K ≥6.0 mmol/L to address the Committee's comment in ACD2 Section 3.3 and 3.7 that some clinicians may wish to treat hyperkalaemia at higher S-K thresholds than previously modelled. The Committee chair also expressed interest in the cost-effectiveness of SZC at this higher threshold at the second Committee meeting. (HF only)
- The effect of RAASi on mortality and CV events has been changed back to the ORs based on the comparison of RAASi with placebo, to align with the Committee's preference stated in the ACD2 Section 3.22. (CKD only)
- The health state utility values for CKD patients have been updated according to the ERG base case. (CKD only)
- A confidential PAS discount has been applied to the 10 g dose to improve cost-effectiveness. The PAS price is [redacted] for the 10 g sachet (equivalent to a [redacted] discount) and would be available for patients in both the emergency care setting and the outpatient setting. The price of the 5 g sachet remains unchanged at £7.12 per sachet. The PAS price will only be available if SZC is recommended in the outpatient setting, in addition to the emergency care setting as SZC has already been deemed to be cost-effective in the emergency care setting at the current price (current draft recommendation). If the current draft recommendation remains unchanged, the original price of £7.12 and £14.24 per 5 g and 10 g sachet, respectively, will apply.

The updated company ACD2 base case combines all the changes listed above and results in ICERs of [redacted] and [redacted] for HF and CKD patients, respectively. The differences between the updated company ACD2 base cases and the ERG base cases are primarily driven by the confidential PAS discount and by the higher S-K treatment threshold in the HF population.

Table 1. Updated company ACD2 base case for HF patients

#	Scenario	ΔCosts	ΔQALYs	ICER
1	Company base case submitted in the ACD1 response	£14,860	0.818	£18,158
2	Company ACD1 base case + applying a 3-day S-K reduction in the correction phase *(as per the ERG base case)*	£13,928	0.641	£21,729
3	Company ACD1 base case + setting the RAASi discontinuation, down-titration and re-initiation rates in SZC to that of SoC *(as per the ERG base case)*	£12,293	0.634	£19,385
4	Company ACD1 base case + life-time SZC treatment *(as per Committee's preference, ACD2 Section 3.19)*	£17,003	0.938	£18,125
5	Company ACD1 base case + threshold for treatment changed to S-K ≥6.0 mmol/L *(as per Committee's preference, ACD2 Section 3.7 and discussions at second Committee meeting)*	£7,883	0.965	£8,172
6	Company ACD1 base case + [redacted] confidential PAS discount for the SZC 10 g dose	[redacted]	[redacted]	[redacted]
7	Combining 1+2+3+4+6 above (i.e. threshold for treatment maintained at S-K ≥5.5 mmol/L)	[redacted]	[redacted]	[redacted]

#	Scenario	ΔCosts	ΔQALYs	ICER
8	**Updated company ACD2 base case (combining 1+2+3+4+5+6 above)** (i.e. threshold for treatment changed to S-K ≥6.0 mmol/L)	[redacted]	[redacted]	[redacted]
9	ERG base case in critique of company response to ACD1 (note this scenario retains treatment threshold at S-K ≥5.5 mmol/L)	£11,531	0.475	£24,291

Abbreviations: ACD1, first appraisal consultation document; ACD2, second appraisal consultation document; ERG, evidence review group; HF, heart failure; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SoC, standard care; SZC, sodium zirconium cyclosilicate; ΔCosts, incremental costs; ΔQALYs, incremental QALYs.

Table 2. Updated company ACD2 base case for CKD patients

#	Scenario	ΔCosts	ΔQALYs	ICER
1	Company base case submitted in the ACD1 response	£8,249	0.708	£11,644
2	Company ACD1 base case + applying a 3-day S-K reduction in the correction phase *(as per the ERG base case)*	£11,362	0.573	£19,815
3	Company ACD1 base case + setting the RAASi discontinuation, down-titration and re-initiation rates in SZC to that of SoC *(as per the ERG base case)*	£1,397	0.443	£3,155
4	Company ACD1 base case + life-time SZC treatment *(as per Committee's preference, ACD2 Section 3.19)*	£9,225	0.879	£10,491
5	Company ACD1 base case + using OR for RAASi compared to placebo *(as per Committee's preference, ACD2 Section 3.22)*	£8,249	0.708	£11,644
6	Company ACD1 base case + amending the utility values for people with CKD *(as per the ERG base case)*	£8,249	0.654	£12,605
7	Company ACD1 base case + [redacted] confidential PAS discount for the SZC 10 g dose	[redacted]	[redacted]	[redacted]
8	**Updated company ACD2 base case (combining 1+2+3+4+5+6+7 above)**	[redacted]	[redacted]	[redacted]
9	ERG base case in critique of company response to ACD1	£5,282	0.307	£17,179

Abbreviations: ACD1, first appraisal consultation document; ACD2, second appraisal consultation document; CKD, chronic kidney disease; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; RAASi, renin-angiotensin-aldosterone system inhibitor; PAS, patient access scheme; S-K, serum potassium; SoC, standard care; SZC, sodium zirconium cyclosilicate; ΔCosts, incremental costs; ΔQALYs, incremental quality adjusted life-years.

6.2 Scenario analyses in the outpatient setting

Additional scenario analyses have been conducted to address potential residual uncertainties, as outlined below and as summarised in Table 3 and Table 4.

6.2.1 Removal of relationships between S-K and adverse clinical outcomes (scenario 2)

The Committee has requested to see a scenario where no relationships between S-K and adverse clinical outcomes are modelled. AstraZeneca strongly believe that this scenario is overly pessimistic, given the abundance of systematically identified evidence from the literature demonstrating this relationship across geographies and comorbid populations, and given clinical guidelines that recommend high S-K levels to be managed through RAASi down-titration/discontinuation and low potassium diet (e.g. NICE CG182). The ERG has also highlighted this scenario is unlikely to reflect clinical reality, and the Committee has itself acknowledged that *"a relationship between lowering S-K to normal range and fewer adverse outcomes was biologically plausible for a subset of endpoints"*. As such, this scenario analysis should be viewed as exploratory and at most represent an extreme upper limit of the ICER, and should not to be used as the basis for decision making.

When 100% of the relationships between S-K and adverse clinical outcomes are removed (scenario 2), the ICERs increase by ~£15,000 and ~£9,300 compared to the updated company ACD2 base

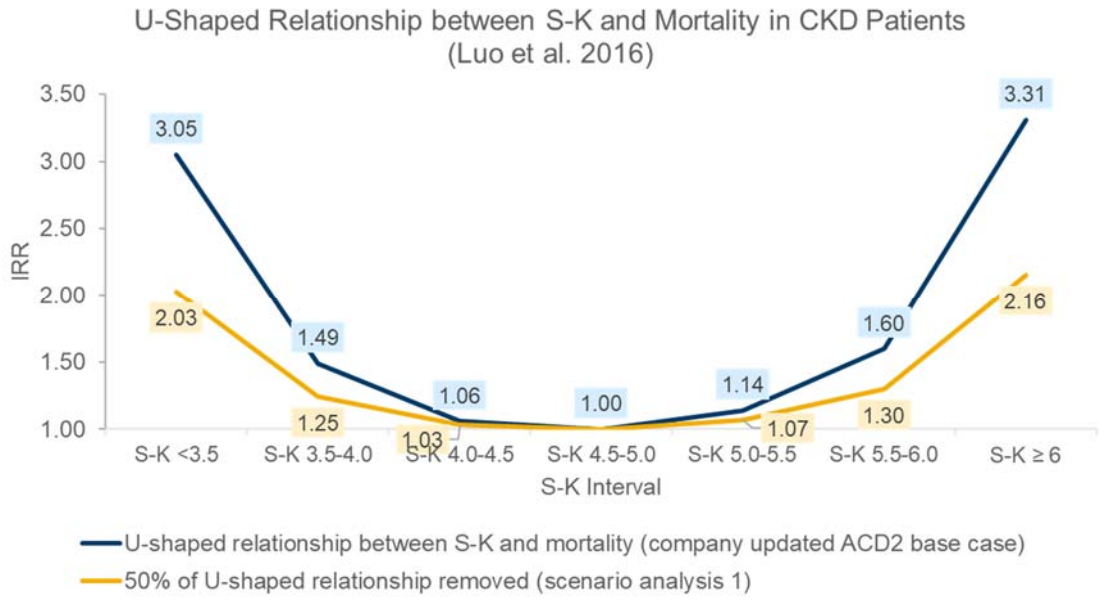
case for HF and CKD patients, respectively (Table 3 and Table 4 #2). This scenario is exploratory and is likely to grossly underestimate the benefits of SZC, as benefits from reduced clinical events (mortality, CV events and hospitalisation) mediated through the lowering of S-K levels are not captured at all. As advised by the NICE technical team, the ICER threshold for decision making should be towards the upper end of the £20,000-£30,000/QALY range when there are uncaptured benefits in the cost-effectiveness analysis, as in this case.

6.2.2 Reduction of the relationships between S-K and adverse clinical outcomes by 50% (scenario 1)

Despite the documented evidence supporting a strong relationship between hyperkalaemia and long-term adverse clinical outcomes, and the approaches taken to account for time-dependant confounding (see Section 3.3) an alternative scenario is provided with 50% of the relationships between S-K and adverse clinical outcomes removed (scenario 1). This alternative scenario should be considered to be more reflective of UK clinical practice compared with assuming no relationship, given the wealth of evidence supporting the relationships between S-K and adverse clinical outcomes, and the biological plausibility for this relationship as acknowledged by the Committee. This alternative scenario analysis was conducted by scaling the IRRs associated with hypo- and hyperkalaemia for mortality and hospitalisation in HF patients, and the IRRs for mortality, CV events and hospitalisation in CKD patients, so that the risk of events in patients with hypo- and hyperkalaemia reduced compared with the base case (see Figure 3 for the relationship between S-K and mortality as an example).

When 50% of the relationships between S-K and adverse clinical outcomes are removed (scenario 1), the ICER increases by ~£1,500 and ~£2,000 compared to the updated company ACD2 base case for HF and CKD, respectively (Table 3 and Table 4, #1). AstraZeneca consider this scenario to be more relevant for decision making, as some of the relationships between S-K and adverse clinical outcomes have been retained, even though a large proportion of the relationship has been conservatively removed. The ICERs in this scenario remain well below [redacted] in both the HF and CKD population, and as such SZC should be considered as a cost-effective treatment option for hyperkalaemia in the outpatient setting.

Figure 3. U-shaped relationship between S-K and mortality modelled in the base case (blue line) and in scenario 1 where 50% of the relationships between S-K and adverse clinical outcomes have been removed (orange line)



The relationships between S-K and other adverse clinical outcomes for HF and CKD patients were also similarly adjusted as in Figure 3.

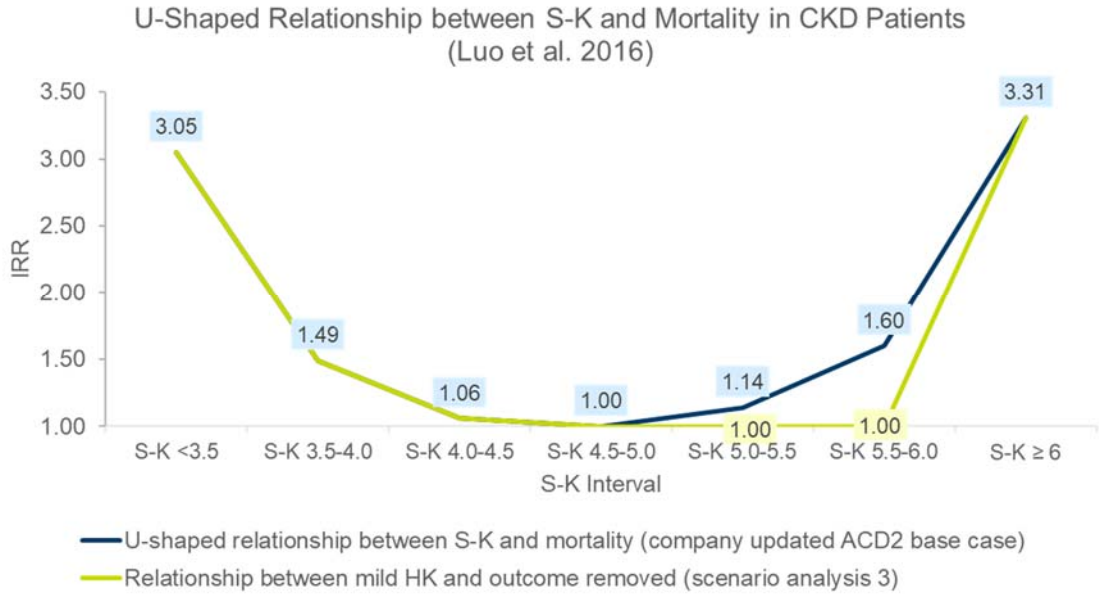
Abbreviations: ACD2, second appraisal consultation document; IRR, incidence rate ratio; S-K, serum potassium.

6.2.3 Removal of the relationships between mild hyperkalaemia and adverse clinical outcomes (scenario 3)

Based on the Committee's understanding that severe hyperkalaemia in the emergency care setting is associated with life-threatening arrhythmias, a scenario analysis (scenario 3) has been conducted where the U-shaped relationships between S-K and adverse clinical outcomes have been modulated to remove the relationships between mild hyperkalaemia and adverse clinical outcomes, whilst the relationships between severe hyperkalaemia and adverse clinical outcomes have been retained. As a conservative assumption, the full relationships between hypokalaemia (regardless of severity of hypokalaemia) and adverse clinical outcomes have been retained, in line with the Committee's comment about the adverse effects of hypokalaemia in ACD2 Section 3.11 (see Figure 4 for the relationship between S-K and mortality as an example).

Scenario 3 shows that the ICERs for both the HF and CKD populations remain below [redacted], at [redacted] and [redacted], respectively, even when the relationships between mild hyperkalaemia and adverse clinical outcomes (death, CV events, hospitalisation) were removed, whilst the full relationships between hypokalaemia and adverse clinical outcomes were fully retained (Table 3 and Table 4, #3).

Figure 4. U-shaped relationship between S-K and mortality modelled in the base case (blue line) and in scenario 3 where the relationships between mild hyperkalaemia and adverse clinical outcomes have been removed (green line)



The relationships between S-K and other adverse clinical outcomes for HF and CKD patients were also similarly adjusted as in Figure 4.
Abbreviations: ACD2, second appraisal consultation document; IRR, incidence rate ratio; S-K, serum potassium.

6.2.4 Dose distribution (scenarios 4 and 5)

In the base case analysis as submitted by the company in the ACD1 response, the daily cost of SZC maintenance therapy was calculated as the weighted average cost based on the actual SZC doses received by patients during the maintenance phase of the ZS-005 trial. In the maintenance phase of ZS-005, the starting dose was SZC 5 g OD. Thereafter, the dose was maintained, or increased to a maximum of 15 g OD or decreased to a minimum of 5 g once every other day if potassium increased to >5.5 mmol/L or decreased to between 3.0 and 3.4 mmol/L, respectively.

Because the S-K treatment goal is less stringent in UK clinical practice (S-K <5.5 mmol/L and <6.0 mmol/L for HF and CKD patients, respectively) compared with those in the ZS-005 trial, it is likely that a smaller proportion of patients in UK clinical practice require dose up-titration in order to achieve

normokalaemia as defined in the UK clinical practice. Therefore, scenario analyses were carried out where the proportion of patients who require the 10 g daily dose was reduced to 10% and 20%, compared with 37.4% in the base case.

Due to a lower weighted average daily cost, the ICER in these scenarios were £1,000–£2,200 lower than the updated company ACD2 base case (Table 3 and Table 4, #4 and #5).

6.2.5 Relationships between S-K and adverse clinical outcomes modelled based on Furuland et al. 2018 (scenario 6, CKD only)

During the second Committee meeting, the Committee criticised the use of Luo et al. 2016 to inform the relationships between S-K and adverse clinical outcomes in CKD patients, due to the non-UK data in this study. To address this, a scenario analysis based on the relationships between S-K and adverse clinical outcomes reported by Furuland et al. 2018 has been conducted. Furuland et al. 2018 was a study of 191,964 UK CKD patients listed in the Clinical Practice Research Datalink (CPRD) and is therefore likely to be representative of UK clinical practice. Details of the statistical model used by Furuland et al. 2018 to account for time-dependent covariates are also provided in Section 3.3.

The ICER in the scenario analysis with Furuland et al. is ~£1,300 lower than the updated company ACD2 base case (Table 4, #6).

Table 3. Additional scenarios based on the company ACD2 base case for HF patients

#	Scenario	ΔCosts	ΔQALYs	ICER
-	**Updated company ACD2 base case** Relationships between S-K and adverse clinical outcomes modelled as per Desai et al. 2018 Dose distribution modelled as 5 g one every other day/5 g once daily/10 g once daily: 0.9%/61.7%/37.4%	[redacted]	[redacted]	[redacted]
1	Updated company ACD2 base case + remove 50% of relationships between S-K and adverse clinical outcomes	[redacted]	[redacted]	[redacted]
2	Updated company ACD2 base case + remove 100% of relationships between S-K and adverse clinical outcomes	[redacted]	[redacted]	[redacted]
3	Updated company ACD2 base case + remove relationships between *mild* S-K and adverse clinical outcomes	[redacted]	[redacted]	[redacted]
4	Updated company ACD2 base case + alternative dose distribution (5 g one every other day/5 g once daily/10 g once daily: 0.9%/79.1%/20%)	[redacted]	[redacted]	[redacted]
5	Updated company ACD2 base case + alternative dose distribution (5 g one every other day/5 g once daily/10 g once daily: 0.9%/89.1%/10%)	[redacted]	[redacted]	[redacted]

Abbreviations: ACD2, second appraisal consultation document; HF, heart failure; ICER, incremental cost-effectiveness ratio; S-K, serum potassium; ΔCosts, incremental costs; ΔQALYs, incremental QALYs.

Table 4. Additional scenarios based on the company ACD2 base case for CKD patients

#	Scenario	ΔCosts	ΔQALYs	ICER
-	**Updated company ACD2 base case** Relationships between S-K and adverse clinical outcomes modelled as per Luo et al. 2018 Dose distribution modelled as 5 g one every other day/5 g once daily/10 g once daily: 0.9%/61.7%/37.4%	[redacted]	[redacted]	[redacted]
1	Updated company ACD2 base case + remove 50% of relationships between S-K and adverse clinical outcomes	[redacted]	[redacted]	[redacted]
2	Updated company ACD2 base case + remove 100% of relationships between S-K and adverse clinical outcomes	[redacted]	[redacted]	[redacted]

3	Updated company ACD2 base case + remove relationship between mild S-K and adverse clinical outcomes	[redacted]	[redacted]	[redacted]
4	Updated company ACD2 base case + alternative dose distribution (5 g one every other day/5 g once daily/10 g once daily: 0.9%/79.1%/20%)	[redacted]	[redacted]	[redacted]
5	Updated company ACD2 base case + alternative dose distribution (5 g one every other day/5 g once daily/10 g once daily: 0.9%/89.1%/10%)	[redacted]	[redacted]	[redacted]
6	Updated company ACD2 base case + relationships between S-K and adverse clinical outcomes modelled based on Furuland et al. 2018 *(as per Committee's preference to use UK data)*	[redacted]	[redacted]	[redacted]

Abbreviations: ACD2, second appraisal consultation document; CKD, chronic kidney disease; ICER, incremental cost-effectiveness ratio; S-K, serum potassium; ΔCosts, incremental costs; ΔQALYs, incremental quality adjusted life-years.

6.3 Probabilistic sensitivity analyses in the outpatient setting

6.3.1 Updated company ACD2 base cases

The cost-effectiveness plane from the PSA of the updated company ACD2 base case for HF is presented in Figure 5 and the CEAC is presented in Figure 6.

The probabilistic ICERs in the HF population of [redacted] is similar to the determinist ICER of [redacted] (see Section 6.2). The PSA shows that there is a [redacted] likelihood for SZC to be cost-effective at willingness to pay (WTP) thresholds of £20,000–£30,000/QALY in the HF population.

The cost-effectiveness plane from the PSA of the updated company ACD2 base case for CKD is presented in Figure 8 and the cost-effectiveness acceptability curve is presented in

Figure 9. The probabilistic ICERs in the CKD population of [redacted] is similar to the determinist ICER of [redacted] (see Section 6.2). The PSA shows that there is an [redacted] likelihood for SZC to be cost-effective at WTP thresholds of £20,000–£30,000/QALY in the CKD population.

Figure 7 and **Figure 10** show that a sufficient number of simulations have been conducted for the ICERs to converge in the PSAs for the HF population and CKD population, respectively.

Figure 5. Cost-effectiveness plane for the updated company ACD2 base case, HF population

[redacted]

Abbreviations: ACD2, second appraisal consultation document; CE, cost-effectiveness, HF, heart failure, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; WTP, willingness to pay.

Figure 6. CEAC for the updated company ACD2 base case, HF population

[redacted]

Abbreviations: ACD2, second appraisal consultation document; CEAC, cost-effectiveness acceptability curve; HF, heart failure, QALY, quality-adjusted life years; WTP, willingness to pay.

Figure 7. Graph showing ICER convergence with increasing number of PSA simulations in the updated company ACD2 base case, HF population

Abbreviations: ACD2, second appraisal consultation document; HF, heart failure; ICER, incremental cost-effectiveness analysis; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life years.]

Figure 8. Cost-effectiveness plane for the updated company ACD2 base case, CKD population

Abbreviations: ACD2, second appraisal consultation document; CE, cost-effectiveness, CKD, chronic kidney disease, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; WTP, willingness to pay.

Figure 9. CEAC for the updated company ACD2 base case, CKD population

Abbreviations: ACD2, second appraisal consultation document; CEAC, cost-effectiveness acceptability curve; CKD, chronic kidney disease, QALY, quality-adjusted life years; WTP, willingness to pay

Figure 10. Graph showing ICER convergence with increasing number of PSA simulations in the updated company ACD2 base case, CKD population

Abbreviations: ACD2, second appraisal consultation document; HF, heart failure; ICER, incremental cost-effectiveness analysis; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life years.

6.3.2 Scenario analyses where the relationships between S-K and adverse clinical outcomes have been entirely removed

The cost-effectiveness plane from the PSA of the scenario analyses in HF patients where the relationships between S-K and adverse clinical outcomes have been entirely removed is presented in Figure 11 and the cost-effectiveness acceptability curve is presented in

Figure 12. The probabilistic ICERs in the HF population of [redacted] is similar to the determinist ICER of [redacted] (see Section 6.2). The PSA shows that there is a [redacted] likelihood for SZC to be cost-effective at WTP thresholds of £20,000–£30,000/QALY in the HF population.

The cost-effectiveness plane from the PSA of the scenario analyses in CKD patients where the relationships between S-K and adverse clinical outcomes have been entirely removed is presented in

Figure 14 and the cost-effectiveness acceptability curve is presented in Figure 15. The probabilistic ICERs in the CKD population of [redacted] is similar to the determinist ICER of [redacted] (see Section 6.2). The PSA shows that there is a [redacted] likelihood for SZC to be cost-effective at WTP thresholds of £20,000–£30,000/QALY in the CKD population. Given the substantial uncaptured benefits in these scenarios, the ICER threshold (WTP threshold) should be towards the upper end of the £20,000-£30,000/QALY range, as advised by the NICE technical team. Therefore, there is a high likelihood for SZC to be cost-effective even in these overly pessimistic scenarios.

Figure 13 and Figure 16 show that a sufficient number of simulations have been conducted for the ICERs to converge in the PSAs for the HF population and CKD population, respectively.

Figure 11. Cost-effectiveness plane for the scenario analysis where the relationships between S-K and adverse clinical outcomes have been entirely removed, HF population

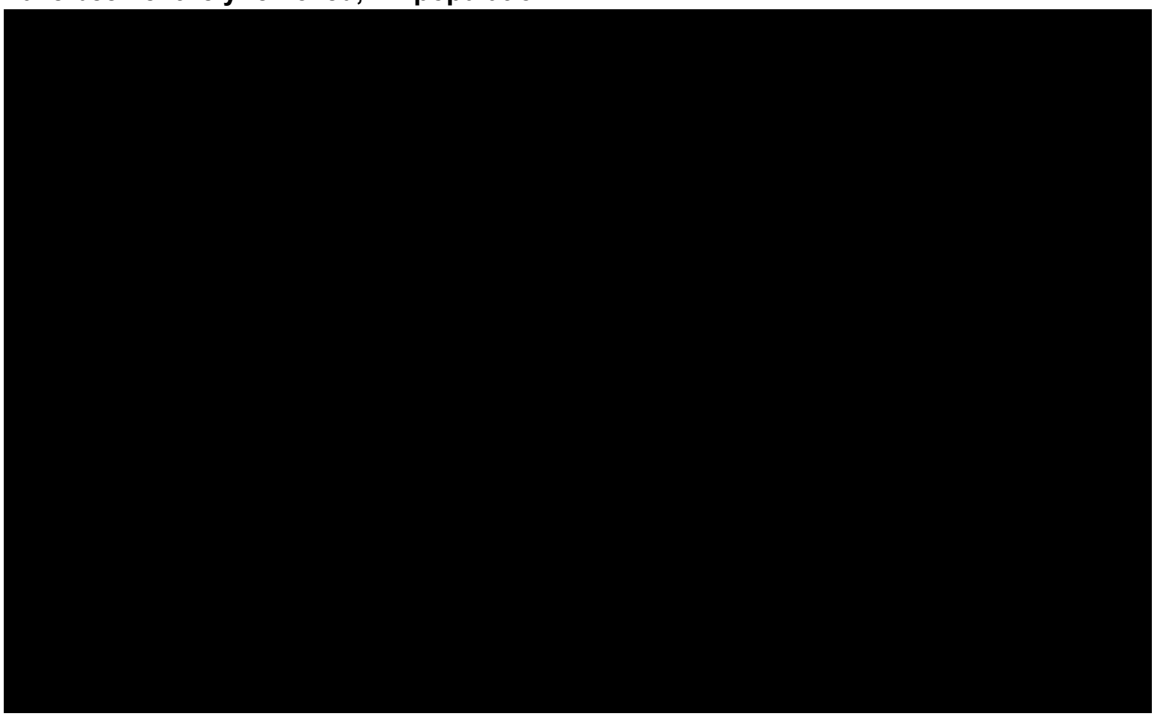
Abbreviations: ACD2, second appraisal consultation document; CE, cost-effectiveness, HF, heart failure, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; S-K, serum potassium; WTP, willingness to pay.

Figure 12. CEAC for the scenario analysis where the relationships between S-K and adverse

clinical outcomes have been entirely removed, HF population

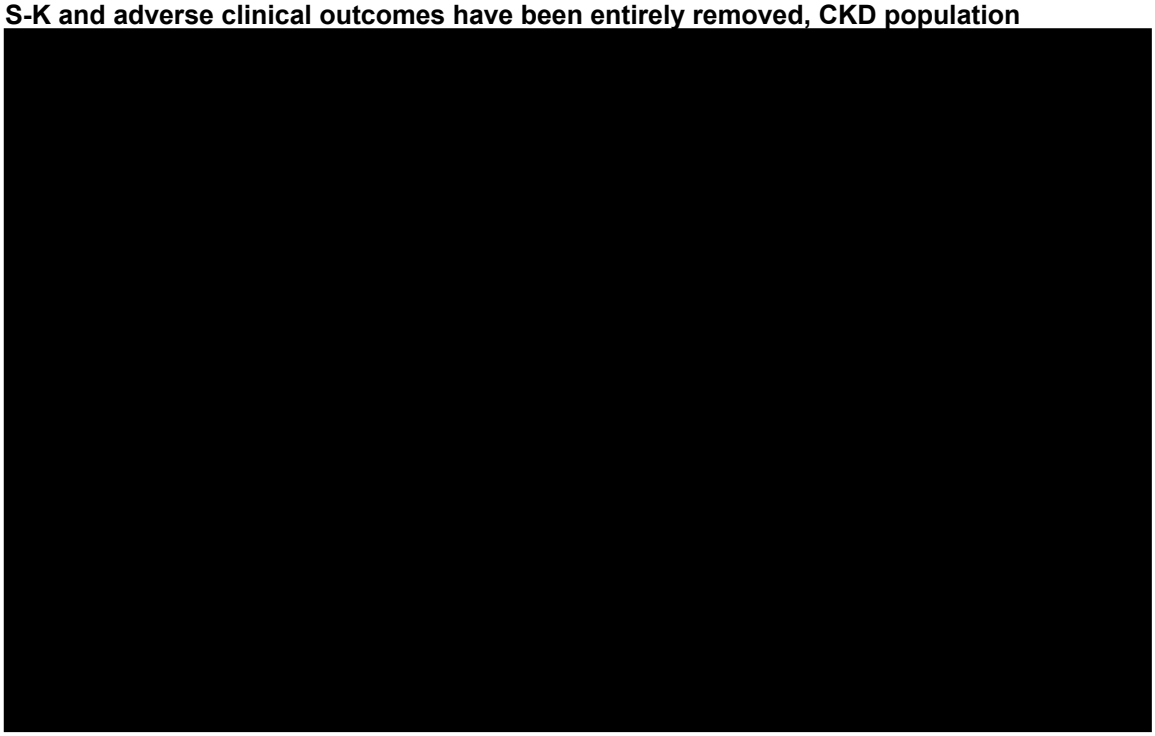
Abbreviations: ACD2, second appraisal consultation document; CEAC, cost-effectiveness acceptability curve; HF, heart failure, QALY, quality-adjusted life years; S-K, serum potassium; WTP, willingness to pay.

Figure 13. Graph showing ICER convergence with increasing number of PSA simulations in the scenario analysis where the relationships between S-K and adverse clinical outcomes have been entirely removed, HF population



Abbreviations: ACD2, second appraisal consultation document; HF, heart failure; ICER, incremental cost-effectiveness analysis; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life years; S-K, serum potassium.

Figure 14. Cost-effectiveness plane for the scenario analysis where the relationships between S-K and adverse clinical outcomes have been entirely removed, CKD population



Abbreviations: ACD2, second appraisal consultation document; CE, cost-effectiveness, CKD, chronic kidney disease, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; S-K, serum potassium; WTP, willingness to pay.

Figure 15. CEAC for the scenario analysis where the relationships between S-K and adverse clinical outcomes have been entirely removed, CKD population

Abbreviations: ACD2, second appraisal consultation document; CEAC, cost-effectiveness acceptability curve; CKD, chronic kidney disease, QALY, quality-adjusted life years; S-K, serum potassium; WTP, willingness to pay.

Figure 16. Graph showing ICER convergence with increasing number of PSA simulations in the scenario analysis where the relationships between S-K and adverse clinical outcomes have been entirely removed, CKD population

Abbreviations: ACD2, second appraisal consultation document; CKD, chronic kidney disease; ICER, incremental cost-effectiveness analysis; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life years; S-K, serum potassium.

7 Factual inaccuracies identified in the ACD

Table 5: Factual inaccuracies identified in the ACD2

Section	ACD2 statement	Comments/Corrections
Section 3.1, page 5	• The company defined high serum potassium values as above 5.0 mmol/litre, […] • The committee concluded that the company's clinical definition of hyperkalaemia as serum potassium levels above 5.0 mmol/litre was not widely accepted. It also concluded that, unless they need emergency treatment, few patients in the NHS with serum potassium levels above 5.0 mmol/litre have treatment to lower potassium.	• These statements in the ACD2 are misleading, as the company defined clinically relevant hyperkalaemia as S-K ≥5.5 mmol/L in HF patients and S-K ≥6.0 mmol/L in CKD patients in response to the ACD1. • The treatment threshold in the SZC trials were set at S-K ≥5.1 mmol/L. If the statement in the ACD2 referred to the S-K threshold used in the SZC trials, then this should be clarified to avoid misunderstanding.
Section 3.4, page 9	• The committee was aware that an NIHR-funded trial is evaluating the potential benefit of withdrawing ACE inhibitors and ARBs in people with stage 4 or 5 chronic kidney disease.	• As responded to by Dr McCafferty at the second Committee meeting, this NIHR-funded trial aims to test the hypothesis that RAASi induced reduction in GFR could adversely influence outcomes and management e.g. earlier instigation of dialysis. This study has not reported and therefore implications are currently unknown and are of no importance to a decision on hyperkalaemia management. • The positioning of SZC is to support RAASi where RAASi is clinically indicated.
Section 3.4, page 9	• The British Society for Heart Failure's response to consultation and a clinical expert present at the second meeting both noted that RAAS inhibitors may be of greater benefit in people with heart failure with reduced ejection fraction compared with people with preserved ejection fraction.	• AstraZeneca would like to clarify that RAASi therapy is not indicated in HFpEF patients, and that we are positioning SZC as a treatment option where RAASi therapy is proven to give mortality and disease modification benefits such as HFrEF.
Section 3.5, page 10	• The clinical experts explained that they consider the diet worth trying, that it is recommended by NICE, and that it lowers serum potassium compared with an unrestricted diet.	• Based on clinical expert engagement, dietitian-supported low potassium diets are only used by patients with later stage CKD in UK clinical practice. For HF patients, only high-level advice on low potassium diets are provided which is of no proven benefit.
Section 3.5, page 10	• The committee concluded that sodium zirconium cyclosilicate is unlikely to replace a low-potassium diet.	• SZC is not positioned to replace a low potassium diet. • SZC is positioned to be used alongside low potassium diet where clinically appropriate, when a strict low potassium diet is not possible, or when low potassium diet does not work. • SZC may allow patients to have a less restrictive low potassium diet.
Section 3.7, page 11	• The company proposed that sodium zirconium cyclosilicate would be used: o In an outpatient setting, as an alternative to stopping RAAS inhibitors and a strict low-potassium diet to manage chronic hyperkalaemia and prevent it developing into life-threatening hyperkalaemia	

	• In people with hyperkalaemia identified through routine monitoring; the clinical and patient experts did not expect sodium zirconium cyclosilicate to replace the need for a low-potassium diet (see section 3.5).	
Section 3.11, page 16	• The committee also noted the wording from the European Medicines Agency that the risk of intestinal perforation is currently unknown but has been reported with polymers that act in the gastrointestinal tract. The committee concluded that sodium zirconium cyclosilicate is associated with adverse effects.	• Intestinal perforation is a complication associated with polymers/sorbitol and has therefore been added to the SmPC as a precaution. There is no biological rationale for this complication to occur with SZC, and clinical trials show that gastrointestinal side effects are not seen more commonly with SZC (ZS-004: 6.7% [5 g OD] and 2.0% [10 g OD] of patients in the maintenance phase) compared to placebo (ZS-004: 14.1% of patients during the maintenance phase).We would also like to clarify that SZC is not a polymer, unlike calcium resonium. • The SmPC states: *"The risk for intestinal perforation with the use of Lokelma is currently unknown. No events of intestinal perforation have been reported with Lokelma. Since intestinal perforation has been reported 4 with polymers that act in the gastrointestinal tract, specific attention should be paid to signs and symptoms related to intestinal perforation."*
Section 3.23, page 28	• The patient experts stated that, if the company had shown evidence for these benefits, then sodium zirconium cyclosilicate would be innovative.	• This sentence is misleading as it does not represent our understanding of the views expressed by the patient expert at the first and second Committee meetings. This patient expert should be specifically asked the question about innovation to ensure ACD accurately represents their views. •

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

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Contributions of authors

Matt Stevenson and Andrew Rawdin critiqued the health economic analysis and clinical evidence submitted by the company. Lesley Uttley critiqued the literature review within the company's submission and clinical evidence. All authors were involved in drafting and commenting on the final report.

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1. Executive Summary

Sodium Zirconium Cyclosilicate (SZC) for the treatment of hyperkalaemia (HK) was appraised by NICE in October 2018, which resulted in a negative recommendation within the initial 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 first ACD.[2]

Following the second appraisal committee, NICE issued a second ACD, which recommended SZC as an option for treating HK in adults only if it needs treating in an emergency care setting and the drug is stopped after 28 days of maintenance treatment, or earlier if the HK resolves. The company responded to the second ACD by submitting a 31-page document, a slightly amended model and a two-page document summarising the implementation changes within the model. Subsequently, following a change in the proposed patient access scheme (PAS) the company submitted a revised document (32 pages) and a four-page document detailing the ICERs without the PAS. Collectively, these documents will be termed the company's response to the second ACD. The company's response to the second ACD focusses only on the use of SZC in the outpatient setting as will this report.

The company's executive summary in its response to the second ACD focussed on six 'key issues' which are:

1. The significant need to provide an alternative option for treating HK in the outpatient setting to that of management of renin-angiotensin-aldosterone system inhibitors (RAASi) dose.
2. That the company do not consider clinically relevant HK to be defined as a serum potassium (S-K) levels >5.0mmol/L.
3. That there is a multitude of data which support an association between S-K levels and long-term outcomes.
4. That the risk of hypokalaemia is low for patients with starting S-K levels ≥5.5mmol/L.
5. That the company and independent professional bodies consider that SZC is innovative.
6. That following the introduction of a PAS which provides a simple discount on the price of SZC and a change increasing the S-K level required for treatment of HK in patients with Heart Failure (HF) from ≥5.5mmol/L to ≥6.0mmol/L, SZC is a cost-effective treatment for the management of HK in an outpatient setting.

The six key issues are critiqued in turn within this report by the evidence review group (ERG). However, many of the issues are believed to be either outside of the remit of the ERG or continuations

of discussions held at the Committee where the ERG has no additional information; these are issues 1, 2, 4 and 5 which are not critiqued.

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 provided. The ERG has verified that these have been implemented correctly. Finally, following a request by NICE, an alternative set of results have been produced using an S-K level of ≥5.5mmol/L for patients with HF to show the impact of the change in treatment threshold for this group.

At list price, the base case results produced by the company within the acute setting are approximately £21,000 per QALY gained for patients with chronic kidney disease (CKD) and £13,000 per QALY gained for patients with HF, although these values increase to approximately £36,000 for patients with CKD and £44,000 for patients with HF, if it is believed that there is no relationship between S-K levels and adverse events. If the threshold for treatment is reduced from 6.0mmol/L to 5.5mmol/L for the population with HF the base case value increases to approximately £27,000, and the ICER increases to approximately £87,000 assuming no relationship between S-K levels and adverse events. Results produced when incorporating the PAS proposed by the company are contained in the confidential appendices.

The ERG acknowledges considerable uncertainty within the results which is detailed in Section 5.2. The ERG comments that many of these limitations could be resolved if a clinical trial were conducted comparing SZC to an active control which represents standard care in the outpatient setting 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 possible improved management of RAASi therapy.

2. The key issues

Note that key issues 1, 2, 4 and 5 were not critiqued by the ERG.

2.1 Key Issue 3 – The link between S-K levels and adverse outcomes.

ACD2 comment (Section 3.12): *The committee noted that the observational data did not guarantee an independent association between high serum potassium levels and death……The committee concluded that there was insufficient evidence to prove definitively that lowering serum potassium levels in the outpatient setting leads to improved outcomes*."

ACD2 comment (Section 3.16): *The committee concluded that it would like to have seen that sodium zirconium cyclosilicate was cost effective in the absence of an association between serum potassium and adverse outcomes, including death*."

ACD2 comment (Section 3.19): [*The committee] also noted that the studies may have been affected by time-dependent confounding, for example, because increasing serum potassium levels affects RAAS inhibitor use, which in turn affects subsequent serum potassium levels and long-term outcomes. Therefore, RAAS inhibitor use is a time-dependent confounder. The committee was aware that using standard regression adjustment is not appropriate when attempting to estimate causal effects from observational data affected by time-dependent confounding, and noted that the company was unable to show that alternative appropriate methods had been used.*"

ACD2 comment (Section 3.22): [The committee] *agreed that an ICER for decision making would lie near the ERG's scenario analysis removing the association between serum potassium levels and outcomes.*"

2.1.1 The review undertaken by the company

The company state that they have undertaken a systematic review to support a link between S-K levels and adverse events. The ERG contends that the term systematic review should not be applied. Elaboration of this issue is provided in Appendix 1. The company summarise the evidence base in Section 3 of its response to the second ACD and state that it would '*be inappropriate to base decision making on a scenario where the relationships between S-K levels and adverse clinical outcomes are entirely removed*.' and cite that NICE clinical guidelines use S-K levels as a basis for treatment decisions.

2.1.2 Time-dependent variables

To acknowledge the comments made by the committee related to the potential for time-dependent confounding the company provided further details on the methods employed within the published literature (Section 3.3 of the company's response to the second ACD). The company has maintained the relationship between S-K levels and adverse events used previously in the base case, whilst scenario analyses have been conducted where (i) the relationship is removed and (ii) the relationship is set to half that within the base case.

The ERG comments that the key papers, Luo *et al*.[3] and Furuland *et al*.,[4] identify associations between S-K levels and adverse events (long-term outcomes) rather than proving that the adverse events are caused by S-K levels, a feature which is acknowledged within the papers. Thus, there remains a possibility that there could be no association between S-K levels and long-term outcomes, however it is the belief of the ERG that this is highly unlikely given the clinical intervention in patients with high S-K levels in the emergency setting and NICE guidance related to RAASi use in patients with high S-K levels.[5]

2.1.3 ERG summary of key issue 1

The company base case assumes full causality between changes in S-K levels and changes in the risks of adverse events reported in the literature which is likely to be favourable to SZC. The ERG considers that an analysis where the relationship between a change in S-K levels and changes in the risks of adverse events is removed is highly unlikely, and will be unfavourable to SZC.

2.2 Key Issue 6 – The cost-effectiveness of SZC in the outpatient setting following a PAS and an increase in the threshold for treatment for those with HF

2.2.1 The PAS

In its response to the second ACD, the company submitted a PAS (a simple discount) [redacted]

The ERG had verified the results produced using the initially submitted PAS and has assumed that the ICERs reported by the company for the new PAS are correct (the model associated with the new PAS was not provided to the ERG). As the PAS has not been formally approved the results incorporating the PAS have been contained in (confidential) Appendix 2, with results relating to the list price contained in the main document.

2.2.2 The increase in treatment threshold from ≥5.5mmol/L to ≥6.0mmol/L for patients with HF

The company state that the change was made to address '*the Committee's comment at the second Committee meeting that some clinicians may treat HF patients at higher S-K thresholds than previously modelled*.' The ERG comment that this represents a changed position from the company who had stated in the response to clarification[6] and the response to the first ACD[2] that S-K levels ≥5.5mmol/L was the appropriate threshold for treating people with HF. As such, it is unclear whether the change in threshold put forward by the company is related to a change in belief relating to clinical judgement, or whether the company are focusing on treating patients with higher S-K levels, and therefore higher risks of adverse events.

2.2.3 ERG summary of key issue 6

The ERG is satisfied that the company implemented the original PAS as intended. The rationale for the increase in treatment threshold for patients with HF is unclear. As such the ERG has conducted analyses using the previous threshold, of ≥5.5mmol/L to allow the committee to see the implications of the threshold change.

3 The cost-effectiveness results presented by the company

3.1 The company's base case values

The deterministic base case results from the company have been provided in Table 1. The company presented probabilistic analyses which produced similar results to the deterministic ones. As such, only deterministic values are presented in this report.

Table 1: The base case results estimated by the company

Underlying disease	Δ Costs	Δ QALYs	Cost per QALY
CKD	£9,750	0.472	£20,674
HF	£10,624	0.811	£13,100

The company changed its base case to take into consideration the preferences of the NICE Appraisal Committee and to adopt some of the assumptions within the ERG base case. The ERG is content that these changes are appropriate, with further details on each provided in the previous ERG report.[7] A key additional change was made for patients with HF in that the threshold for treatment has been increased, as detailed in Section 2.2.2.

The impacts of each component of the changes between the company's base case following the first ACD and the company's new base case (at list price) are shown in Table 2 for patients with CKD and in Table 3 for patients with HF. The ERG obtained a different result for reducing the threshold for treating HF to ≥5.5mmol/L in the company base case than the company did. The reason for this is unknown.

Table 2: The impact of changes between the company's base case following ACD1 and the new base case (at list price) for patients with CKD

#	Scenario	Δ Costs	Δ QALYs	ICER
1	Company base case submitted in the ACD1 response	£8,249	0.708	£11,644
2	Company ACD1 base case + applying a 3-day S-K reduction in the correction phase *(as per the ERG base case)*	£11,362	0.573	£19,815
3	Company ACD1 base case + setting the RAASi discontinuation, down-titration and re-initiation rates in SZC to that of SoC *(as per the ERG base case)*	£1,397	0.443	£3,155
4	Company ACD1 base case + life-time SZC treatment *(as per Committee's preference, ACD2 Section 3.19)*	£9,225	0.879	£10,491
5	Company ACD1 base case + using OR for RAASi compared to placebo *(as per Committee's preference, ACD2 Section 3.22)*	£8,249	0.708	£11,644
6	Company ACD1 base case + amending the utility values for people with CKD *(as per the ERG base case)*	£8,249	0.654	£12,605
7	Updated company ACD2 base case (combining 1-6)	£9,750	0.472	£20,674

Table 3: The impact of changes between the company's base case following ACD1 and the new base case (at list price) for patients with HF

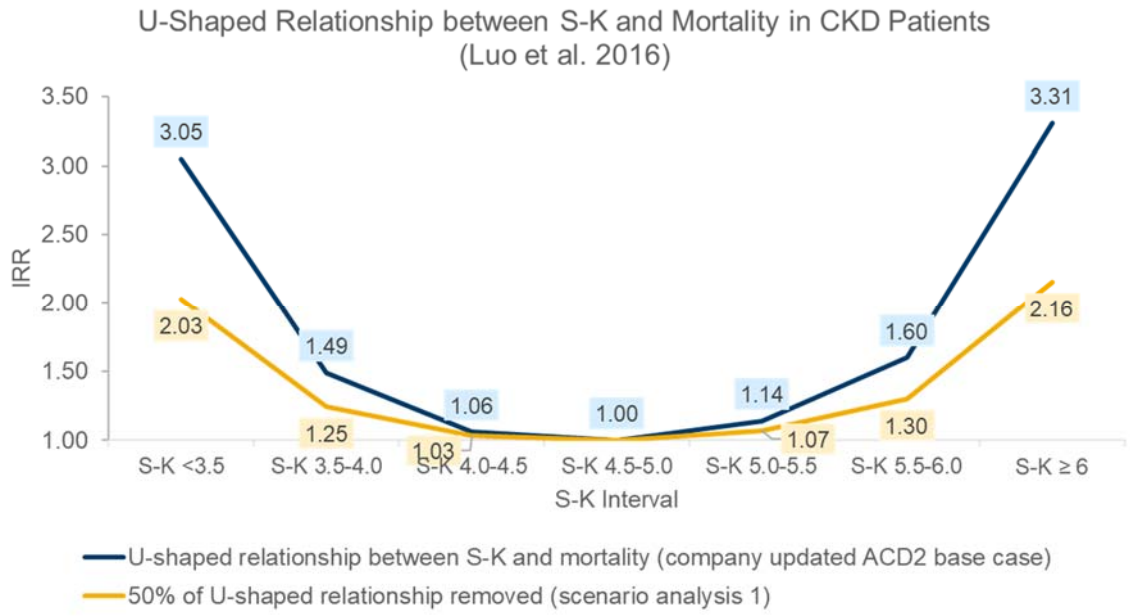
#	Scenario	Δ Costs	Δ QALYs	ICER
1	Company base case submitted in the ACD1 response	£14,860	0.818	£18,158
2	Company ACD1 base case + applying a 3-day S-K reduction in the correction phase *(as per the ERG base case)*	£13,928	0.641	£21,729
3	Company ACD1 base case + setting the RAASi discontinuation, down-titration and re-initiation rates in SZC to that of SoC *(as per the ERG base case)*	£12,293	0.634	£19,385
4	Company ACD1 base case + life-time SZC treatment *(as per Committee's preference, ACD2 Section 3.19)*	£17,003	0.938	£18,125
5	Company ACD1 base case + threshold for treatment changed to S-K ≥6.0 mmol/L *(as per Committee's preference, ACD2 Section 3.7 and discussions at second Committee meeting)*	£7,883	0.965	£8,172
6	Updated company ACD2 base case (combining 1-5)	£10,624	0.811	£13,100
7	Updated company ACD2 base case reverting to a threshold of ≥5.5mmol/L*	£18,183	0.664	£27,370

*The ERG produced these results whereas the company had an ICER of £26,127 (ΔC = £16,100; ΔQ = 0.616)

The company undertook a number of scenario analyses related to the use of SZC in the outpatient setting. These are detailed in turn.

Scenario 1: Reducing the assumed relationships between S-K and adverse clinical outcomes to half that in the base case. An example of this is shown in Figure 1.

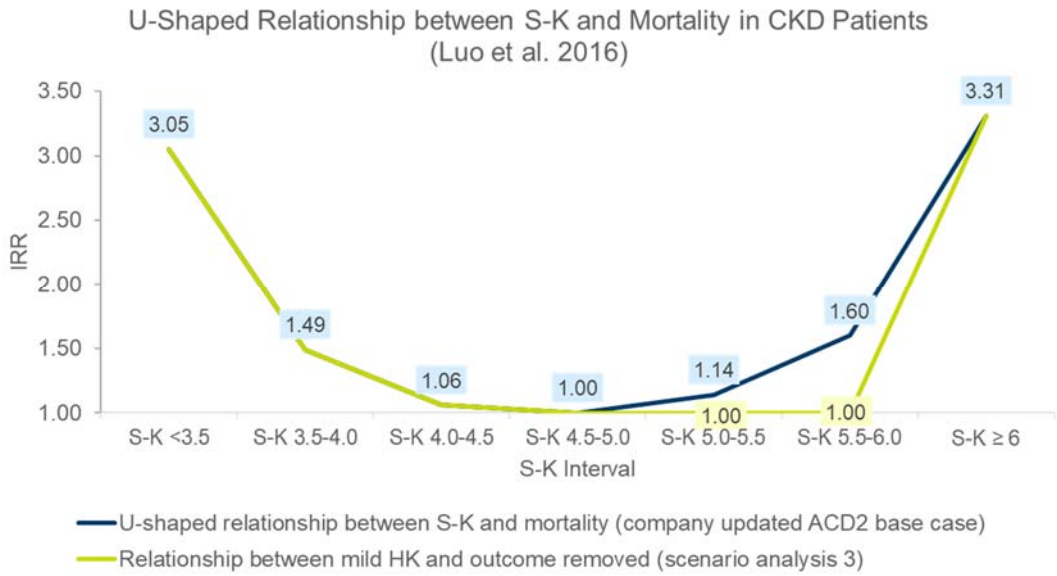
Figure 1: An example of the reduced relationship between S-K levels and adverse events.



Scenario 2: Removing the assumed relationships between S-K levels and adverse clinical outcomes to half that in the base case. This would be akin to using a line that was horizontal at 1.00 in Figure 1.

Scenario 3: Removing the assumed relationship between S-K levels and adverse clinical outcomes for patients with mild HK. This is depicted within Figure 2. Unlike scenarios 1 and 2 the ERG sees no clear rationale for this scenario analyses.

Figure 2: An example of the relationship between S-K levels and adverse events assumed in Scenario 3.



Scenarios 4 and 5: Reducing the assumed proportion of people receiving 10g of SZC daily (list price £14.24 per sachet) from 37.4% to 20% (Scenario 4) and 10% (Scenario 5). In these scenarios it is assumed that the reduction in the 10g dose is counterbalanced by an increase in the 5g group (list price £7.12). The company state the rationale for these scenario analyses is '*because the S-K treatment goal is less stringent in UK clinical practice (S-K <5.5 mmol/L and <6.0 mmol/L for HF and CKD patients, respectively) compared with those in the ZS-005 trial, it is likely that a smaller proportion of patients in UK clinical practice require dose up-titration in order to achieve normokalaemia as defined in the UK clinical practice*'. The ERG comments that the company has not provided the breakdown of drug distributions within the studies for patients with an S-K level ≥6.0mmol/L and thus it is also plausible that these would need more SZC than the average person in these studies, so that the drug cost may be underestimated. As such, the ERG does not believe that these scenario analyses should be factored into decision making. The ERG also comments that in the statement the company appear to be suggesting a threshold for treatment of ≥5.5mmol/L in HF which contradicts the threshold used in the base case (≥5.5mmol/L in HF).

Scenario 6: Using data from Furuland *et al.*[4] to populate the relationship between S-K level and adverse events for patients with CKD rather than from Desai *et al.*[8] The company has performed this scenario analysis as the data presented in Furuland *et al.*[4] are likely to be more representative of UK patients, as the study used data from the Clinical Practice Research Datalink.

The results from the scenario analyses at list price are shown in Table 4 for patients with CKD and in Table 5 for patients with HF.

Table 4: Scenario analyses run by the company for patients with CKD (at list price)

#	Scenario	Δ Costs	Δ QALYs	ICER
B	Updated company ACD2 base case	£9,750	0.472	£20,674
1	B + removing 50% of relationships between S-K and adverse clinical outcomes	£8,863	0.366	£24,211
2	B + removing 100% of relationships between S-K and adverse clinical outcomes	£7,893	0.219	£35,962
3	B + removing relationship between *mild* hyperkalaemia and adverse clinical outcomes	£8,962	0.397	£22,552
4	B + assuming 20% of patients receive 10g SZC daily	£8,092	0.472	£17,158
5	B + assuming 10% of patients receive 10g SZC daily	£7,140	0.472	£15,139
6	B + relationships between S-K and adverse clinical outcomes modelled based on Furuland *et al*.	£10,426	0.529	£19,709

Table 5: Scenario analyses run by the company for patients with HF (at list price)

#	Scenario	Δ Costs	Δ QALYs	ICER
B	Updated company ACD2 base case	£10,624	0.811	£13,100
1	B + removing 50% of relationships between S-K and adverse clinical outcomes	£9,559	0.593	£16,110
2	B + removing 100% of relationships between S-K and adverse clinical outcomes	£7,172	0.164	£43,781
3	B + removing relationship between *mild* hyperkalaemia and adverse clinical outcomes	£11,107	0.600	£18,508
4	B + assuming 20% of patients receive 10g SZC daily	£8,603	0.811	£10,608
5	B + assuming 10% of patients receive 10g SZC daily	£7,442	0.811	£9,177

4 Exploratory analyses undertaken by the ERG

4.1 Reverting to a treatment threshold of ≥5.5mmol/L for patients with HF

The ERG reran the analyses undertaken by the company (at list price) for patients with HF using the threshold that the company had stated was the most appropriate throughout the appraisal until the response to the second ACD. These results are shown in Table 6.

Table 6: Scenario analyses run by the ERG for patients with HF (list price) assuming a treatment threshold of ≥5.5mmol/L

#	Scenario	Δ Costs	Δ QALYs	ICER
B	Updated company ACD2 base case but using a threshold of ≥5.5mmol/L*	£18,183	0.66	£27,370
1	B + removing 50% of relationships between S-K and adverse clinical outcomes	£18,775	0.49	£38,137
2	B + removing 100% of relationships between S-K and adverse clinical outcomes	£19,326	0.22	£87,170
3	B + removing relationship between *mild* hyperkalaemia and adverse clinical outcomes	£19,619	0.35	£55,505
4	B + assuming 20% of patients receive 10g SZC daily	£15,848	0.66	£23,855
5	B + assuming 10% of patients receive 10g SZC daily	£14,507	0.66	£21,836

* The ERG produced these results whereas the company had an ICER of £26,127 (ΔC = £16,100; ΔQ = 0.616)

5 Discussion

5.1 Summarising the cost-effectiveness results

The base case results produced by the company are below £21,000 per QALY gained for both patients with CKD, and patients with HF in the outpatient setting. The ICERs for both groups of patients increase considerably when it is assumed that there is no relationship between S-K levels and adverse events increasing to over £35,000 in patients with CKD and to over £43,000 in patients with HF. The ICERs also increase for patients with HF when it is assumed that the threshold for treatment on HK is reduced to ≥5.5mmol/L as previously stated by the company. In this circumstance, the base case ICER is approximately £26,000 and increases to over £87,000 when the assumption of a relationship between S-K levels and adverse outcomes is removed. These values are at list price; however, the company have proposed a PAS, the consequences of which are shown in (confidential) Appendix 2.

5.2 Limitations

The is still considerable uncertainty within the decision problem. 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 the maintenance phase. 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. The ERG notes 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 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 diabetes mellitus 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.

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 the outpatient setting 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 possible improved management of RAASi therapy.

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Appendix 1: ERG critique of the company identification of evidence

The company response to the first ACD (January 2019) described that a systematic review had been conducted on the relationship between S-K and longer-term poor clinical outcomes (mortality, adverse cardiac events and hospitalisation). The ERG notes the following concerns with the review presented in the company's response to the ACD which preclude the review being considered as "systematic":

1. It is not clear from the description of excluded studies how the 123 studies identified as being included studies in the preferred reporting guidelines for systematic reviews and meta-analyses (PRISMA) diagrams (and provided as the list of included studies) becomes 59 studies. Reasons for omission of the other 64 studies from the review are not provided. The review is therefore not transparent.

2. The searches were not appropriately conceptualised to identify all relevant evidence and would not be adequate to enable publication as a systematic review in a high-quality peer-reviewed journal. The review is therefore not comprehensive.

3. Some papers are described for more "granular" analysis relevant to the review question. This selectively highlights certain studies that support the company's hypothesis. Some of these studies are funded by/affiliated with the company (e.g., [redacted])[13]. In a systematic review, all included studies must be given equal weight. The review is therefore not impartial.

4. There is no quality assessment to appraise the relevance, scientific rigour or value of the included studies to the review question. Critical appraisal is a hallmark of systematic review methodology. The review is therefore not rigorous.

5. It is not clear whether the numbers in the PRISMA chart include results excluded on the basis of date. The review is therefore not replicable.

6. It is not clear what proportion of citations or data were independently checked by a second reviewer. The review is therefore not good practice.

Company identification of evidence to support assumptions about RAASi therapy

The company response (January 2019) also described that "targeted" reviews on RAASi therapy and S-K levels, RAASi down-titration or discontinuation on S-K levels had been conducted as there was not sufficient time to conduct a systematic review. It is not clear from the company response how the targeted review methods differ from the systematic review methods, where an unclear selection of papers which support the company's position are highlighted without critical appraisal.

The company's targeted reviews resulted in the selection of a low number of studies on:

- RAASi and clinical outcomes in CKD patients
- RAASi down-titration or discontinuation on mortality, hospitality and cardiovascular outcomes
- RAASi therapy for delaying progression of CKD and HF
- Change from RAASi to another hypertensive drug

The company response to ACD1 described plans to complement the targeted literature review approach with a thorough systematic literature review of the evidence, but stated that "*however, outputs of this will not be available in advance of responding to the ACD.*" During the appraisal committee meeting (26th March, 2019), the ERG enquired if the update of the targeted review to systematic review was available and the company stated that they would make it available. No further reviews have been received from the company by the ERG since the company's response to the ACD1 in January 2019.

ERG concluding comment

The ERG highlight that systematic reviews designed and conducted to support a one-sided argument are a contradiction in terms. The sole purpose of conducting a systematic review is to perform an unbiased and rigorous appraisal of all relevant literature. The company-identified evidence through bibliographic databases support a correlative U-shaped relationship between S-K levels and poor clinical outcomes. As highlighted previously, there are no primary clinical trials or systematic reviews to demonstrate a causal relationship that lowering S-K reduces poor clinical outcomes. There are also no data to support that lowering S-K facilitates patients receiving optimised RAASi therapy.

Appendix 2: Cost-effectiveness results applying the PAS initially submitted by the company

The results contained in this appendix have incorporated the PAS submitted by the company in response to the second ACD which is a simple discount of [redacted] on both the 5g and 10g doses. The ICERs produced by the company using the PAS within the base case are shown in Table 7 for patients with CKD and in Table 8 for patients with HF. Analyses run by the company assuming a threshold of ≥5.5mmol/L for treating patients with HF are shown in Table 9, although these results were not obtained by the ERG; the reason for this is unclear. The results produced by the ERG are provided in Table 10.

The base case results produced by the company within the acute setting are approximately [redacted] per QALY gained for patients with chronic kidney disease (CKD) and [redacted] per QALY gained for patients with HF, although these values increase to approximately [redacted] for both patient groups if it is believed that there is no relationship between S-K levels and adverse events. If the threshold for treatment is reduced from 6.0mmol/L to 5.5mmol/L the ICERs for the population with HF are approximately [redacted] (base case) and over [redacted] (when there is no association between S-K levels and adverse events).

Table 7: Scenario analyses run by the company for patients with CKD (PAS price)

#	Scenario	Δ Costs	Δ QALYs	ICER
B	Updated company ACD2 base case	£9,750	0.472	£20,674
1	B + incorporation of a [redacted] PAS	[redacted]	[redacted]	[redacted]
2	1 + removing 50% of relationships between S-K and adverse clinical outcomes	[redacted]	[redacted]	[redacted]
3	1 + removing 100% of relationships between S-K and adverse clinical outcomes	[redacted]	[redacted]	[redacted]
4	1 + removing relationship between *mild* hyperkalaemia and adverse clinical outcomes	[redacted]	[redacted]	[redacted]
5	1 + assuming 20% of patients receive 10g SZC daily	[redacted]	[redacted]	[redacted]
6	1 + assuming 10% of patients receive 10g SZC daily	[redacted]	[redacted]	[redacted]
7	1 + relationships between S-K and adverse clinical outcomes modelled based on Furuland *et al*.	[redacted]	[redacted]	[redacted]

Table 8: Scenario analyses run by the company for patients with HF (PAS price)

#	Scenario	Δ Costs	Δ QALYs	ICER
B	Updated company ACD2 base case	£10,624	0.811	£13,100
1	B + incorporation of a [redacted] PAS	[redacted]	[redacted]	[redacted]
2	1 + removing 50% of relationships between S-K and adverse clinical outcomes	[redacted]	[redacted]	[redacted]
3	1 + removing 100% of relationships between S-K and adverse clinical outcomes	[redacted]	[redacted]	[redacted]
4	1 + removing relationship between *mild* hyperkalaemia and adverse clinical outcomes	[redacted]	[redacted]	[redacted]
5	1 + assuming 20% of patients receive 10g SZC daily	[redacted]	[redacted]	[redacted]
6	1 + assuming 10% of patients receive 10g SZC daily	[redacted]	[redacted]	[redacted]

Table 9: Scenario analyses run by the company for patients with HF (PAS price) assuming a threshold of ≥5.5mmol/L for patients with HF.

#	Scenario	Δ Costs	Δ QALYs	ICER
B	Updated company ACD2 base case (with PAS)	[redacted]	[redacted]	[redacted]
1	B + changing the threshold for treatment of HK to ≥5.5mmol/L	[redacted]	[redacted]	[redacted]
2	1 + removing 50% of relationships between S-K and adverse clinical outcomes	[redacted]	[redacted]	[redacted]
3	1 + removing 100% of relationships between S-K and adverse clinical outcomes	[redacted]	[redacted]	[redacted]
4	1 + removing relationship between *mild* hyperkalaemia and adverse clinical outcomes	[redacted]	[redacted]	[redacted]
5	1 + assuming 20% of patients receive 10g SZC daily	[redacted]	[redacted]	[redacted]
6	1 + assuming 10% of patients receive 10g SZC daily	[redacted]	[redacted]	[redacted]

Table 10: Scenario analyses run by the ERG for patients with HF (PAS price) assuming a threshold of ≥5.5mmol/L for patients with HF.

#	Scenario	Δ Costs	Δ QALYs	ICER
B	Updated company ACD2 base case (with PAS)	[redacted]	[redacted]	[redacted]
1	B + changing the threshold for treatment of HK to ≥5.5mmol/L	[redacted]	[redacted]	[redacted]
2	1 + removing 50% of relationships between S-K and adverse clinical outcomes	[redacted]	[redacted]	[redacted]
3	1 + removing 100% of relationships between S-K and adverse clinical outcomes	[redacted]	[redacted]	[redacted]
4	1 + removing relationship between *mild* hyperkalaemia and adverse clinical outcomes	[redacted]	[redacted]	[redacted]
5	1 + assuming 20% of patients receive 10g SZC daily	[redacted]	[redacted]	[redacted]
6	1 + assuming 10% of patients receive 10g SZC daily	[redacted]	[redacted]	[redacted]