


BMJ Open Randomised, blinded, cross-over evaluation of the palatability of and preference for different potassium binders in participants with chronic hyperkalaemia in the USA, Canada and Europe: the APPETIZE study

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ABSTRACT

Objectives Traditional potassium (K⁺) binders for treating hyperkalaemia are unpalatable and poorly tolerated. Newer K⁺ binders are reportedly better tolerated; however, no published data describe their palatability, a determinant of long-term adherence. This study evaluated the palatability of and preference for three K⁺ binders: sodium and calcium polystyrene sulfonate (S/CPS), sodium zirconium cyclosilicate (SZC) and calcium patiromer sorbitex (patiromer).

Design Phase 4, randomised, participant-blinded, cross-over study. Participants were randomised to one of six taste sequences and, using a 'sip and spit' approach, tasted each K⁺ binder before completing a survey.

Setting 17 centres across the USA, Canada and European Union.

Participants 144 participants with chronic kidney disease, hyperkalaemia and no recent use of K⁺ binders.

Main outcome measures For the primary (USA) and key secondary (Canada and European Union) endpoints, participants rated palatability attributes (taste, texture, smell and mouthfeel) and willingness to take each K⁺ binder on a scale of 0–10 (rational evaluation). Feelings about each attribute, and the idea of taking the product once daily, were evaluated using a non-verbal, visual measure of emotional response. Finally, participants ranked the K⁺ binders according to palatability.

Results In each region, SZC and patiromer outperformed S/CPS on overall palatability (a composite of taste, texture, smell and mouthfeel), based on rational evaluation and emotional response. Taking the product once daily was more appealing for SZC and patiromer, creating greater receptivity than the idea of taking S/CPS. The emotional response to mouthfeel had the strongest influence on feelings about taking each product. In each region, a numerically greater proportion of participants ranked SZC as the most preferred K⁺ binder versus patiromer or S/CPS.

Conclusions Preference for more palatable K⁺ binders such as SZC and patiromer may provide an opportunity

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study compared three K⁺ binders in terms of palatability, an important contributing factor to long-term medication adherence.
- ⇒ The palatability attributes evaluated were considered important to medication adherence by patients receiving long-term treatment; a patient advisory board guided key aspects of study design.
- ⇒ The AdSAM tool captured participants' instinctive feelings about each K⁺ binder undiluted by rationalisation, mimicking how the brain processes emotions.
- ⇒ This exploratory study is the first example of emotional responses being evaluated in participants receiving different pharmacotherapies.
- ⇒ The main limitations of the study are the small sample size and the high proportion of missing data for the final ranking of the three K⁺ binders.

to improve adherence to long-term treatment of hyperkalaemia.

Trial registration number NCT04566653.

INTRODUCTION

Hyperkalaemia is a potentially life-threatening electrolyte abnormality, usually defined as serum potassium (K⁺) >5.0 mEq/L.¹ Patients with chronic kidney disease (CKD) receiving guideline-recommended treatment with renin–angiotensin–aldosterone system inhibitors (RAASi)² are at high risk of hyperkalaemia^{3–5} and consequently of adverse clinical outcomes and mortality.^{6–9}

While physicians frequently manage hyperkalaemia by downtitrating or discontinuing RAASi, this approach denies patients with

CKD the well-reported clinical benefits of RAASi and raises the risk of cardiovascular events, hospitalisation and mortality.^{3 5 10 11} Sodium and calcium polystyrene sulfonates (S/CPS) are traditional K⁺ binders composed of large shard-like particles with a sand-like mouthfeel, and are often described by recipients as being unpalatable.^{12 13} SPS is also associated with gastrointestinal complications ranging from constipation to more serious events such as bleeding, ischaemic colitis, colonic necrosis and colon perforation.^{14 15} Poor palatability and tolerability can negatively impact long-term treatment adherence; in a multicountry survey of patients taking S/CPS for hyperkalaemia, 60% took their K⁺ binder less than once a week and 54% discontinued due to gastrointestinal side effects.¹⁶ Poor adherence is associated with increased healthcare costs and resource utilisation, elevated K⁺ and worse outcomes.^{17 18}

Better tolerated and more palatable K⁺ binders are needed to allow treatment with RAASi to continue in patients with CKD who have, or are at risk of, hyperkalaemia. Two recently approved K⁺ binders, sodium zirconium cyclosilicate (SZC) and calcium patiromer sorbitex (patiromer), have been reported to be well tolerated in patients with hyperkalaemia,^{19–22} and to allow patients with CKD to maintain or even increase their RAASi dose.^{20 22–27} Both are recommended for persistent hyperkalaemia that prevents patients with CKD from receiving the optimum RAASi dose.^{28 29} However, the palatability of SZC and patiromer has yet to be determined. The APPE-TIZE study, therefore, aimed to determine the palatability of SZC, patiromer and S/CPS in participants with CKD and hyperkalaemia.

A plain language summary of this article is provided in online supplemental appendix 1 and an infographic summarising the findings in online supplemental appendix 2.

METHODS

Trial design

APPE-TIZE (ClinicalTrials.gov identifier: NCT04566653) was a multicentre, non-interventional, exploratory, phase 4, single-blind, cross-sectional, randomised, cross-over study performed in 17 centres across the USA, Canada and a European Union (EU) region comprising France, Spain and Italy. Screening occurred at visit 1, within 7 days of visit 2 (tasting day), to gather baseline safety, laboratory and electrocardiogram (ECG) data, and to confirm that eligibility criteria were met. On visit 2 (tasting day), eligible participants began tasting the products in a randomised sequence. One day or more after completing the tasting period, participants were followed up with a telephone call or site visit to assess safety.

The study adhered to the protocol and principles of the Declaration of Helsinki, and Council for International Organisations of Medical Sciences International Ethical Guidelines. The informed consent form and protocol were approved by independent ethics committees/

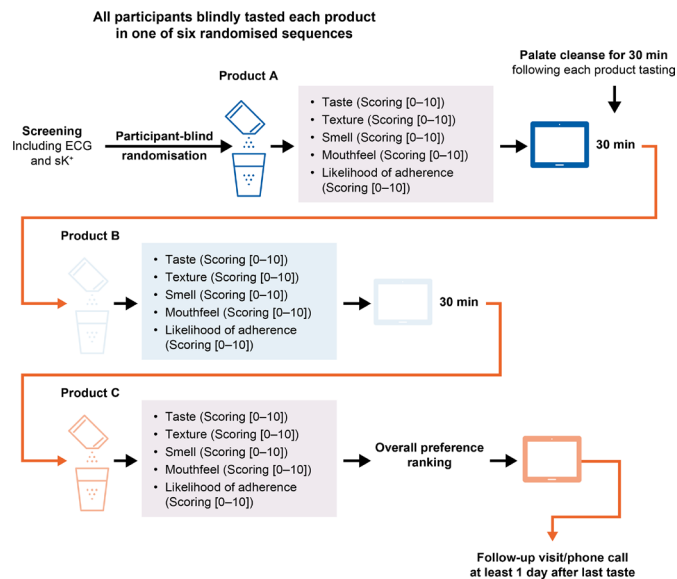


Figure 1 APPE-TIZE study design. ECG, electrocardiogram; sK⁺, serum potassium.

institutional review boards at each centre (online supplemental table S1) before study initiation. All participants provided written informed consent. This study was funded by AstraZeneca, who had a collaborative role in the study design/conduct.

Participants

Eligible participants were aged ≥ 18 years with dialysis-dependent or non-dialysis-dependent CKD (defined as two estimated glomerular filtration rate measurements < 60 mL/min/1.73 m², recorded at least 90 days apart) and hyperkalaemia (defined as serum K⁺ > 5.0 mmol/L). Participants were ineligible if they had a serum K⁺ value that necessitated immediate medical attention, were already receiving a K⁺ binder at screening/enrolment or had a condition that impaired their sense of taste or smell. Participants receiving concomitant oral medications were required to hold their medications from 3 hours pretasting through to 3 hours post-tasting to prevent drug–drug interactions. Full exclusion criteria are reported in the online supplemental appendix.

Randomisation and tasting

On visit 2 (tasting day), eligible participants were randomised 1:1:1:1:1:1 to one of six tasting sequences using an interactive web response system, based on a computer-generated randomisation schedule (figure 1). Randomisation was performed centrally to reduce potential bias and was stratified by region (USA, Canada and EU) and by whether participants were receiving dialysis (capped at 50% of the study cohort). Reduced participant numbers caused by early termination of recruitment in France resulted in a study protocol amendment and the merging of data from France, Spain and Italy to create one EU region and aid timely completion of the study.

Participants were blinded to what they were tasting. Site and sponsor personnel were not blinded; however, all

efforts were made to ensure that participant blinding was maintained. As the study objectives were based on subjective participant assessments and not objective assessment, random order assignment and participant blinding were deemed sufficient for bias mitigation.

The products were prepared according to local prescribing information and typical daily maintenance doses as follows: SZC 5 g for participants on dialysis or 10 g for participants not on dialysis, prepared with 45 mL of water; patiromer 8.4 g per 80 mL of water and S/CPS 15 g per 60 mL of water.

Participants were instructed to taste each product using the 'sip and spit' technique,¹² which involved taking a sip/mouthful of the product and swirling it around the mouth for 5 s, before expelling it into a measuring cup. The amount sipped and expectorated was at the discretion of each participant; participants were asked to take a sip/mouthful that was appropriate to them. Participants were required to expel the product back into a measuring cup to confirm that the product was not fully ($\geq 75\%$) ingested during tasting. The first tasting session occurred at least 2 hours after breakfast or lunch, and there was a palate cleanse (water and crackers) of 30 min or more between tastings. No food or drink was allowed during the tasting period other than the palate cleanse. If a participant ingested a full dose ($\geq 75\%$) of any product, they tasted no further products and preplanned safety assessments were performed. Medical intervention was implemented if they had serum $K^+ < 3$ mmol/L, corrected QT interval (QTc) > 550 ms or an increase in QTc interval > 60 ms from baseline.

Assessments

After tasting each product, participants completed an electronic questionnaire assessing four palatability attributes of taste, texture, smell and mouthfeel (the tactile aspects of texture perception during consumption^{30 31}), and participant willingness to take the product (theoretical likelihood of adherence).

Participants first rated how much they liked/disliked each attribute on a scale of 0–10 (rational evaluation). Scores for each attribute were combined to obtain an overall rational palatability composite score (0–40 per product). Participants then indicated how they felt about each attribute using AdSAM, a non-verbal, visual measure of emotional response. Emotional responses are measured in three fundamental dimensions (appeal, engagement and empowerment), which in combination define specific feelings.^{32 33} Briefly, three rows of Self-Assessment Manikins (icons) provided a visual representation of these dimensions. Participants quickly indicated their feelings by selecting one place on each row. For each dimension, responses were converted to numeric scores (1–9) for emotional response modelling, which included Perceptual Mapping and Emotion Group analysis, and for statistical analysis. In this study, scores for the four attributes were also combined to create an overall emotional composite score for palatability (4–36)

for each dimension. In addition, an Emotional Strength Indicator (ESI) score of 0–300 was derived from Emotion Group results for each attribute, and then ESI scores were combined to create a composite palatability ESI of 0–1200. ESI scores are weighted measures of positive, influential emotional connections based on the proportion of respondents expressing feelings that are most predictive of behaviour and the strength of influence those feelings have. More details of the AdSAM measure and the AdSAM Emotion Group analysis are provided in the online supplemental appendix.

Based on overall palatability, participants were then required to indicate how they would feel about taking the product once daily to manage K^+ levels. Finally, after tasting each product, participants ranked the three products in order of preference based on their overall tasting experience: 1=most preferred product; 2=second most preferred product and 3=least preferred product.

Safety was assessed based on the observation of adverse events (coded using Medical Dictionary for Regulatory Activities V.24.1), 12-lead ECG readings, blood pressure and clinical safety laboratory parameters.

The overall approach used in this study was designed to enable greater understanding of the palatability experience and how that may influence willingness to take a K^+ binder. The 0–10 rational palatability scoring provided a simple means of evaluation based on degree of like/dislike, while the AdSAM measure captures instinctive feelings about individual attributes. The nature of the emotional response and the feelings evoked provide insights into how the palatability attributes impact the tasting experience, and how those feelings influence willingness to take the product. For example, does the palatability create a pleasing experience that contributes to strong receptivity to taking the product? Does it leave participants with feelings of ambivalence or indifference? Does it create apprehension about taking the product? Does it disincentivise participants and make them disinterested in taking the product, or create a very unpleasant experience that creates strong aversion to the product?

Objectives

The primary objective was to compare overall rational palatability composite scores (0–40) between SZC and patiromer, and between SZC and S/CPS, in the USA. The primary objective was previously planned to be the difference in scores for taste in the total data. A protocol amendment prior to any analysis, and database lock, changed the primary objective to the overall rational palatability score (composite of taste, texture, smell and mouthfeel) in the USA instead to ensure an equal weighting of attributes and to reduce any confusion with a taste study.

Secondary objectives included evaluating overall rational palatability composite scores (0–40) between SZC and patiromer, and between SZC and S/CPS, in the combined EU countries and in Canada. Other secondary endpoints evaluated in each region were how willing patients would be to take each K^+ binder to help manage

their serum potassium (score 0–10), and the overall preference ranking of the three products (1–3). The change from evaluating the objectives in the total data to evaluating each of the regions (USA, Canada and EU) separately was made to focus on regional results.

A corresponding update was also made for the secondary objectives of the AdSAM endpoints, in that we compared AdSAM responses to individual emotional palatability attributes (4–36 composite scores for each of the appeal, engagement and empowerment dimensions) for each product in each region. Additional secondary objectives on AdSAM endpoints included: comparing ESI scores for each attribute, individually (score 0–300 each) and overall (composite score 0–1200); comparing willingness to take a K⁺ binder (1–9 for each of the appeal, engagement and empowerment dimensions); comparing ESI scores for willingness to take a K⁺ binder (score 0–300); other emotional response analytics.

Statistical analysis

The primary endpoint was a rational palatability composite score of taste, texture, smell and mouthfeel attributes. A type I error of 0.025 is assumed (Holm's procedure) to conservatively take into account that two comparisons were made for the primary endpoint (USA), this was also used for the corresponding endpoints in Canada and the EU. Prior to the protocol amendment, the sample size estimates were based on a mean difference of 1.2 and standard deviation (SD) of 2.7 in taste score (0–10); where the estimate of SD was based on a previous study of K⁺ binders which assessed acceptability on a 9-point scale.¹² Using a score range of 0–10 may imply a larger SD. If conservatively adding two participants with scores of 0 and 10, respectively, to each K⁺ formulation previously reported,¹² and assuming a within-participant correlation of 0.3, the result is an SD of 2.7 for the paired difference. Furthermore, it is assumed that a paired mean difference of 1.2 is sensible to detect.

To update the sample size calculations for the new primary endpoint, it was assumed that the paired mean difference between products and SD is the same for all attributes as it is for taste (mean, 1.2; SD, 2.7). Together with the conservative assumption of perfect correlation between components, a sample size of 51 participants per country or region (USA, Canada and EU) was required. The study, therefore, aimed to randomise at least 60 participants per region (USA, Canada and EU) to ensure this sample size was acquired, and to ensure an equal number of participants (10) per randomised sequence (comparable to a 15% overall drop-out risk).

Analyses of primary and secondary outcomes were performed in the full-analysis set, comprising all randomised participants who tasted at least one product and who completed any post-taste measurement, with participants analysed as randomised rather than as treated. As is common for modelling mean values in a cross-over design, the primary objective was analysed with a linear mixed-effects model, using participants within

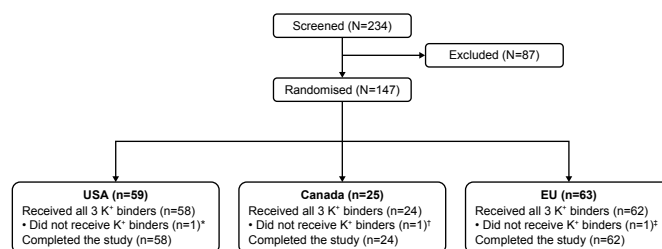


Figure 2 Participant disposition. *Other reason. †Eligibility criteria not met. ‡Screening failure. EU, European Union region comprising France, Spain and Italy; K⁺, potassium; USA, United States of America.

sequence as a random effect and the following as fixed effects: treatment (SZC, patiromer or S/CPS); treatment sequence (1–6); the order of products being tasted (first, second or third) and stratification factor at randomisation (dialysis-dependent vs non-dialysis-dependent CKD).

Patient involvement

A patient advisory board held in 2019 guided the attributes chosen for assessment in this study. Taste, texture, smell and mouthfeel were identified as being especially important to medication adherence by patients receiving long-term treatment.

RESULTS

Participants

Between 23 October 2020 and 12 January 2022, 234 participants were screened for eligibility and enrolled; 87 were excluded. The study randomised 147 participants, 144 of whom from the USA (n=58), Canada (n=24; recruitment was prematurely stopped due to slow recruitment) and the EU (n=62) completed the study and tasted each K⁺ binder; three participants did not taste any K⁺ binders due to not meeting the eligibility criteria (n=1), screening failure (n=1) or another reason (n=1) (figure 2). There was no severe non-compliance to the study protocol and no participants discontinued from the study due to an adverse event or development of study-specific discontinuation criteria. No participants accidentally ingested a full dose of any product.

Of the 144 participants who completed the study, mean age was 66 years, 71% were male and 53% were dialysis dependent (table 1). During the study, 30.6% of participants took concomitant angiotensin II receptor blockers and 20.8% took concomitant angiotensin-converting enzyme inhibitors.

Rational responses to palatability

With respect to the primary endpoint (composite rational palatability score) among participants from the USA, SZC performed significantly better than S/CPS (least squares [LS] mean [95% CI] 25.0 [22.7 to 27.2] vs 18.8 [16.6 to 21.1]; p<0.001), although there was no significant difference between SZC and patiromer (p=0.893) (figure 3).

Table 1 Participant baseline characteristics (full-analysis set)

Characteristic	USA (n=58)	Canada (n=24)	EU (n=62)	Overall (N=144)
Mean age, years	65	69	66	66
Male, n (%)	37 (64)	17 (71)	48 (77)	102 (71)
Race, n (%)				
White	28 (48)	NC	NC	NC
Black/African American	27 (47)	NC	NC	NC
Asian	1 (2)	NC	NC	NC
Other*	2 (3)	NC	NC	NC
Ethnicity, n (%)				
Hispanic or Latino	11 (19)	0	6 (10)	17 (12)
Not Hispanic or Latino	47 (81)	24 (100)	42 (68)	113 (78)
Not collected	0	0	14 (23)	14 (10)
Caffeine consumption [†] , n (%)	0	0	1 (1.6)	1 (0.7)
Alcohol consumption [†] , n (%)	14 (24)	8 (33)	9 (15)	31 (22)
Dialysis dependent, n (%)	29 (50)	18 (75)	30 (48)	77 (53)
Heart failure, n (%)	7 (12)	3 (13)	7 (11)	17 (12)
No previous K ⁺ binder use, n (%)	58 (100)	24 (100)	62 (100)	144 (100)

*American Indian or Alaska native, native Hawaiian or other Pacific Islander, other or not reported.
[†]Within 2 hours of, or during, tasting.
 EU, European Union region comprising France, Spain and Italy; K⁺, potassium; NC, not collected; USA, United States of America.

Among participants from Canada, SZC performed significantly better than S/CPS (LS mean [95% CI] 27.2 [22.5 to 32.0] vs 15.8 [11.1 to 20.6]; $p < 0.001$); there was no significant difference between SZC and patiromer ($p = 0.176$) (figure 3).

Among participants from the EU, SZC performed significantly better than S/CPS (LS mean [95% CI] 22.5 [19.9 to 25.1] vs 18.7 [16.1 to 21.3]; $p = 0.017$); there was no significant difference between SZC and patiromer (LS mean [95% CI] 22.5 vs 21.8 [19.2 to 24.4]; $p = 0.660$) (figure 3).

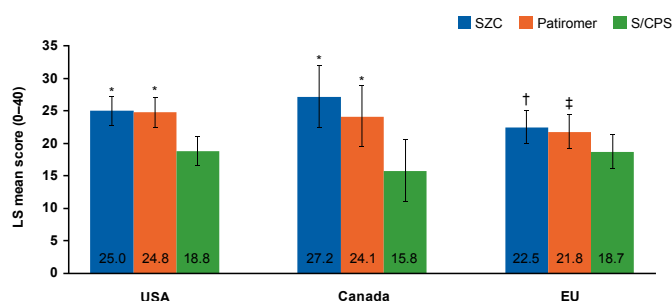


Figure 3 Overall composite palatability score (rational evaluation). * $p < 0.001$ and passes Holm procedure versus S/CPS; [†] $p = 0.017$ and passes Holm procedure versus S/CPS; [‡] $p = 0.05$ and did not pass Holm procedure. EU, European Union region comprising France, Spain and Italy; LS, least squares; patiromer, calcium patiromer sorbitex; S/CPS, sodium and calcium polystyrene sulfonate; SZC, sodium zirconium cyclosilicate.

Emotional responses to palatability

In each region, the overall palatability of SZC and patiromer was more appealing than that of S/CPS. Among participants from the USA, the overall palatability of patiromer elicited more engaged emotional responses than that of S/CPS. Among participants from the EU, the overall palatability of SZC and patiromer elicited greater feelings of empowerment than that of S/CPS, indicating greater personal conviction of benefit.

Among participants from the USA, the overall palatability of SZC was significantly more appealing than that of S/CPS (LS mean 23.2 vs 18.9; nominal $p < 0.001$); the overall palatability of patiromer was more appealing than that of S/CPS (LS mean 22.9 vs 18.9; nominal $p < 0.001$) and more engaging (LS mean 17.7 vs 15.4; nominal $p = 0.026$) (online supplemental figure S1A). For each product, smell (or lack of smell) created a more pleasing experience than the other attributes. SZC's lack of smell was very pleasing to more participants overall (47%) than the smell of S/CPS (41%) or patiromer (36%). Twice as many participants had enthusiastic emotional responses (high appeal, high engagement scores; 'excited', 'exuberant', 'aspiring') to the smell of SZC (28%) than to the smell of patiromer (14%) or S/CPS (14%).

Participants from Canada found the overall palatability of SZC significantly more appealing than that of S/CPS (LS mean 24.6 vs 16.4; nominal $p \leq 0.002$) (online supplemental figure S1B). Similarly, the overall palatability of patiromer was found to be significantly more appealing than that of S/CPS (LS mean 22.7 vs 16.4; nominal

$p \leq 0.002$). The mouthfeel of patiromer and SZC strongly appealed to more participants than the mouthfeel of S/CPS (44% and 43%, respectively, vs 30%), predominantly putting participants at ease ('relaxed', 'comfortable', 'untroubled'). The mouthfeel of S/CPS elicited negative feelings ('unimpressed', 'uninterested', 'regretful', 'discontented', 'aggravated') among 41% of participants (vs 24% for SZC and 33% for patiromer), indicating that it is more likely to create aversion to taking the product. The smell/lack of smell of SZC and patiromer created a very pleasant experience for more participants compared with the smell of S/CPS (50% and 46%, respectively, vs 37%), predominantly putting participants at ease.

Participants from the EU found the overall palatability of SZC significantly more appealing than that of S/CPS (LS mean 22.2 vs 18.9; nominal $p=0.013$) and significantly more empowering (LS mean 23.0 vs 20.0; nominal $p=0.018$) (online supplemental figure S1C). Participants also found the overall palatability of patiromer more appealing than that of S/CPS (LS mean 22.0 vs 18.9; nominal $p=0.017$) and more empowering (LS mean 23.6 vs 20.0; nominal $p=0.005$). More participants expressed negative feelings about the taste, texture and smell of S/CPS than of SZC and patiromer, and more participants expressed negative feelings about the mouthfeel of S/CPS than patiromer. Notably, the texture of S/CPS elicited feelings of disinterest, dissatisfaction, defiance and aggravation among 41% of EU participants (vs 36% for SZC and 25% for patiromer). The mouthfeel of SZC elicited more negative emotional responses ('aggravated', 'stressed', 'dissatisfied', 'sluggish', 'unexcited', 'defiant') (39%) than the mouthfeel of S/CPS (33%) or patiromer (23%).

Willingness to take a K⁺ binder

In each region, participants' emotional responses indicated a greater willingness to take SZC or patiromer once daily to manage K⁺ levels than S/CPS.

Among participants from the USA, the thought of taking patiromer was significantly more appealing than the thought of taking S/CPS (LS mean 5.9 vs 4.5; nominal $p < 0.001$) and more engaging (LS mean 4.8 vs 3.9; nominal $p=0.005$) (online supplemental figure S2A). Some participants expressed greater feelings of satisfaction (higher appeal) as well as more energised enthusiasm (higher appeal and engagement) about taking patiromer compared with the emotional response to taking S/CPS. However, the higher level of engagement in emotional responses to taking patiromer was partially due to some participants who felt more stressed and aggravated about the idea of taking patiromer once daily. The thought of taking SZC was significantly more appealing than the thought of taking S/CPS (LS mean 5.6 vs 4.5; $p \leq 0.002$). The higher level of appeal was primarily a result of more participants expressing enthusiastic feelings about taking SZC, which indicates greater receptivity and willingness.

In Canada, the thought of taking SZC or patiromer was significantly more appealing to participants than the

thought of taking S/CPS (LS mean 6.0 vs 4.0; nominal $p=0.007$ and LS mean 5.8 vs 4.0; nominal $p=0.013$, respectively) (online supplemental figure S2B). In Canada, the significantly higher appeal was a result of more participants feeling comfortable, at ease and satisfied with the thought of taking SZC or patiromer.

In the EU, the thought of taking SZC was significantly more appealing to participants than the thought of taking S/CPS (LS mean 6.0 vs 4.8; nominal $p=0.004$) and more empowering (LS mean 6.1 vs 5.2; nominal $p=0.014$) (online supplemental figure S2C). The thought of taking patiromer was also more appealing than the thought of taking S/CPS (LS mean 6.0 vs 4.8; nominal $p=0.004$) and more empowering (LS mean 6.2 vs 5.2; nominal $p=0.010$). With respect to engagement, participants in the EU felt more passive towards SZC and patiromer than towards S/CPS. This indicates that, overall, participants had greater receptivity and felt more at ease about taking SZC or patiromer than about taking S/CPS to manage their K⁺ levels. In the EU, the significantly higher level of engagement in the emotional response to taking S/CPS (LS mean 5.5 vs 4.6 for SZC [nominal $p=0.022$] and vs 4.4 for patiromer [nominal $p=0.004$]) was largely because more participants had emotional responses that were apprehensive ('aggressive', 'anxious') or alarmed ('terrified', 'stressed', 'aggravated') in nature, which indicates stronger resistance to taking S/CPS.

ESI scores for willingness to take a K⁺ binder are shown in online supplemental table S2.

Influence of emotional response to palatability on emotional response to taking K⁺ binders

For each K⁺ binder, exploratory linear regression modelling was performed post hoc to assess the influence of each palatability attribute on feelings about taking the K⁺ binder. Linear regression was done for each emotional dimension, with willingness to take the product as the dependent variable, and taste, texture, smell and mouthfeel as the independent variables. Analyses were performed based on the full dataset for all countries combined ($n=144$). Parameter estimates for attributes having a significant influence on feelings towards taking a product are provided in online supplemental table S3.

ESI scores for the palatability attributes of each K⁺ binder are reported in online supplemental table S4. These show that for all three products, smell created stronger, more positive emotional connections than the other attributes. Emotion Group analyses of participant feelings about the products are summarised in online supplemental figure S3. These show that positive emotional responses to smell ('enthusiastic', 'warmed', 'comfortable') are closest to the positive emotional response to taking each K⁺ binder. However, the positive emotional responses to mouthfeel are tempered somewhat by similarly strong negative emotions ('apprehensive', 'sullen', 'troubled', 'alarmed'), suggesting that mouthfeel can help or equally undermine feelings about taking the product.

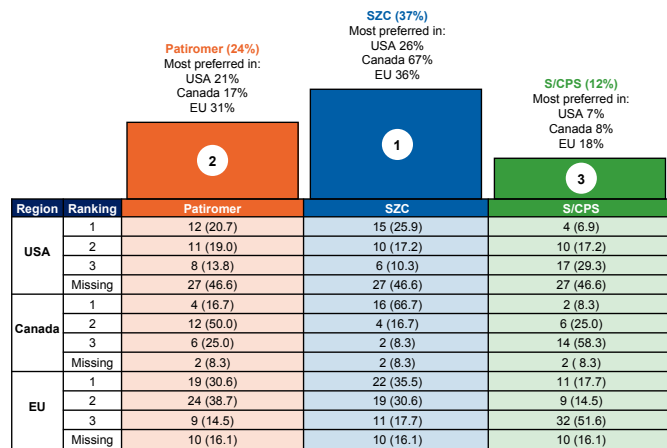


Figure 4 Overall preference ranking. EU, European Union region comprising France, Spain and Italy; Patiromer, calcium patiromer sorbitex; S/CPS, sodium and calcium polystyrene sulfonate; SZC, sodium zirconium cyclosilicate; USA, United States of America.

Overall preference ranking

In the USA, SZC, patiromer and S/CPS were numerically the most preferred K⁺ binders of 15 (25.9%), 12 (20.7%) and four (6.9%) participants, respectively; data were not captured for 27 (46.6%) participants. In Canada, SZC, patiromer and S/CPS were numerically the most preferred K⁺ binders of 16 (66.7%), four (16.7%) and two (8.3%) participants, respectively; data were not captured for two (8.3%) participants. In the EU, SZC, patiromer and S/CPS were numerically the most preferred K⁺ binders of 22 (35.5%), 19 (30.6%) and 11 (17.7%) participants, respectively; data were not captured for 10 (16.1%) participants (figure 4).

Safety

Adverse events were not anticipated as participants were not required to ingest any of the products. A single mild adverse event (nocturnal leg cramps) did occur in one patient 1 day after tasting, but this was not deemed related to the study products and resolved spontaneously. No discontinuations or deaths were reported.

DISCUSSION

Palatability is an under-recognised factor in drug development that can have a significant impact on long-term treatment adherence among patients and prescribing patterns among physicians.^{34–38} Studies evaluating the palatability of K⁺ binders¹² or other medications^{35–38} are scarce. In one phase I study, three formulations of a calcium-containing polystyrene sulfonate (RDX7675) were evaluated versus SPS.¹² Twenty healthy volunteers tasted each formulation using the ‘sip and spit’ approach before ranking seven palatability attributes (smell, sweetness, bitterness, flavour, mouthfeel, grittiness and after-taste) on a 9-point scale and providing an overall ranking. The spherical particles and higher swelling ratio associated with RDX7675 provided a smoother and softer

mouthfeel compared with the shard-like and sand-like properties of SPS, and palatability improved significantly across five attributes. However, this study was conducted at a single centre, participants received older cation exchange resins only and the palatability attributes evaluated were not patient-guided. International guidelines recommend using patient and public perspectives to guide and improve the design of research studies.^{39–41} In APPETIZE, the palatability attributes chosen for evaluation were guided by the outcome of a patient advisory board held in 2019, where patients receiving long-term treatment identified taste, texture, smell and mouthfeel as being especially important to medication adherence. Additional patient input acquired via a patient representative was used to optimise the study design. Following the evaluation of these attributes in SZC, patiromer and S/CPS, emotional responses to palatability were then evaluated using AdSAM, a non-verbal, visual technique that captures instinctive responses undiluted by rationalisation (i.e., participants are not required to contemplate or characterise an emotion, or to choose from a finite list of preselected emotions). AdSAM captures emotional responses very similarly to how the brain processes emotions.^{33–42–44} APPETIZE is, therefore, a first-of-its-kind study, using an innovative methodology and patient-centred approach to identify the factors that might impact medication adherence among individuals with CKD and hyperkalaemia.

A cross-over design with randomisation to the selected six tasting sequences was employed to increase the precision of the effect estimates versus a parallel design and to avoid separate site visits. The cross-over design and palate cleansing between product tasting were also used so that potential carry-over effects were deemed to be sufficiently mitigated. However, given the complexity of the palatability endpoint assessed, some carry-over is expected and the results have to be interpreted in the context of this limitation.

Regardless of region, individual and composite rational palatability scores for SZC were comparable to patiromer and superior to S/CPS. Overall, SZC was numerically the most preferred K⁺ binder in each region (although data were not captured for 46.6% of US participants due to an error at one centre), followed by patiromer; S/CPS was numerically the least preferred K⁺ binder. Finally, participant willingness to take a K⁺ binder was higher for SZC and patiromer versus S/CPS in each region.

The overall emotional response scores for palatability confirmed that the palatability of SZC and patiromer created a more appealing experience than the palatability of S/CPS. Subsequently, feelings about taking the newer K⁺ binders were higher in terms of appeal than feelings about taking S/CPS, indicating greater receptivity. The higher levels of empowerment observed in the mean emotional responses to the palatability of, and willingness to take, SZC and patiromer, compared with S/CPS, is further indication that participants were more likely to accept the newer K⁺ binders. Moreover, in agreement



with findings reported elsewhere,¹² the emotional impact of mouthfeel had a strong influence on willingness to take each of the three K⁺ binders. Smell was also strongly influential, with the smell (or lack of smell) of SZC and patiromer creating a more pleasant experience for participants than the smell of S/CPS. Unlike the rational evaluation of the three K⁺ binders, which was based on a forced choice, the emotional responses captured by AdSAM were based on the participants' experiences of tasting each product. Therefore, the more favourable feelings about taking SZC and patiromer compared with S/CPS are an encouraging sign that improving palatability can improve the patient experience, and therefore, increase willingness to take a novel K⁺ binder long-term to manage hyperkalaemia. Consequently, improving adherence to long-term treatment for hyperkalaemia might allow patients with CKD to maintain or even increase their dose of guideline-recommended RAASi, as demonstrated in clinical trials.^{20 22–27} However, any suggestion that improved palatability and emotional response with novel K⁺ binders could be associated with improved medication adherence must be interpreted with caution for several reasons. In particular, the non-interventional, exploratory study design of APPETIZE prevented assessment of medication adherence, and in clinical practice, medication adherence and willingness to take a drug is impacted by many other factors, such as adverse events following ingestion.^{17 45}

While our study design is unique, we acknowledge that it has limitations. AdSAM is a validated tool for evaluating emotional responses in humans.^{33 42–44} However, placing rational evaluation questions before the AdSAM measure can influence the emotional response because the unbiased emotional response is not captured prior to cognitive evaluation. In this study, each palatability attribute was scored rationally before the AdSAM measure. In addition, each product was tasted using the 'sip and spit' technique.¹² No product was ingested, which could have created new palatability experiences. Participants were blinded to study treatment, but site and sponsor personnel were not; it is possible that this approach could have affected participant blinding. Our results must also be interpreted in view of reduced participant numbers caused by early termination of recruitment in Canada, which limited this cohort to 24 participants, and in France, which resulted in the merging of data from France, Spain and Italy to create one EU region and aid timely completion of the study. Furthermore, SPS and CPS were combined into a single comparator group (S/CPS) for several reasons, including differing use of the products across countries and timely attainment of enrolment targets, which limited assessment of the individual products. The overall ranking of the products is not supported by statistical analyses and should also be interpreted in view of missing data, especially for US participants. Finally, this was an exploratory study and, to the best of our knowledge, is the first example of AdSAM being

used to evaluate emotional responses in participants receiving different pharmacotherapies.

It is also important to remember that emotional dimensions are orthogonal, and that emotional responses are defined by the combination of levels of appeal, engagement and empowerment. In particular, implications regarding the level of engagement in the emotional response are reliant on the level of appeal (high appeal and high engagement scores indicate strong perceived benefit and strong positive motivation; however, low appeal and high engagement scores indicate strong negative/agitated feelings). Engagement scores should be interpreted in terms of level of passiveness (lower scores) versus level of activation/intensity (higher scores).

CONCLUSION

Our results suggest that participants had an overall preference for SZC and patiromer over S/CPS, and that this preference is being driven by palatability. The palatability of SZC was superior to that of S/CPS and comparable to that of patiromer. These results offer promise that adherence to long-term treatment for hyperkalaemia may be improved in patients prescribed newer, more palatable K⁺ binders.

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Competing interests DCW reports an ongoing consultancy contract with AstraZeneca and honoraria/speaker fees from Astellas, Bayer, Boehringer Ingelheim, George Clinical, GSK, Gilead, Janssen, Merck Sharp and Dohme, ProKidney, Tricida, Vfior and Zydus. HS has nothing to disclose. KH, JH, AA, H-LC, MN, GS, EW and JK are employees of and may hold stock in AstraZeneca. JM and CG are employees of AdSAM.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

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Data availability statement Data are available on reasonable request. Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at <https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure>. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at <https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/>. AstraZeneca Vivli member page is also available outlining further details: <https://vivli.org/ourmember/astrazeneca/>.

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Supplementary appendix

Supplementary methods

Exclusion criteria

Participants were ineligible if they met any of the following criteria:

- Serum K⁺ value at screening which, in the opinion of the investigator, warranted immediate medical intervention that could not wait until after tasting procedures
- Evidence of any condition which, in the investigator's opinion, made participation undesirable
- Known history of drug or alcohol abuse within 6 months of screening
- History of QT prolongation associated with other medications that required discontinuation of that medication, including congenital long QT syndrome
- Symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia (participants with atrial fibrillation controlled by medication were permitted)
- Life expectancy <6 months
- 12-lead electrocardiogram with reported QTcF >550 ms at screening
- Current smoker
- Mouth ulcers/mouth infection, respiratory infection, nasal congestion, or other condition, medication or procedure that may interfere with sense of smell or taste in the opinion of the investigator

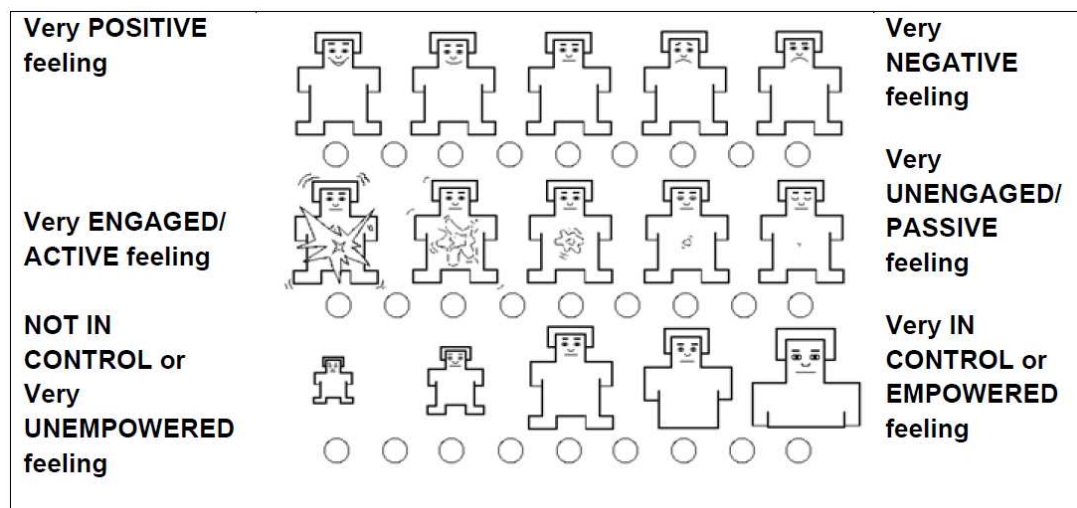
- Already receiving a K⁺ binder at time of screening/enrolment
- Unable to hold any other oral medications from 3 hours prior to the start of tasting through 3 hours after the end of tasting
- Currently participating in another clinical study, or had been participating in another clinical study within 28 days of screening, where an investigational medicinal product is/was administered
- Known hypersensitivity to any of the investigational medicinal products or their excipients
- Involvement in the planning and/or conduct of the study (eg, AstraZeneca staff and/or any staff at the study site)
- Judgment by the investigator that the participant is unlikely to be able to comply with the study procedures, restrictions and requirements
- Previous enrolment or randomisation in the present study
- Pregnant (confirmed with positive pregnancy test) or breastfeeding
- Unable to read the local language and therefore unable to complete the questionnaires

Overview of AdSAM[®] emotional response measure

The AdSAM[®] tool provides a simple and quick way for participants to indicate their emotional response without using words. AdSAM[®] consists of three different rows of graphic characters (Self-Assessment Manikins), which visually represent the participants' feelings. Each row of Manikins conveys a different aspect of the

emotional response, and participants are encouraged to focus on the range of feelings that the Manikins in each row visually represent. To indicate their feelings, participants select one place on each of the three rows, either under a Manikin or between two. Participants are encouraged to simply look at the manikins on each row and choose the place on each row that best represents how they feel. Each row consists of a nine-point scale and the responses are converted into numeric values.

- The top row represents the level of ‘Appeal’ in the emotional response and signifies how positive or negative the feeling is (scored 9 to 1 from left to right).
- The middle row represents the level of ‘Engagement’ in the emotional response and signifies how active or passive the feeling is (scored 9 to 1 from left to right).
- The bottom row represents the level of ‘Empowerment’ in the emotional response and signifies how in control/empowered the person feels (scored 1 to 9 from left to right).



Emotions are multidimensional, and the combination of dimensions is what defines the emotional response; therefore, all three dimensions must be considered to

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determine the emotional response. It is important, however, to interpret the individual dimensions in the context of implications and influence regarding the type/nature of emotional response. The nature of the emotional response and the specific feelings evoked have implications with respect to consideration, acceptance and behaviour.

Below is a questionnaire example for taste (the same questionnaire will be completed for attributes of texture, smell, mouthfeel and likelihood of adherence):

Scoring (0-10) and AdSAM

Taste

Q. How do you like the taste of this product? Answer the question by selecting one box.										
0	1	2	3	4	5	6	7	8	9	10
I dislike it very much										I like it very much

Q. How do you feel about the **taste** of this product? Indicate your feelings by selecting one location on each of the three rows.

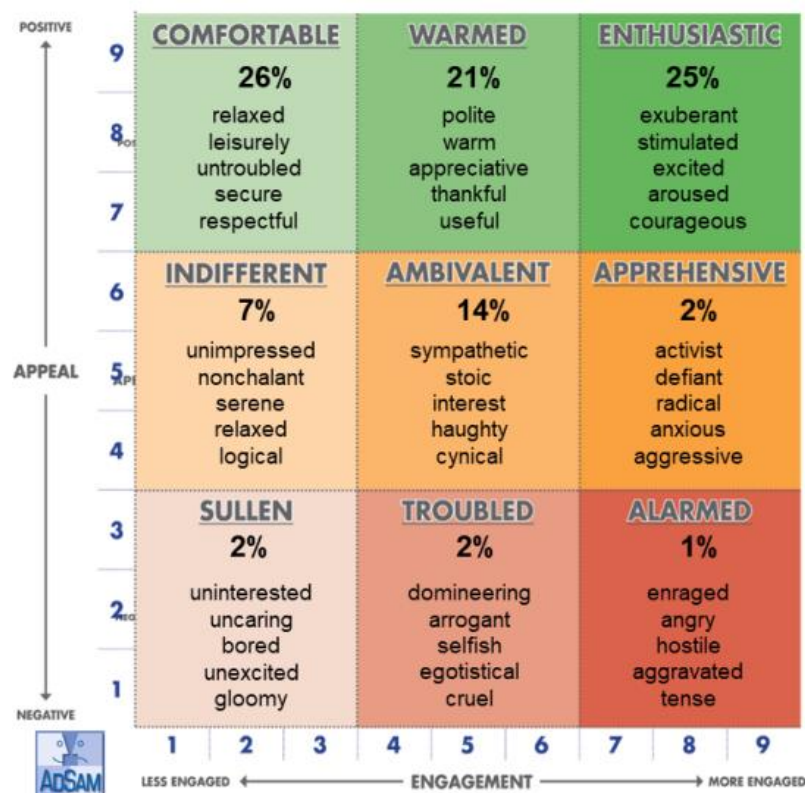
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AdSAM® Emotion Group® analysis

Numeric scores from individual dimensions are run through the AdSAM® model and several outputs are produced for analysis. The Emotion Group® output displays the percentage of responses by nature of the emotional response (eg, enthusiastic, warmed, comfortable, apprehensive, ambivalent, indifferent, sullen, troubled, alarmed) and describes the specific feelings expressed by the people whose emotional responses fall within each group. The 9 Emotion Groups are defined by the combination of Appeal and Engagement scores, and the specific emotion descriptors displayed within each group are based on the combination of Appeal, Engagement and Empowerment scores.

AdSAM® Emotion Group® Output Example



The AdSAM model contains 190 emotional response descriptors, each defined by a specific combination of appeal, engagement, and empowerment scores. Emotional

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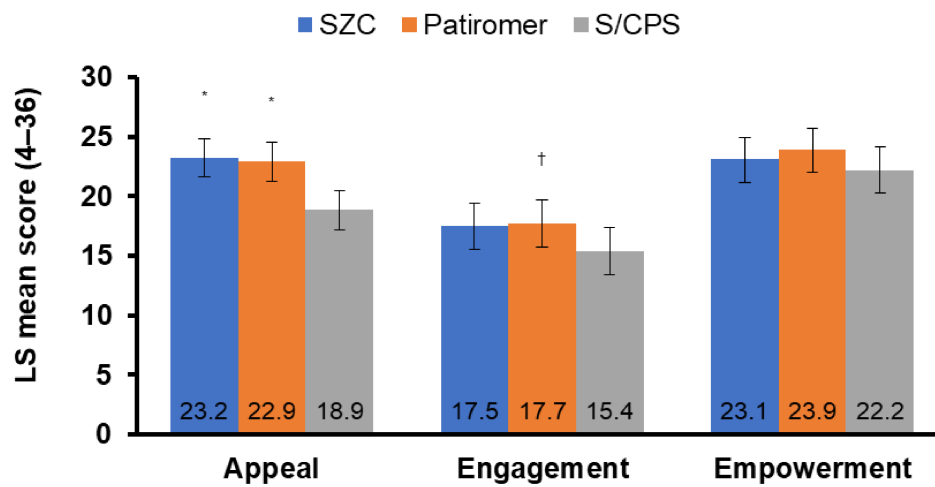
strength indicator scores are used to summarise the strength of emotional impact in terms of positive influence on persuasion and behaviour. Independent empirical studies have demonstrated that enthusiastic emotional responses are most predictive of persuasion and behaviour, followed by warmed, comfortable, and then ambivalent emotional responses. ESI scores are calculated by weighting the percentage of responses in each of the influential emotion groups. ESI scores range from 0 to 300, and the higher the number, the greater the strength of the influential emotional connections or responses. ESI scores provide a simple way to rank based on strength of positive impact.

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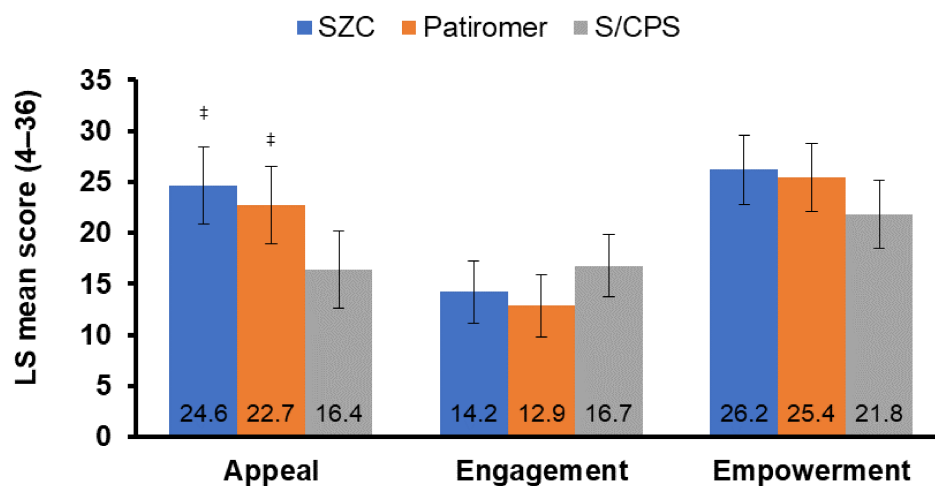
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Supplementary results**Figure S1. Emotional responses to overall emotional composite palatability in (A) the US, (B) Canada and (C) the EU.**

(A)



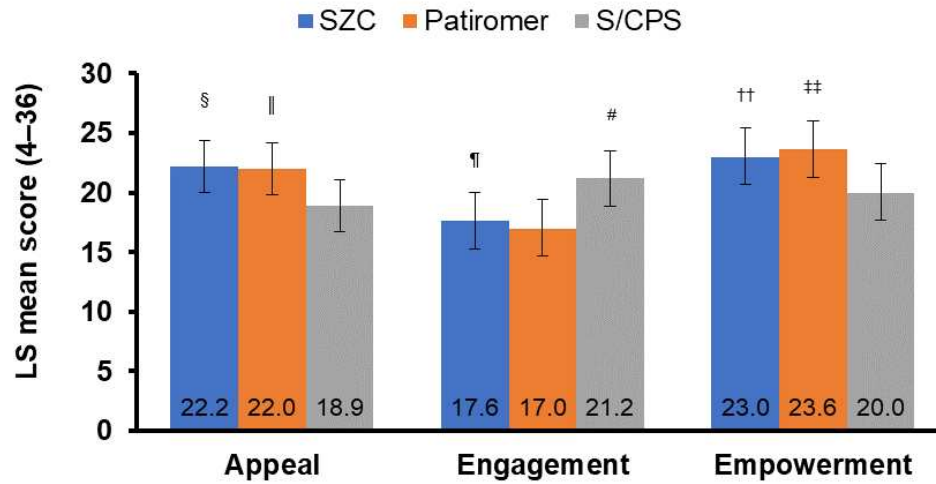
(B)



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(C)



*Nominal $p < 0.001$ versus S/CPS; †Nominal $p = 0.026$ versus S/CPS; ‡Nominal $p \leq 0.002$ versus S/CPS; §Nominal $p = 0.013$ versus S/CPS; ¶Nominal $p = 0.017$ versus S/CPS; ¶Nominal $p = 0.003$ versus S/CPS; #Nominal $p < 0.001$ versus patiromer; ††Nominal $p = 0.018$ versus S/CPS; ††Nominal $p = 0.005$ versus S/CPS.

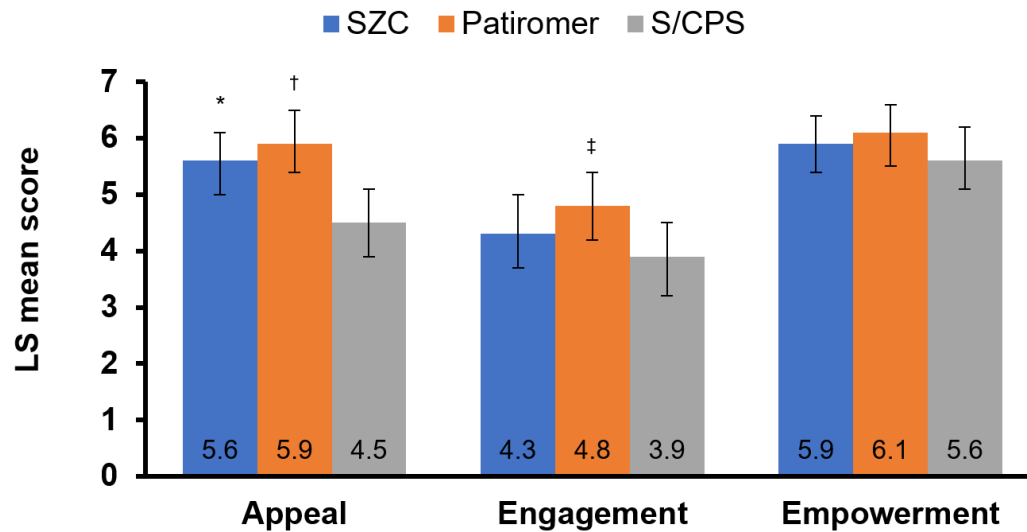
EU, European Union region comprising France, Spain and Italy; LS, least squares; patiromer, calcium patiromer sorbitex; S/CPS, sodium or calcium polystyrene sulphonate; SZC, sodium zirconium cyclosilicate.

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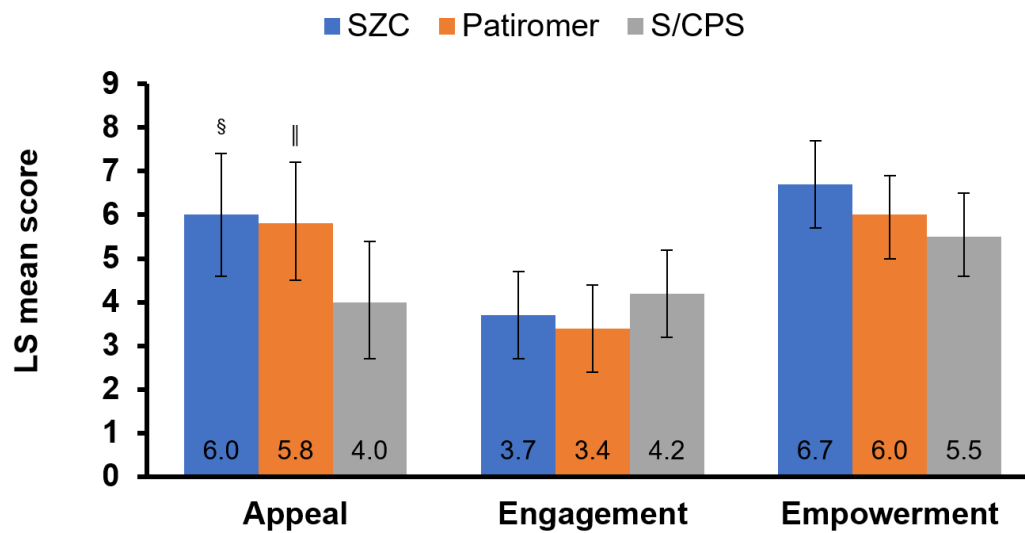
APPETIZE study

Figure S2. Willingness to take the K⁺ binder in (A) the US, (B) Canada and (C) the EU

(A)



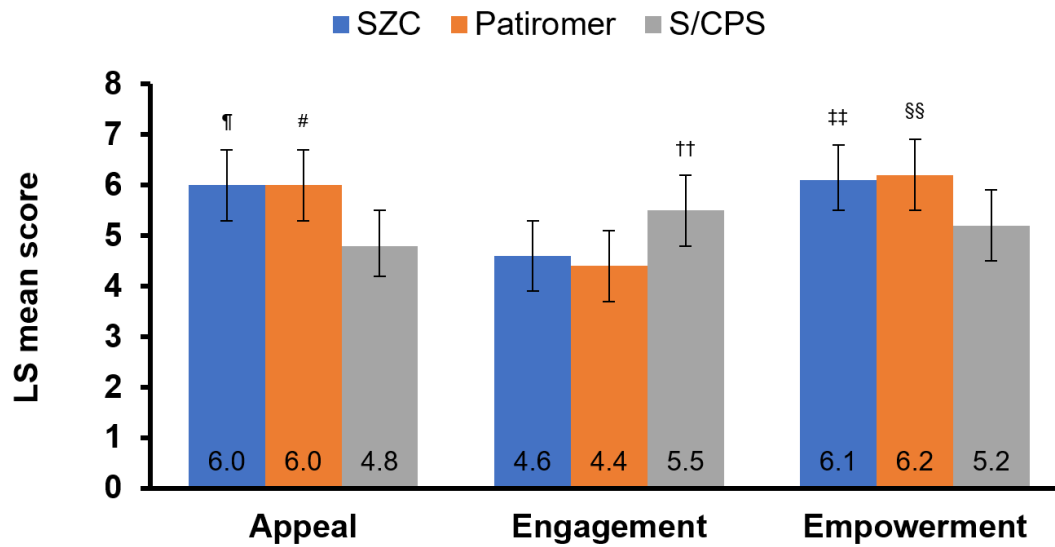
(B)



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(C)



*Nominal $p \leq 0.002$ versus S/CPS; †Nominal $p < 0.001$ versus S/CPS; ‡Nominal $p = 0.005$ versus S/CPS; §Nominal $p = 0.007$ versus S/CPS; ¶Nominal $p = 0.013$ versus S/CPS; ¶¶Nominal $p = 0.004$ versus S/CPS; #Nominal $p = 0.004$ versus S/CPS; ¶¶Nominal $p = 0.022$ versus SZC and nominal $p = 0.004$ versus patiromer; ¶¶Nominal $p = 0.014$ versus S/CPS; §§Nominal $p = 0.010$ versus S/CPS.

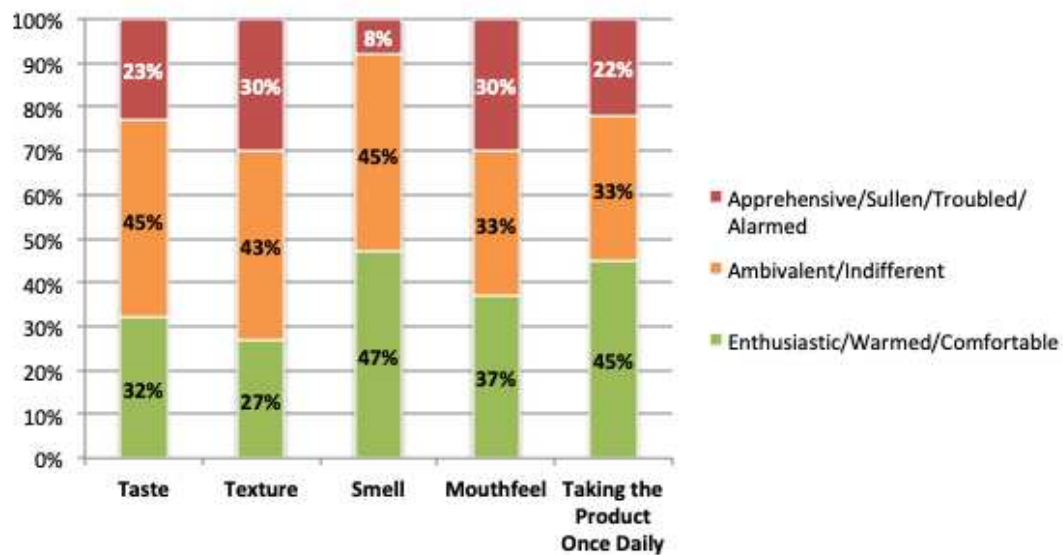
EU, European Union region comprising France, Spain and Italy; LS, least squares; patiromer, calcium patiromer sorbitex; S/CPS, sodium or calcium polystyrene sulphonate; SZC, sodium zirconium cyclosilicate.

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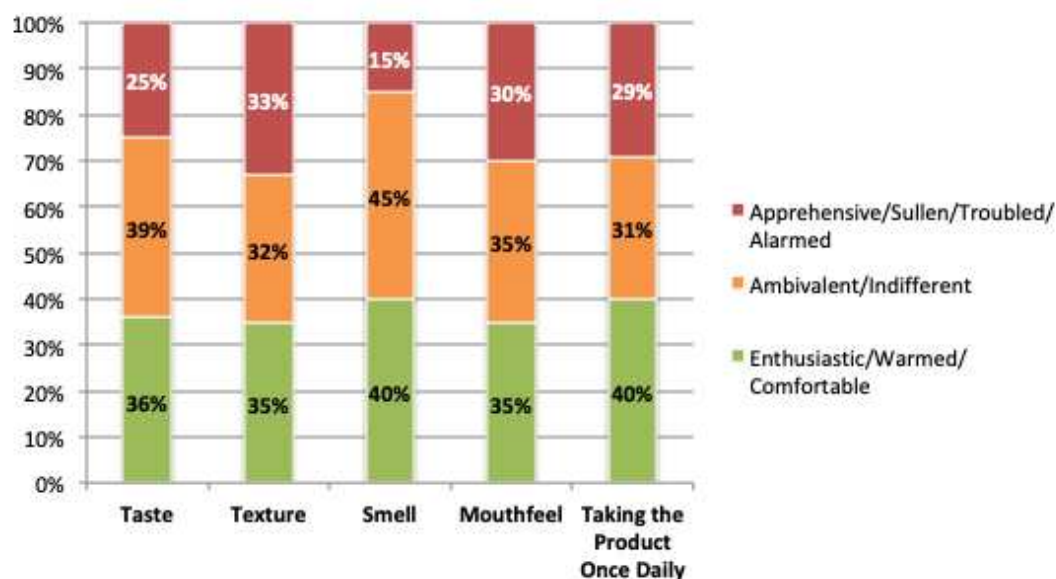
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Figure S3. AdSAM® Emotion Group® results: summary of feelings about the palatability attributes, and about taking the product once daily, for (A) SZC, (B) patiromer and (C) S/CPS (global)

(A) SZC

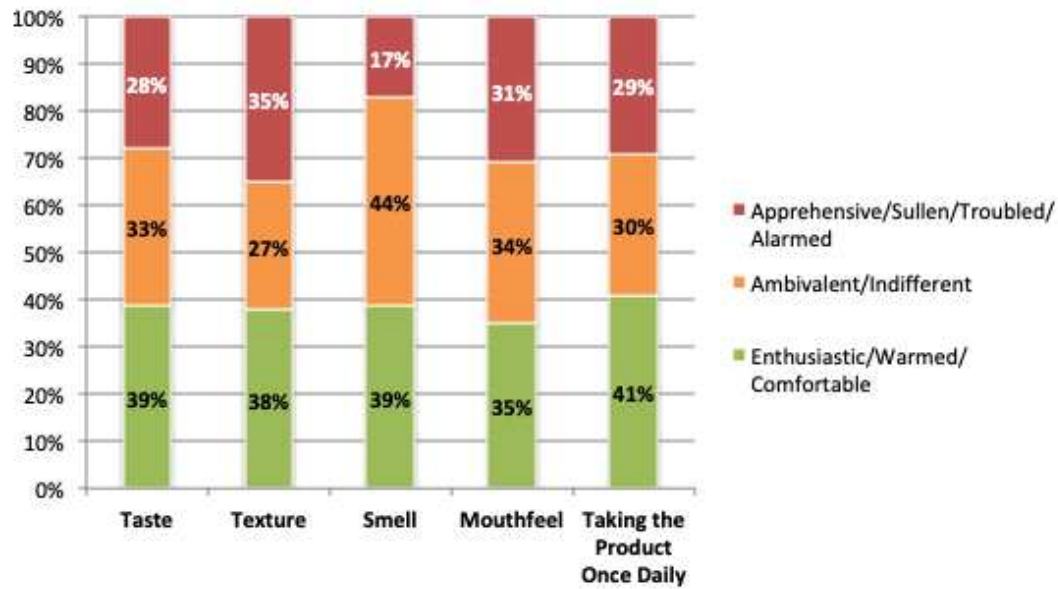


(B) Patiromer



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(C) S/CPS

Patiromer, calcium patiromer sorbitex; S/CPS, sodium or calcium polystyrene sulphonate; SZC, sodium zirconium cyclosilicate.

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Table S1. Independent ethics committees/Institutional review boards

Country	Site no.	Principal investigator	IRB Name	IRB Address
Canada	1001	Charmaine Lok	University Health Network Research Ethics Board	10th Floor, Room 1056 700 University Ave. Toronto, Ontario, M5G 1Z5
Canada	1002	Jean-Philippe Lafrance	Research Ethics Board of the CISSS of Montréal-Centre	6363, Hudson Road, office 061 Lindsay Pavilion of the IURDPM Montreal QC H3S 1M9
Canada	1003	Serge Cournoyer	Research Ethics Board of the CISSS of Montréal-Centre	6363, Hudson Road, office 061 Lindsay Pavilion of the IURDPM Montreal QC H3S 1M9
Canada	1004	Fabrice Mac-Way	Research Ethics Board of the CISSS of Montréal-Centre	6363, Hudson Road, office 061 Lindsay Pavilion of the IURDPM Montreal QC H3S 1M9
France	2301	Vincent Esnault	Ile-de-France VI Ethics Committee	Pitié-Salpêtrière Hospital Group 4 bâtiment de la Force 47, boulevard de l'Hôpital 75013 PARIS
France	2303	Marie Essig	Ile-de-France VI Ethics Committee	Pitié-Salpêtrière Hospital Group 4 bâtiment de la Force 47, boulevard de l'Hôpital 75013 PARIS
France	2304	Gabriel Choukroun	Ile-de-France VI Ethics Committee	Pitié-Salpêtrière Hospital Group 4 bâtiment de la Force 47, boulevard de l'Hôpital 75013 PARIS

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Italy	4101	Loreto Gesualdo	Independent Ethics Committee Azienda Ospedaliero-Universitaria "Consoziale Policlinico"	Piazza Giulio Cesare, 11 70124 Bari
Italy	4102	Daria Motta	Comitato Etico Interaziendale	Corso Bramante, 88/90 10126 Turin
Italy	4103	Ciro Esposito	Istituti Clinici Scientifici Maugeri SpA SB	Via Salvatore Maugeri, 4 27100 Pavia
Italy	4104	Roberto Scarpioni	Comitato Etico dell'Area Vasta Emilia Nord	Via G. Taverna, 49 29121 Piacenza
Italy	4106	Pasquale Esposito	Comitato Etico Regionale	Largo Rosanna Benzi, 10 16132 GENOA
Italy	4107	Enrico Fiaccadori	Comitato Etico dell'Area Vasta Emilia Nord	Via Gramsci 14 43126 Parma
Spain	7002	Marisa Generosa Crespo-Leiro	Hospital Universitario A Coruña	As Xubias, 84, 15006 A Coruña
Spain	7003	Patricia de Sequera Ortiz	Drug Research Ethics Committee of the Gregorio Marañón General University Hospital	46, Pabellón de Gobierno Primera Planta, 28007 Madrid
Spain	7004	Alejandro Martin-Malo	Hospital Universitario Reina Sofía	Avda. Menéndez Pidal, s/n 14004 - Córdoba
Spain	7005	Maria Jose Soler Romeo	Drug Research Ethics Committee of the Vall d'Hebron University Hospital of Barcelona	Pg. de la Vall d'Hebron, 119, 08035 Barcelona
Spain	7006	José Luis Gorriz Teruel	Drug Research Ethics Committee of the Valencia University Clinical Hospital	Av. Blasco Ibáñez, 13. 46010 València
US	7801	Pablo Ruiz Ramon	WCG Institutional Review Board	1019 39th Ave., SE Suite 120, Puyallup, WA 98374

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US	7802	Wayne Kotzker	WCG Institutional Review Board	1019 39th Ave., SE Suite 120, Puyallup, WA 98374
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CISSS, Centre Intégré de Santé et de Services Sociaux; WCG, Western Institutional Review Board-Copernicus Group.

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Table S2. ESI scores for willingness to take a K⁺ binder

ESI score	US			Canada			EU		
	SZC (n=57)	Patiromer (n=58)	S/CPS (n=57)	SZC (n=24)	Patiromer (n=24)	S/CPS (n=24)	SZC (n=62)	Patiromer (n=62)	S/CPS (n=62)
Willingness to take K ⁺ binder (0–300)	107	84	104	92	88	58	119	113	108
Ranking	1 st	3 rd	2 nd	1 st	2 nd	3 rd	1 st	2 nd	3 rd

ESI, Emotional Strength Indicator; patiromer, calcium patiromer sorbitex; EU, European Union region comprising France, Spain and Italy; S/CPS, sodium or calcium polystyrene sulphonate; SZC, sodium zirconium cyclosilicate.

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Table S3. Influence of palatability attributes on willingness to take the K⁺ binder

Palatability attribute	Dimension	SZC			Patiromer			S/CPS		
		PE	95% CI	P value	PE	95% CI	P value	PE	95% CI	P value
Taste	Appeal	0.1	-12, 0.32	0.3664	0.0	-0.16, 0.20	0.8609	0.0	-0.24, 0.15	0.6496
	Engagement	0.3	0.10, 0.43	0.0023	-0.1	-0.26, 0.09	0.3568	-0.1	-0.32, 0.10	0.2956
	Empowerment	0.3	0.05, 0.46	0.0137	0.0	-0.21, 0.12	0.6127	-0.1	-0.27, 0.07	0.2469
Texture	Appeal	0.1	-0.15, 0.32	0.4828	0.2	0.01, 0.39	0.0359	0.4	0.10, 0.64	0.0069
	Engagement	0.2	-0.04, 0.35	0.1118	0.3	0.08, 0.46	0.0068	0.3	0.08, 0.46	0.0068
	Empowerment	0.0	-0.21, 0.16	0.7704	0.2	0.03, 0.40	0.0247	0.5	0.25, 0.70	<0.0001
Smell	Appeal	0.3	0.10, 0.43	0.0023	0.2	0.01, 0.34	0.0426	0.2	0.02, 0.35	0.0311
	Engagement	0.2	0.03, 0.38	0.0253	0.2	0.06, 0.37	0.0059	0.2	0.03, 0.31	0.0186
	Empowerment	0.1	-0.05, 0.26	0.1718	0.0	-0.09, 0.18	0.5151	0.1	-0.01, 0.26	0.0623
Mouthfeel	Appeal	0.5	0.34, 0.75	<0.0001	0.6	0.37, 0.73	<0.0001	0.5	0.21, 0.71	0.0004
	Engagement	0.4	0.18, 0.60	0.0003	0.7	0.51, 0.85	<0.0001	0.4	0.22, 0.59	<0.0001
	Empowerment	0.7	0.49, 0.83	<0.0001	0.8	0.62, 0.94	<0.0001	0.6	0.40, 0.74	<0.0001

Parameter estimates calculated using a linear regression model, with AdSAM[®] score for willingness to take the K⁺ binder as the dependent variable, and the palatability attributes of taste, texture, smell and mouthfeel as the independent variables. The linear regression model was done for each emotional dimension (Appeal, Engagement and Empowerment). Statistically significant results are shown **in bold**. A parameter estimate >0 demonstrates increased willingness to take.

CI, confidence interval; K⁺, potassium; patiromer, calcium patiromer sorbitex; PE, parameter estimate; S/CPS, sodium or calcium polystyrene sulphonate; SZC, sodium zirconium cyclosilicate.

Table S4. ESI scores for palatability attributes

ESI score	US			Canada			EU		
	SZC (n=57)	Patiromer (n=58)	S/CPS (n=57)	SZC (n=24)	Patiromer (n=24)	S/CPS (n=24)	SZC (n=62)	Patiromer (n=62)	S/CPS (n=62)
Taste (0–300)	109	86	107	58	71	58	79	100	95
Texture (0–300)	81	71	109	63	71	54	79	98	95
Smell (0–300)	142	119	116	83	79	75	113	106	111
Mouthfeel (0–300)	114	84	109	71	75	54	87	102	102
Composite (0–1200)	446	360	441	275	296	241	358	406	403

ESI scores are used to summarise the strength of emotional impact in terms of positive influence on persuasion and behaviour. Independent empirical studies have demonstrated that enthusiastic emotional responses are most predictive of persuasion and behaviour, followed by warmed, comfortable, and then ambivalent emotional responses. ESI scores are calculated by weighting the percentage of responses in each of the influential Emotion Groups. ESI scores range from 0 to 300, and the higher the number, the greater the strength of the influential emotional connections or responses. ESI scores provide a simple way to rank based on strength of positive impact.

ESI, Emotional Strength Indicator; patiromer, calcium patiromer sorbitex; EU, European Union region comprising France, Spain and Italy; S/CPS, sodium or calcium polystyrene sulphonate; SZC, sodium zirconium cyclosilicate.

Supplementary appendix 1

APPETIZE manuscript – Plain language summary

Individuals with kidney disease can have a condition where the amount of potassium found in their blood is higher than normal (hyperkalaemia). To treat hyperkalaemia, patients are often prescribed drugs in powdered form that can be dissolved in water to drink. Commonly prescribed medicines, such as sodium polystyrene sulfonate (SPS) and calcium polystyrene sulfonate (CPS), can cause side effects and are unpleasant to taste. Researchers wanted to find out whether individuals with kidney disease preferred the taste of two newer medicines and found them more pleasant to take, compared with SPS and CPS. The two newer medicines are called sodium zirconium cyclosilicate (SZC) and calcium patiromer sorbitex (patiromer).

APPETIZE is a large study performed in the US, Canada, and Europe, in patients with kidney disease and hyperkalaemia. The participants tasted each of the medicines using a “sip and spit” approach (where they did not swallow the medicine) before completing an electronic survey. The participants scored each medicine based on its taste, texture, smell, and mouthfeel (sensation of the product in the mouth). The participants also used a visual tool called AdSAM[®] to indicate how they felt about them and how they felt about taking them once daily. Finally, the participants ranked the medicines in order of preference.

Across all three regions, participants preferred the taste of SZC and patiromer and found them more pleasant to take, compared with SPS and CPS. In addition, participants were more willing to take SZC or patiromer once daily than to take SPS or CPS. Notably, how participants felt about the mouthfeel of the medicines had the

strongest effect on how willing they would be to take them. Overall, more participants ranked SZC as their preferred medicine than patiromer, or SPS and CPS.

Researchers expect that if the newer medicines are more pleasant to take, individuals may be more likely to continue taking them as recommended by their doctor.

APPETIZE

An exploratory phase 4 study of patient-reported overall palatability and preference of three potassium (K⁺) binders in participants with chronic kidney disease (CKD) and hyperkalaemia (HK)



The APPETIZE study was a non-interventional, randomised, crossover study

Participants



144 adults
Aged ≥18 years



CKD: eGFR <60 mL/min/1.73 m²
HK >5.0 mmol/L



eGFR, estimated glomerular filtration rate.

Design

Taste testing

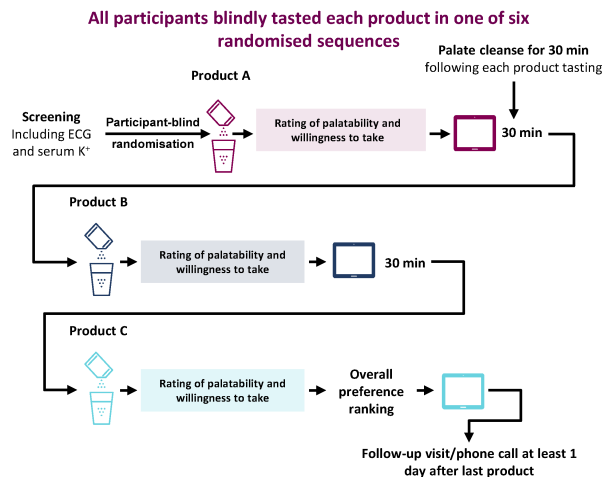
'Sip and spit' technique; not ingested

Patient advisory board guided key aspects of study design

Taste, texture, smell, mouthfeel

3 K⁺ binders

Sodium zirconium cyclosilicate (SZC), patiromer, sodium or calcium polystyrene sulphonate (S/CPS)



Outcomes were patient centric

Outcomes

Composite palatability

Taste, texture, smell and mouthfeel scored on:

- Rational response (scale of 0–10)
- Emotional response, using the AdSAM[®] emotional response measure

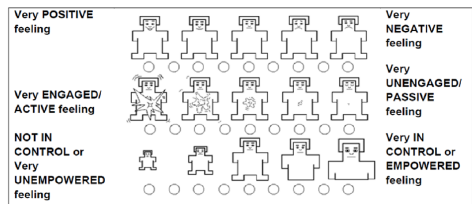
Overall preference ranking

Willingness to take

- Emotional response, using the AdSAM[®] emotional response measure

Nonverbal and visual emotional response measure

Participants rated their emotional response in terms of appeal, engagement and empowerment using the following visual system:



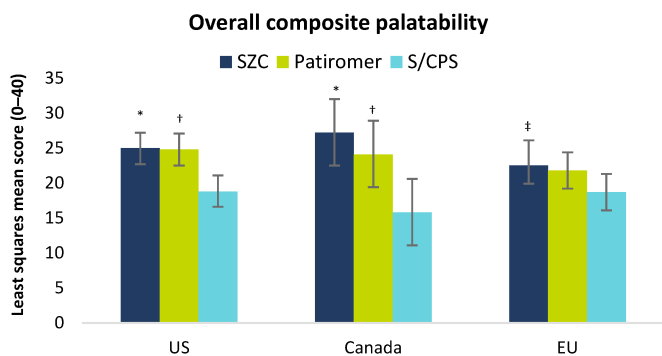
Participants had a preference for newer K⁺ binders (SZC, patiromer) over older K⁺ binders (S/CPS), likely driven by the improved palatability



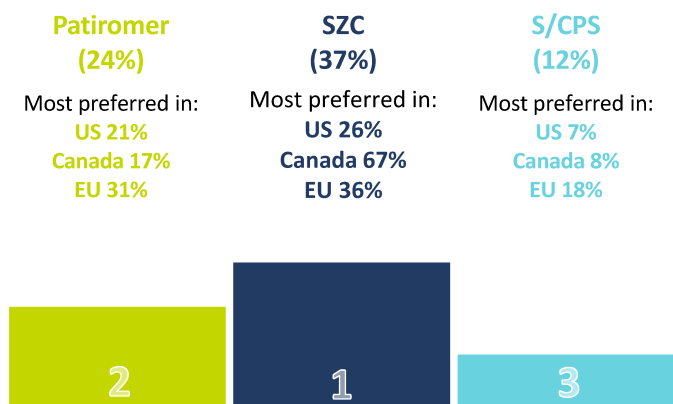
In the US, Canada and the EU, palatability of SZC was superior to S/CPS and similar to that of patiromer



In each region, more patients ranked SZC as the most preferred K⁺ binder than patiromer or S/CPS



*p<0.001 and passes Holm procedure versus S/CPS; †nominal p<0.001 versus S/CPS; ‡p=0.017 and passes Holm procedure versus S/CPS.



SZC and patiromer outperformed S/CPS based on emotional responses

The idea of taking SZC or patiromer was more appealing than S/CPS. Mouthfeel had the strongest influence on these feelings



Conclusion

Patient preference for SZC and patiromer may provide an opportunity to improve long-term adherence to HK treatment