25 January 2018
EMA/93250/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lokelma

International non-proprietary name: sodium zirconium cyclosilicate

Procedure No. EMEA/H/C/004029/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AR	Assessment Report
CHMP	Committee for Medicinal Products for Human use
CPP	Critical process parameter
CQA	Critical Quality Attribute
FT-IR	Fourier Transform Infrared Spectroscopy
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
ICP-MS	Inductively coupled plasma mass spectrometry
INN	International Non-proprietary Name
LDPE	Low Density Polyethylene
LLDPE	Linear Low Density Polyethylene
PET	Polyethylene
QbD	Quality by design
SmPC	Summary of Product Characteristics
TGA	Thermo-Gravimetric Analysis
USAN	United States Adopted Name
XRPD	X-Ray Powder Diffraction
WD-XRF	Wavelength Dispersive X-ray Fluorescence Spectrometry
WWH	World Health Organisation

1. Background information on the procedure

1.1. Submission of the dossier

The applicant ZS Texas Ltd submitted on 3 December 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for Lokelma, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 May 2014.

The applicant applied for the following indication:

Lokelma is indicated for the treatment of hyperkalaemia in adult patients, acute and extended use.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that sodium zirconium cyclosilicate was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0210/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0210/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance sodium zirconium cyclosilicate contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 15/11/2015, 24/07/2014 and 19/09/2013. The

Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Romaldas Mačiulaitis Co-Rapporteur: Piotr Fiedor/Ewa Balkowiec

- The application was received by the EMA on 3 December 2015.
- The procedure started on 31 December 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 21 March 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 18 March 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 1 April 2016.
- During the meeting on 25-28 April 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant 29 April 2016.
- The applicant changed from ZS Texas Ltd to AstraZeneca AB and submitted the responses to the CHMP consolidated List of Questions on 8 September 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 19 October 2016.
- During the PRAC meeting on 24-27 October 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 7-10 November 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 22 December 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 11 January 2017.
- During the CHMP meeting on 23-26 January 2017, the CHMP agreed on a second list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the second CHMP List of Outstanding Issues on 1 February 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the second List of Outstanding Issues to all CHMP members on 8 February 2017.
- During the meeting on 20-23 February 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Lokelma.
    - On 31 March, the EC requested the CHMP to further assess the impact of new information related to the FDA GMP inspections of the ZS Pharma Inc. site on the pending MA application. The results of the FDA inspections, conducted on 17-29 March 2016 and on 18-30 January 2017, were not

available to the CHMP at the time of opinion adoption in February 2017.

- The following GMP inspection was requested by the CHMP and its outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
  - A GMP inspection at ZS Pharma Inc., Coppell, Texas, USA, site responsible for manufacturing of the active substance, between 25-29 September 2017. The final inspection report was issued on 11 January 2018. The GMP certificate was issued on 12 January 2018.

- During their meeting on 25 January 2018, the CHMP, in the light of the scientific data available and the scientific discussion within the Committee, reconsidered the benefit-risk of Lokelma and re-adopted the positive opinion which concluded that the application satisfied the criteria for authorisation and recommended the granting of the marketing authorisation.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Hyperkalaemia is the presence of an abnormally high concentration of potassium in the blood. Most data on the occurrence of hyperkalaemia have been obtained from studies of hospitalised patients, and the incidence ranges from 1 to 10%. There is no agreed definition of hyperkalaemia, since the raised level of potassium at which a treatment should be initiated has not been established. The European Resuscitation Council guidelines consider hyperkalaemia to be a serum potassium (S-K) level > 5.5 mmol/L, with mild elevations defined as 5.5 to 5.9 mmol/L, moderate as 6.0-6.4 mmol/L, and severe as ≥ 6.5 mmol/L. The guidelines also note that extracellular potassium levels are usually between 3.5 and 5.0 mmol/L, which is considered the normal range for adults. However, a number of recent retrospective studies have shown the risk of mortality is increased even with only modest elevations of S-K. Mortality risk has been shown to be significantly higher in chronic kidney disease (CKD) patients with S-K levels > 5.0 mmol/L. In acute myocardial infarction patients, a mean postadmission S-K ≥ 5.5 mmol/L during hospitalisation corresponded to a 12-fold increase in death compared with S-K levels between 3.5 and 4.5 mmol/L but, more importantly, S-K levels between 4.5 and 5.0 mmol/L, which is within the normal range, were associated with a 2-fold increased risk of mortality compared with S-K between 3.5 and 4.5 mmol/L.

2.1.2. Epidemiology

Hyperkalemia develops when there is insufficient elimination, excessive intake, or shift of potassium from the intracellular space. Insufficient elimination, which is the most common cause of hyperkalaemia, can be hormonal (as in aldosterone deficiency), pharmacologic (e.g. treatment with angiotensin-converting enzyme inhibitors [ACEs], angiotensin-receptor blockers [ARBs], mineralocorticoid receptor antagonists) or, most commonly, due to reduced kidney function. Often, the cause is multifactorial (e.g. reduced kidney function combined with drug treatment such as ACEs or ARBs). Increased extracellular potassium levels result in depolarization of the membrane potential of cells. This depolarization opens some voltage gated sodium

channels, but not enough to generate an action potential. After a short period of time, the open sodium channels inactivate and become refractory, increasing the threshold required to generate an action potential. The subsequent impairment of neuromuscular, cardiac, and gastrointestinal organ systems is responsible for the symptoms observed with hyperkalaemia.

2.1.3. Clinical presentation, diagnosis

Symptoms of hyperkalaemia are non-specific and generally include malaise and muscle weakness or signs of cardiac arrhythmias such as palpitations, bradycardia, or tachycardia. Hyperkalaemia is detected via blood testing, often during routine screening for a medical disorder or after complications (such as cardiac arrhythmias) have developed. Of greatest concern is the effect of hyperkalaemia on the cardiac system, where impairment of cardiac conduction sometimes leads to fatal cardiac arrhythmias such as asystole or ventricular fibrillation. Because of the potential for fatal cardiac arrhythmias, severe hyperkalaemia represents an acute metabolic emergency that must be immediately corrected.

2.1.4. Management

Two ion-exchange resins, sodium polystyrene sulfonate (SPS) and calcium polystyrene sulfonate (CPS), are currently authorized for use in the European Union (EU), although their efficacy have never been demonstrated in controlled trials. Neither SPS nor CPS are useful in the acute setting because the drug must reach the colon in order to exert an effect and, thus, time to onset is too slow to make a meaningful impact in patients with severe hyperkalaemia. In addition, due to their ionic contents, SPS can cause sodium overload and CPS can cause hypercalcemia and calcium loading. As both SPS and CPS bind magnesium, hypomagnesaemia can occur, whereas SPS also binds calcium potentially causing hypocalcaemia. Other currently used treatments in the acute setting, such as insulin/dextrose and beta-receptor agonists like albuterol, are not approved by the EU for hyperkalaemia and have several limitations, the most important being that the effect is transient and does not eliminate surplus potassium. Also, neither SPS nor CPS is suitable for continuous maintenance treatment due to poor tolerability, as they require administration with a laxative, such as sorbitol, to induce diarrhea to avoid severe constipation. Hence, poor gastrointestinal tolerability typically makes chronic administration difficult.

About the product

Sodium zirconium cyclosilicate (ZS) has been developed as treatment for hyperkalaemia. The indication applied for is: *Treatment of hyperkalaemia in adult patients, acute and extended use*. ZS is an inorganic cation exchange crystalline compound. ZS has a high capacity to selectively entrap monovalent cations, specifically excess potassium and ammonium ions, over divalent cations such as calcium and magnesium, in the gastrointestinal tract. The high specificity of ZS for potassium is attributable to the chemical composition and diameter of the micro pores, which act in an analogous manner to the selectivity filter utilized by physiologic potassium channels. The exchange with potassium ions occurs throughout the gastrointestinal tract with onset in the upper part of the gastrointestinal tract. The trapped potassium ions are excreted from the body via the faeces, thereby reducing any excess and resolving hyperkalaemia. As claimed by the applicant, ZS demonstrates improved capacity, selectivity, and speed for entrapping excess potassium over currently available options for the treatment of hyperkalaemia. The proposed commercial formulation of ZS is a non-absorbed, insoluble, white crystalline powder for suspension with a specific particle size distribution

profile. The proposed starting dose of ZS for reversal of hyperkalaemia (when serum potassium is > 5.0 mmol/l) is up to 10 g/day, divided in 3 doses (TID) to achieve normokalaemia.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a powder for oral suspension containing 5 g or 10 g of sodium zirconium cyclosilicate as active substance. The finished product contains no excipients.

The product is available in sachets of a PET/LDPE/LLDPE/aluminium foil laminate as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of the active substance is hydrogen sodium zirconium (IV) silicate hydrate. Due to the natural variability in the manufacturing process of the active substance, it is expected to have the formula $Na_{\sim 1.5}H_{\sim 0.5}ZrSi_3O_9 \bullet 2–3\ H_2O$ and relative molecular mass in the range of 390.5 – 408.5. The WHO chose not to designate an INN for the active substance, and a USAN sodium zirconium cyclosilicate is used throughout the dossier and this CHMP AR. The active substance has the following structure:

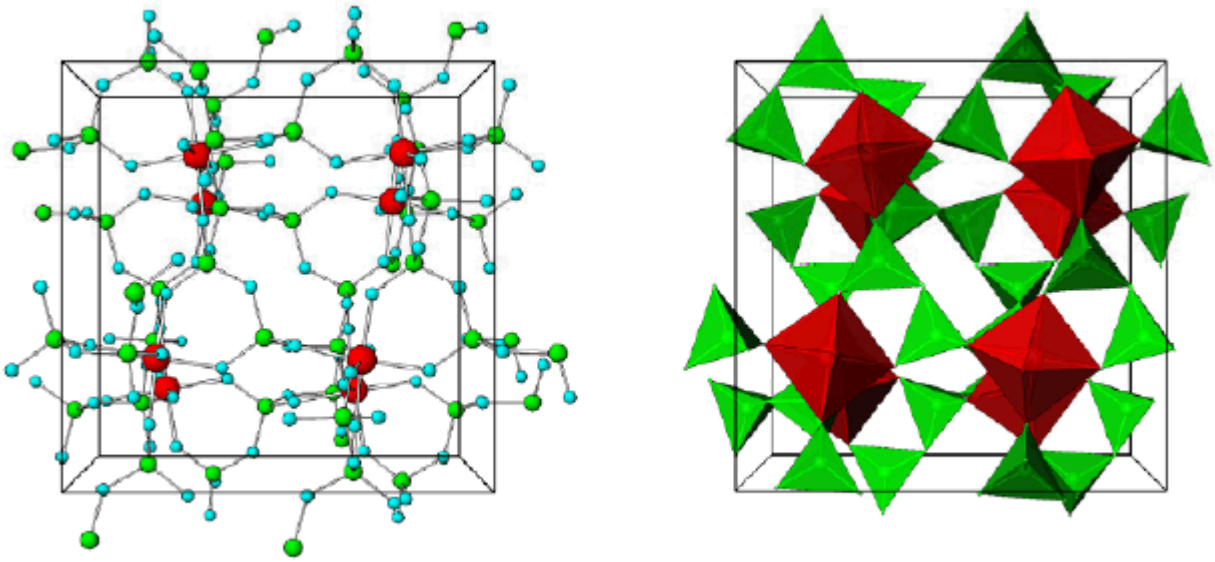


Figure 1. Stick-and-ball (left) and polyhedral (right) unit cell structural representation of the main framework of the microporous sodium zirconium cyclosilicate active substance. Red = zirconium, green = silicon, blue = oxygen atoms. Cations are not pictured.

The structure of sodium zirconium cyclosilicate is a cubic cell arrangement of octahedrally coordinated Zr and tetrahedrally coordinated Si units that interconnect through oxygen bridges as Zr–O–Si and Si–O–Si. The two types of units are observed in a ratio 1:3, respectively, and repeat orderly to form a three-dimensional framework characteristic of the compound. The framework acquires its negative charge from the octahedral fractions, $[ZrO_6]^{2-}$, and features channels and cavities that interconnect and locate the positive ions that counter-balance the negative charge of the framework. Electrostatic interactions between the framework and the cations allow for mobility and possibility of exchange with other cations that would fit and pass the free pore openings of ~ 3.0 Å. The uniform micropore structure allows a high exchange capacity and selectivity for potassium (K^+) and ammonium (NH_4^+) cations, providing the compound with its distinctive ion-exchange selectivity features responsible for its mode of action. *In vitro* characterisation of ion selectivity of sodium zirconium cyclosilicate was provided by the applicant and considered satisfactory.

The structure of sodium zirconium cyclosilicate was confirmed using synchrotron powder diffraction, standard X-ray powder diffraction, ^{29}Si magic angle spinning solid nuclear magnetic resonance studies (^{29}Si-MAS-NMR), Fourier transform infrared spectroscopy, inductive coupled plasma-optical emission spectrometry, wave dispersive X-ray microprobe analysis and thermo-gravimetric analysis. Calculations using proprietary software were also used for structure elucidation.

The active substance is a white crystalline powder. Bonding interactions in the main framework are considered primarily of covalent nature, with some ionic contribution due to the difference in electronegativity between Si–O and Zr–O. The covalent bonding interactions in all directions within the crystals make sodium zirconium cyclosilicate a compound insoluble in water or in organic solvents. It is neither hygroscopic nor sensitive to light and it is resistant to heat.

During the hydrothermal synthesis, the possibility that other crystalline phases are formed exists. The observed crystalline forms are controlled by the manufacturing process parameters and release specifications.

Sodium zirconium cyclosilicate is considered to be a new active substance. The applicant demonstrated that neither it, nor its derivatives have ever been active substances in medicinal products authorised in the EU.

Manufacture, characterisation and process controls

A single manufacturer carries out the entire process. The active substance is manufactured using a hydrothermal synthesis process.

The process was developed using QbD elements although no design space or other regulatory flexibility is requested. Critical process parameters (CPPs) and critical quality attributes (CQAs) of the active substance were identified. Based on this work, adequate in-process controls (IPCs) are applied during the synthesis. The specifications and control methods for starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in double colourless low density polyethylene (LDPE) bags inside a rigid opaque outer container/ drum. The primary packaging complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for: appearance, identity (FT-IR, XRPD), potassium exchange capacity (ion chromatography), crystalline impurities (XRPD), limit of acetate (HPLC), Zr content (WD-XRF), Si content (WD-XRF), Na content (WD-XRF), Hf content (WD-XRF), pH (potentiometry), moisture content (TGA), particle size (laser diffraction) and elemental impurities (ICP-MS).

The release specification is in accordance with the permissible daily exposures (based on a 10 g dose) for oral dosage forms as defined by ICH Q3D Guideline for Elemental Impurities.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for the active substance and impurity testing has been presented.

Batch analysis data on 3 commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

The active substance specifications are based on the active substance critical quality attributes (CQA).

Stability

Stability data on six commercial scale batches of the active substance from the proposed manufacturer stored in a container closure system representative of that intended for commercial production were provided. Data on three batches was provided for 24 months under long term conditions at 25 ºC / 60% RH and for up to 9 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines. Data on three batches was provided for 12 months under long term conditions at 30 ºC / 65% RH and for up to 12 months under conditions at 30 ºC / 75% RH according to the ICH guidelines. Additional supporting data was provided on four batches (including three batches from an additional manufacturer used in early development stages) for 24 months under long term conditions at 25 ºC / 60% RH and for up to 9 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines.

The following parameters were tested: appearance, identity (XRPD), potassium exchange capacity, moisture content and particle size. The analytical methods used were the same as for release and are stability indicating.

All tested parameters were within the specifications and no trends were observed.

Forced degradation studies including forced oxidation with hydrogen peroxide, acid and base conditions, thermal degradation and photolysis were also performed.

Photostability testing following the ICH guideline Q1B was performed on three batches. All results remained within specification and no trends were observed indicating good photostability.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months when stored at or below 30 ºC in

the proposed container, double colourless low density polyethylene (LDPE) bags inside a rigid opaque outer container/ drum.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is a powder for oral suspension containing 5 g or 10 g of sodium zirconium cyclosilicate as active substance. It is readily suspended in water with stirring or swirling.

Powder for oral suspension was selected as the optimal dosage form based on posology requirements. Data was provided to demonstrate that the dose volume, the dosing container, the method of mixing and the order of addition of the finished product and water had no significant effect on the percentage of the dose of the product delivered.

The active substance is completely insoluble. Polymorphism is controlled within the active substance manufacturing process and in the active substance specifications. It was demonstrated that there is no conversion to other crystalline forms on storage.

The finished product manufacturing encompasses only the filling and packaging processes of the active substance.

The active substance was packaged in three different container closure systems (bulk bottle, single-use bottle and pouched material) throughout the clinical program. The differences in packaging presentations or the processes used to fill the finished product did not influence the performance of the product.

The primary packaging is PET/LDPE/LLDPE/aluminium foil laminate. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of two main steps: filling and sealing of the pouches containing the neat active substance. The process is considered to be a standard manufacturing process. Two manufacturers are involved in the process.

Full process validation will be completed in line with the provided protocol, encompassing a minimum of three consecutive commercial scale batches prior to the distribution of the finished product, which was found acceptable and in line with the guidelines. Major steps of the manufacturing process have been validated by a number of studies.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of the manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, identity (FT-IR, XRPD), potassium exchange capacity (ion chromatography), Zr content (WD-XRF), Si content

(WD-XRF), Na content (WD-XRF), Hf content (WD-XRF), moisture content (TGA), particle size (laser diffraction), average delivered weight and microbial limits (Ph. Eur.).

The finished product contains only the active substance, sodium zirconium cyclosilicate. The specifications have been established according to physico-chemical characteristics and properties of the crystalline active substance. The finished product is released to the market based on the above release specifications, through traditional final product release testing.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for the active substance and impurity testing has been presented.

Batch analysis results are provided for three commercial scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Additional supportive results were provided for 30 commercial and pilot scale batches used in the pre—clinical and clinical studies.

Stability of the product

Stability data from three commercial scale batches of the finished product of each strength stored under long term conditions for 24 months at 25 ºC / 60% RH, for 18 months at 30 ºC / 65% RH, for 12 months at 30 ºC / 75% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. In addition, supportive data was provided on pilot scale batches of the finished product stored in HDPE Bottles for 36 months at 25 ºC / 60% RH and for up to 9 months under accelerated conditions at 40 ºC / 75% RH. The batches of Lokelma in the primary stability study are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The following parameters were tested: appearance, identity (XRPD), potassium exchange capacity, moisture content and particle size. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications and no trends were observed.

Forced degradation studies performed on the active substance were considered applicable to the finished product as it contains no excipients. Compatibility with the container closure system was validated with the provided stability data.

Photostability testing following the ICH guideline Q1B was performed on three batches. All results remained within specification and no trends were observed indication good photostability.

Based on available stability data, the proposed shelf-life of 36 months with no special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Lokelma is a non-sterile powder for oral suspension containing the active substance, sodium zirconium cyclosilicate only. Sodium zirconium cyclosilicate forms part of a family of compounds that feature specific ion exchange properties. Sodium zirconium cyclosilicate is white, non-soluble, non-absorbed, inorganic crystalline powder with a uniform micropore structure allowing a high exchange capacity and selectivity for potassium (K^+) and ammonium (NH_4^+) cations, responsible for its mode of action.

GMP Inspection

On 17 March 2017, EMA was made aware of the Food and Drug Administration (FDA) refusal of the AstraZeneca New Drug Application for Lokelma (sodium zirconium cyclosilicate). The FDA Complete Response Letter (CRL), issued on 16 March 2017, stated that the active substance manufacturing, release and stability testing facility (ZS Pharma Inc., Coppell, TX, USA) was found to be GMP non-compliant.

Manufacturers of chemical APIs in 3rd countries are not routinely inspected during the evaluation as the legislation place on the manufacturing authorisation holders the responsibility to use active substances that have been manufactured in accordance with good manufacturing practice for active substances. Further to this new information, the CHMP expressed concerns at its March 2017 plenary meeting on the possible impact of the FDA findings on the marketing authorisation application for Lokelma and asked the European Commission services to consider returning the Opinion in order to allow the CHMP to assess the possible impact of the FDA inspection findings on the marketing authorisation application.

During its plenary meeting on 18-21 April 2017, having discussed the possible impact of the FDA findings on the marketing authorisation application for Lokelma, the CHMP adopted a request for a GMP inspection of the active substance manufacturing, release and stability testing facility (ZS Pharma Inc., Coppell, TX, USA).

The purpose of the inspection was to verify the compliance of the manufacturer with the principles of the EU GMP Part II and relevant GMP Annexes.

The inspection was performed by the Italian Medicines Agency (AIFA) on 25-29 September 2017 and the inspection report was issued on 11 January 2018.

A total of seventeen deficiencies were raised, five of which were categorised as major. After reviewing the answers provided to the initial report, AIFA concluded that the site operates in general compliance with the European Good Manufacturing Practice, and issued a GMP Certificate for the site, valid until 31 January 2019, with certain follow up activities (e.g. provision of a final cleaning validation report) due by October 2018.

On 1 January 2018 the legal ownership of ZS Pharma was officially transferred to AstraZeneca Pharmaceuticals LP, in which name the Certificate was issued.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Lokelma contains the active substance sodium zirconium cyclosilicate for oral suspension that is a microporous zirconium silicate with a high exchange capacity and selectivity for potassium (K+) and ammonium (NH4+) cations. It is developed for the treatment of hyperkalaemia. As stated by the applicant with respect to nonclinical studies, sodium zirconium cyclosilicate was evaluated in a programme of pharmacology and toxicology studies that conformed to current regulatory guidance and scientific standards, with pivotal safety studies conducted in compliance with GLP regulations. Based on the results of the nonclinical pharmacology and safety studies in animals, oral administration of sodium zirconium cyclosilicate is expected to provide therapeutic benefit and to have a reasonable safety margin when used as directed to treat hyperkaliaemic patients.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The non-clinical development was performed predominantly with sodium zirconium cyclosilicate (ZS) but some early pharmacology and toxicity studies of ≤ 14-days duration employed the material (designated ZS-9). The differences between ZS and ZS-9 are the sodium counter-ion content, the particle size distribution and the pH of the aqueous suspensions.

The applicant presented data from 9 sources from studies in vitro and in vivo in rats. The pharmacology (non-GLP) data show the experimental potassium exchange capacity (KEC) value. The sodium zirconium cyclosilicate cation exchange has been shown to be highly selective for small monovalent ions such as sodium (Na+), hydrogen (H+), potassium (K+) and ammonium (NH4+) while divalent cations such as calcium (Ca2+) and magnesium (Mg2+) are not exchanged to any significant extent. The high selectivity for K+ is attributed to the dimensions and possibly the chemical configuration of the micro pores.

In vitro studies in the presence of mixed ion media containing Ca2+ and Mg2+ show that, unlike sodium polystyrene sulfonate (SPS), the KEC of sodium zirconium cyclosilicate and ZS-9 is essentially unaffected by the presence of these ions and is ~9-fold higher than that of SPS when these ions are present. In contrast, SPS was found to selectively take up Ca2+ in preference to K+. The effect of pH on the KEC in different media, buffered to mimic the physiological conditions in different areas of the human gastrointestinal tract

showed minimal effects except at low concentrations under conditions of low pH. At a pH of approximately 1.2 (simulated gastric fluid; SGF) and at concentrations of 0.5 and 5.0 mg/mL, the binding capacity of ZS-9 was decreased by 91% and 67% respectively, compared to the binding capacity observed in water. There was no effect on the KEC at the 50 mg/ml concentration. The decreased exchange at the lower concentrations is attributed to the high H+/K+ ratio, which would favour proton exchange over potassium uptake. Time-course studies to examine the effect of pH on the ion exchange properties of sodium zirconium cyclosilicate at a concentration of ~2 mg/ml showed there was no measurable K+ uptake in SGF. In simulated small intestinal fluid (pH ~4.5; SIF), there was an immediate uptake of K+ followed by a small release; with equilibrium reached in about 20 minutes and in simulated large intestinal fluid (pH 6.8), there was a rapid uptake of K+ during the first 10 minutes, followed by a slower uptake over the next hour. These results show that while potassium exchange in the stomach may be limited and depend on the concentration of sodium zirconium cyclosilicate present, potassium exchange will occur throughout the gastrointestinal tract and the equilibrium will occur quite rapidly.

In vivo, the administration of ZS-9 decreased the urinary excretion of potassium and urea nitrogen and increased the fecal excretion of potassium and urea nitrogen in a dose dependent manner when administered in the diet to Sprague-Dawley rats at doses up to 6 g/kg/day. These changes were accompanied by corresponding increases in urinary sodium concentration and decreases in faecal sodium excretion. There was no effect on the urinary and faecal concentrations of calcium and magnesium. The serum concentrations of all these electrolytes remained unchanged. In the GLP toxicity studies in dogs, oral administration of sodium zirconium cyclosilicate also decreased the urinary fractional excretion of potassium (FE-K) in a dose dependent manner by 85-95% and significantly reduced the serum potassium concentration at the highest doses when administered at 1000 mg/kg/tid for 28 days or at 2000 mg/kg/day for 9 months. These dosages, equivalent to a human dose of ~97 g/day and ~65 g/day, respectively, also resulted in hypokalaemia in some animals, demonstrating that orally administered sodium zirconium cyclosilicate removes potassium from the body.

Presented studies indicate that oral administration of sodium zirconium cyclosilicate can effectively remove potassium from the body.

Secondary pharmacodynamic studies

For the secondary pharmacodynamics development, the applicant presented one study results on ZS water absorption and swelling capacity. ZS has little water absorption capacity and does not swell compared with other preparations, which is an attribute that may account for the very low gastrointestinal adverse event profile. The applicant stated that ZS is not expected to be absorbed due to its insolubility and no interactions with secondary targets are expected. Hence, no in vitro secondary pharmacodynamic studies have been conducted. This is acceptable to the CHMP.

Safety pharmacology programme

The applicant presented bridged data from toxicology studies in beagle dogs. Treatment with ZS-9 had no effect on respiration rate or ECG parameters when administered for 14 days at total daily dosages of up to 4,479 mg/kg (1493 mg/kg/tid; study 14250-10), which is equivalent to a human dose of ~145g/day. ZS also had no effect on qualitative ECG parameters, heart rate, RR or PR intervals or QRS duration when administered for 28 days at dosages up to 3000 mg/kg/day or for 270 days at dosages up to 2000 mg/kg/day. A slight increase in the QTc interval, that was not considered clinically meaningful, was observed

in females at the 1000 mg/kg tid dose in the 28-day study and was considered secondary to the sodium zirconium cyclosilicate-induced hypokalemia in these animals, as it was not observed in animals treated with the same dose of sodium zirconium cyclosilicate that received potassium supplementation or in a second 28-day study used to qualify some of the possible different silicate phases produced in the manufacturing process where no animals became hypokalemic. No adverse effects were noted on the central nervous system or gastric motility in any of the rat and dog GLP toxicity studies, in which rats and dogs were treated for 14-days with ZS-9 or up to 180 days (rats) or 270-days (dogs) with ZS.

From the provided results of the nonclinical pharmacology in vivo and safety studies in animals, oral administration of ZS is expected to provide therapeutic benefit and to have a sufficient safety margin when used as directed to treat hyperkalemic patients.

Pharmacodynamic drug interactions

There has been no pharmacodynamic drug interaction studies have been performed. This is acceptable to the CHMP as potential such interactions are more likely at pharmacokinetic level rather than pharmacodynamic.

2.3.3. Pharmacokinetics

Due to its inorganic composition, sodium zirconium cyclosilicate, is not subject to enzymatic metabolism and due to its insolubility and particle size it is in not a substrate for transporter processes, has no effect of cytochrome P450 metabolism or induction and is systemically not absorbed. The lack of any significant absorption is confirmed by analysis of dog whole blood and urine in which no Zr could be detected following 9 months of daily administration of sodium zirconium cyclosilicate at a dose of 2000 mg/kg/day, equivalent to a human dose of ~65g/day based on a 60 kg body weight. In a rat mass balance study 97-99% of the administered Zr dose was excreted in the faeces within 48 hours of administration.

No significant amounts of United States Pharmacopeia (USP) elements were found to leach from the API following incubation in USP SGF and USP SIF. Of the five elements listed per USP <232> testing that were detected in the Simulated Gastric Fluid (SGF) and Simulated Intestinal Fluid (SIF) supernatants, the amount of each element released was ≤ 1 µg/g sodium zirconium cyclosilicate for aluminium, chromium copper, molybdenum, nickel and palladium and well below the permissible daily exposure limits for these elements when sodium zirconium cyclosilicate is administered at the 5g to 30g dose range. The potential amount of silicon exposure following administration of 5-30 g of sodium zirconium cyclosilicate ranged from ~1 to 10% of the total estimated silicon intake/day and the average amount of zirconium released per gram of sodium zirconium cyclosilicate for batches manufactured at the commercial scale was less than 0.5% of the average daily zirconium intake. Overall, these data indicate that exposure to sodium zirconium cyclosilicate over the proposed 5-30 g dose range does not demonstrate a significant risk of exposure to elemental leaching for USP <232> elements, silicon, zirconium, hafnium or aluminum.

The applicant presented drug drug interaction (DDI) test results with drugs from various therapeutic classes such as: aluminum hydroxide, magnesium carbonate, calcium carbonate, docusate sodium, propranolol hydrochloride, captopril, losartan potassium, digoxin, levothyroxine sodium, lithium carbonate, lanthanum carbonate, docusate sodium, furosemide, glipizide, lisinopril, metformin HCl, quinapril HCl, spironolactone, valsartan, sevelamer carbonate, atorvastatin calcium, erythromycin ethylsuccinate, clopidogrel, ketoconazole, prednisone, warfarin sodium, allopurinol, amlodipine besylate, acetilsalicylic acid, cyclosporine, dabigatran etexilate, phenytoin. In vitro tests were performed according to GLP requirements using USP dissolution

methods as well as aqueous solutions that covered the physiologic range of pH expected within the gastrointestinal tract. There was no evidence of uptake/binding with the exception of calcium and lithium ions where uptake was attributed to the high ion concentration and the absence/low level of other competing ions.

Both, decreases and increases in the tested medicine concentration of >10% were noted in various media in the presence of ZS for atorvastatin calcium, dabigatran etexilate, clopidogrel, erythromycin ethylsuccinate, furosemide, Al(OH)3, MgCO3, glipizide, ketoconazole, levothyroxine sodium, losartan potassium, valsartan. Based on the pH solubility profile and pH study data all changes were attributed to the ZS-induced change in the pH of the media and not to uptake/binding by ZS. The KEC of sodium zirconium cyclosilicate was unaffected by the presence of other drug substances with the possible exception of lithium carbonate capsules, USP 300 mg where a 10 - 12% decrease was noted. This minor decrease was attributed to the high lithium: potassium ratio (100:1) in the test solution.

During follow-up Scientific Advice procedure, the applicant was advised to provide data on any in-vitro interaction with hot fluids and a selection of beverages. Since such data seemed missing, the CHMP requested these during the procedure and the applicant was asked to discuss the potential correlation of ZS and hot fluids and beverages or to present sufficient justification of the lack of this data (see section 2.3.6).

2.3.4. Toxicology

Single dose toxicity

The toxicity of single doses of sodium zirconium cyclosilicate has been investigated via the oral route in the rats and dogs. The studies are summarised below.

Single dose toxicity study with sodium zirconium cyclosilicate

Study ID	Species/Sex/ Number/ Group	Dose (mg/kg b.w.) / Route	Approx. lethal dose / observed max non-lethal dose (mg/kg b.w.)	Major findings
2009-001	Rat (Sprague-Dawley) / 3M;3F/	2000[1]; Oral-qd (gavage);	>2000	**None.** Treatment with ZS-9 did not result in moribundity or mortality or any abnormal clinical findings. Treatment with ZS-9 had no effects on body weights, body weight changes, or food consumption. There were no test article effects on serum chemistry, hematology, routine urinalysis, or urine Na, K, and UUN concentrations in this study. This protocol was designed to determine the maximum tolerated dose (MTD) of ZS-9 in rats, following a single oral dose.
2009-002	Dog Beagle / 1M;1F/	2000[1]; Oral-qd (gavage);	>2000	**None.** Treatment with ZS-9 did not result in moribundity or mortality. There were no treatment related clinical findings. Mucous and soft stool were observed from both male and female dogs. These observations are not treatment related due to the sporadic nature.

M – Male; F – Female;

1 - unprotonated form of sodium zirconium cyclosilicate (ZS-9)

No adverse effects were noted following gavage administration of a single 2000 mg/kg dose of unprotonated Sodium zirconium cyclosilicate (ZS-9) in water at a dose volume of 10 ml/kg to rats or dogs.

Repeat dose toxicity

Study ID	Species/ Sex/ Number/ Group	Dose (mg/kg b.w.)/ Route/	Duration	NOAEL (mg/kg/ day)	Major findings
2009-001/ GLP - No	Rat (Sprague-Dawley)/ M/5 F/5	0, 500, 1000, 2000[1,2] Oral (gavage)	7 days		Treatment with ZS-9 did not result in moribundity or mortality. There was a test article-related increase in plasma mean prothrombin time (PT) in M and F from Group 4 when compared to control Group 1. Treatment with ZS-9 did not result in abnormal gross findings, alterations on absolute or relative organ weights. **Conclusion: Oral dose MTD (maximum tolerated dose) for ZS-9 is 2000 mg/kg/day.**
2010-001/ GLP - No	Rat (Sprague-Dawley)/ M/5 F/5	2000[1,3] Oral (gavage)	7 days		No effect on mortality and no adverse clinical signs. **Conclusion: gavage administration of ZS-9 at up to 2000mg/kg/dose is suitable for use in a 14-day repeat dose study.**
UNTHSC-100/ GLP - Yes	Rat (Sprague-Dawley)/ M/15 F/15	0, 400, 800, 1600[1,3] Oral (gavage)	14 days + 10-day recovery	M – 400 mg/kg/day; F – 800 mg/kg/day;	Thirty-two rats died on study (4 M and 5 F at 0 mg/kg/dose, 5 M and 2 F at 400 mg/kg/dose, 3 M and 5 F at 800 mg/kg/dose and 4 M and 4 Fat 1600 mg/kg/dose). All deaths were attributed to gavage error and were not test article related. *Clinical signs*: Clinical findings were related to issues with the gavage procedure and errors and not test article related. *Body Weight:* ZS-9 administration had no effect on body weight. A decrease in body weight gain across all dose groups including control compared to pre-trial during the 14-day dosing period was attributed to the volume of the dose formulation. *Food Consumption*: A reduction in mean daily food consumption was observed for both the 0 mg/kg/dose (Control) group as well as all the groups administered ZS-9. This reduction in food consumption is most likely reflective of animals receiving a 10 mL/kg dose volume, three times a day. *Hematology:* At Day 15/16 and Day 25, there were no alterations in hematologic values for M and F that were related to ZS-9 administration. At Day 15/16, there was a statistically significant increase in LUC (large unstained cells) for M at 1600 mg/kg/dose and a statistically significant increase in absolute eosinophil count for F at 1600 mg/kg/dose. Both alterations were of low magnitude and were not toxicologically relevant to ZS-9 administration. There were several animals in each group that had hypochromasia (HYPO) of red blood cells noted. However, there were no accompanying changes in hemoglobin, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. Therefore, these red blood cell morphology changes were of no relevance and unrelated to ZS-9 administration. *Clinical Chemistry*: no alterations in serum chemistry values for M and F that were related to ZS-9 administration. For the remaining parameters, a few were statistically significant at either Day 15, Day 16 or Day 25. These

Study ID	Species/ Sex/ Number/ Group	Dose (mg/kg b.w.)/ Route/	Duration	NOAEL (mg/kg/ day)	Major findings
					included a statistically significant decrease in alkaline phosphatase (ALP) for M at 800 mg/kg/dose and F at 400 mg/kg/dose and 800 mg/kg/dose; a statistically significant decrease in glucose (GLU) for F at 400 mg/kg/dose; and a statistically significant decrease in potassium (K) for M at 1600 mg/kg/dose at Day 25. These alterations were either of low magnitude and/or showed no dose-related patterns or trends to suggest they were toxicologically relevant or associated with ZS-9 administration. *Urinalysis*: a statistically significant decrease in specific gravity for M at 400 mg/kg/dose; Overall urinary potassium was decreased by 35 to 55% in M and 32 to 49% in F. Mean urinary urea nitrogen concentration largest decreases of ~ 50% were seen at the 400 mg/kg/dose falling to ~10% at the 1600 mg/kg/dose. Dose-related increases in urinary sodium concentration were observed in M treated with ≥ 400 mg/kg/dose and in F treated with ≥ 800mg/kg/dose. The decreases in urinary potassium and urea nitrogen concentrations and increase in urinary sodium concentration were considered to be due to the cation exchange properties of ZS-9 and were not considered toxicologically adverse. Increases in the urine pH (pH ≥ 9) were noted in M and F rats treated with ZS-9 across all dose groups. *Microscopic:* At Day 15/16 there were a few microscopic findings of minimal to slight extent involving the urinary bladder that occurred with slightly increased incidence and/or intensity in test article-treated M (Group 2, 3, and 4) and F (Group 4) as compared to their respective vehicle-treated controls (Group 1). The more notable findings included: acute inflammation in Group 4 M and F; and dose related mononuclear cell infiltration and mucosal hyperplasia in M of Groups 2, 3, and 4. The presence of mucosal hyperplasia with accompanying inflammatory cell infiltrates was likely a consequence of irritation of the urinary bladder mucosa. A definitive relationship between these urinary bladder findings and ZS-9 treatment was uncertain. Following the 10-day recovery period, there were no microscopic observations involving the urinary bladder in Group 6 M and F suggesting reversibility of these possible ZS-9- related findings.

Study ID	Species/ Sex/ Number/ Group	Dose (mg/kg b.w.)/ Route/	Duration	NOAEL (mg/kg/ day)	Major findings
524020/ GLP - Yes	Rat (Sprague-Dawley)/ M/10 F/10 (5M;5F – recovery)	0, 300, 1000, $(2000)^3$, $(2000)^2$ Oral (gavage)	28 days + 14-day recovery	(2000mg/kg /dose)^3 = 6000mg/kg/ day; (2000mg/kg /dose)^2	*Motrality:* No *Clinical signs* : Light coloured faeces were recorded in some of the animals receiving ZS. In animals receiving 3000 mg/kg/day this was recorded in 4/10 M and 6/10 F during Week 1. In animals receiving 6000 mg/kg/day this was noted in the majority of M throughout the treatment period and in 3/15 F during Week 1. The finding was not noted in animals receiving 900 mg/kg/day or those receiving 2000 mg/kg/day. *Body Weight:* no body weight differences that were considered to be related to treatment with ZS. *Food Consumption*: Food consumption was unaffected by treatment with ZS. *Hematology:* Haematology parameters were unaffected by treatment with ZS. The only differences in haematology parameters potentially related to ZS were slightly lower red blood cell mass to plasma ratios in F receiving 2000 mg/kg/day or 6000 mg/kg/day (2000 mg/kg/dose TID), reflected in lower group mean red blood cell counts, haemoglobin concentrations, and haematocrits, when compared with controls. *Clinical Chemistry*: Clinical chemistry was unaffected by treatment with ZS. There were a few statistically significant differences in group mean clinical chemistry parameters compared with controls. These included a slightly lower sodium concentration in F receiving 900 mg/kg/day, slightly lower concentrations of urea, triglycerides, and sodium in F receiving 3000 mg/kg/day, and slightly lower triglyceride concentrations and higher chloride concentrations in F receiving 2000 mg/kg/day or 6000 mg/kg/day. *Urinalysis*: ZS treatment resulted in dose-related effects on the urinary excretion of electrolyte. Sodium (UNa) and the sodium:creatinine ratio (NaC-R) were higher and potassium (UK), the potassium:creatinine ratio (KC-R) and chloride (UCl) and chloride:creatinine ratio (ClC-R) were lower, when compared with controls. A statistically significant lower urea:creatinine ratio was noted in F receiving 2000 mg/kg/day and 3000 mg/kg/day, when compared with controls. Urinary pH was statistically significantly lower in M receiving 2000 or 6000 mg/kg/day (2000 mg/kg/dose TID), when compared with controls. *Gross Pathology*: no test article-related gross findings noted. The gross findings observed were considered incidental, of the nature commonly observed in this strain and age of rat, and/or were of similar incidence in control and treated animals and, therefore, were considered unrelated to administration of ZS. *Microscopic:* no test article-related microscopic findings were noted. The microscopic findings observed were considered incidental, of the nature commonly observed in this strain and age of rat, and/or were of similar

Study ID	Species/ Sex/ Number/ Group	Dose (mg/kg b.w.)/ Route/	Duration	NOAEL (mg/kg/ day)	Major findings
					incidence and severity in control and treated animals and, therefore, were considered unrelated to administration of ZS.
524942/ GLP - Yes	Rat (Sprague-Dawley)/ M/10-20 F/10-20 (10M;10F – recovery)	0, 333, 1000, 2000[3] Oral (gavage)	180 days + 28-day recovery	6000 mg/kg/day	*Mortality:* 6 unscheduled deaths, none of which were considered to be related to treatment with ZS. *Clinical observations*: no clinical signs indicative of systemic toxicity noted during the observation period. Pale coloured faeces were recorded only in animals receiving 6000 mg/kg/day of ZS. This was recorded from Day 32 with the finding recorded in all male cages from Day 50. In F this finding was recorded in all cages from Day 36. ZS is insoluble in aqueous media and would not be expected to be systemically absorbed. The change in the colour of the faeces of some animals was considered due to the excretion of ZS. *Body Weight:* no body weight differences that were considered to be related to treatment with ZS. *Food Consumption*: Food consumption was unaffected by treatment with ZS. *Clinical Chemistry*: * At Week 13 and Week 26, lower mean plasma potassium concentrations in M dosed with 6000 mg/kg/day, and at Week 13, in F that dosed with ≥3000mg/kg/day; * At Week 13, lower mean plasma urea in F that received ≥3000 mg/kg/day, and at Week 26 in F that received 6000 mg/kg/day; * At Week 26, minimally lower mean plasma sodium in sodium zirconium cyclosilicate-treated F; * At Week 26, minimally lower mean plasma chloride in M treated with

Study ID	Species/ Sex/ Number/ Group	Dose (mg/kg b.w.)/ Route/	Duration	NOAEL (mg/kg/ day)	Major findings
					≥3000 mg/kg/day and F treated with ≥1000 mg/kg/day; * At Week 13, slightly lower mean plasma magnesium in M that received 6000 mg/kg/day, and at Week 26 in M that received ≥1000 mg/kg/day and in F that received 1000 or 6000 mg/kg/day. * At the end of the 4 week recovery period, lower magnesium was also noted in M previously treated with 6000 mg/kg/day; * At Week 26, higher mean bicarbonate in M that received 6000 mg/kg/day and all sodium zirconium cyclosilicate treated F; * At Week 26, slightly (approximately 17%) lower mean glucose in M that received≥3000 mg/kg/day and F treated with ≥1000 mg/kg/day. *Urinalysis*: * Dose-related increases in mean urinary sodium at Weeks 13 and 26 with and without correction for creatinine of up to 390% (M) and 212% (F); * Dose-related increases in mean urinary chloride, with and without correction for creatinine, at Week 13 in sodium zirconium cyclosilicate-treated M, and at Week 26, in M that received ≥3000 mg/kg/day; * Dose related decreases in mean urinary potassium, with and without correction for creatinine, at Week 13 and Week 26 that reached up to 94% in M and 80% in F; * Treatment related decrease in mean urinary urea and creatinine at Week 26 in M that received ≥3000 mg/kg/day; * Treatment related decreases in mean urinary magnesium in F at ≥3000 mg/kg/day, and M at 6000 mg/kg/day at Week 13 and in M treated with ≥3000 mg/kg/day and F treated with ≥1000 mg/kg/day at Week 26. Following correction for creatinine significant decreases were observed in F treated with 6000 mg/kg/day at Week 13 and ≥ 3000 mg/kg at Week 26; * Slightly higher urinary pH in animals treated with sodium zirconium cyclosilicate at all time points. Sodium zirconium cyclosilicate treatment had no effect on organ weights, and there were no treatment related macro- or microscopic findings.
2009-002/ GLP - No	Dog (beagle)/ M/2 F/2	0, 500, 1000, 2000[1,2] Oral (gavage)	7 days		Treatment with ZS-9 had no effect on mortality, body weights, body weight changes, food consumption, serum chemistry, hematology, coagulation, routine urinalysis parameters, urine chemistry (Na+, K+ and urine urea nitrogen [UUN]), absolute or relative organ weights. No test article related effects were detected following microscopic evaluation of the kidney tissue sections from Groups 1 to 4 dogs. Clinical signs 2 were confined to the presence of white material mixed with feces in all ZS-9 treated animals and was attributed to excreted test article. **Conclusion**: The **MTD** established in this study for repeat administration in beagle dogs **was 2000 mg/kg**.

Study ID	Species/ Sex/ Number/ Group	Dose (mg/kg b.w.)/ Route/	Duration	NOAEL (mg/kg/ day)	Major findings
14175-10/ GLP - No	Dog (beagle) M/2 F/2	1300[1,3] Oral in food	7 days		There were no adverse effects on food consumption but body weight decreased by around 0.2 kg over the 7-day treatment period but in the absence of control animals it is not clear whether this effect was test article related. Clinical signs were limited to the observation of white material, presumed to be test article, in the feces of each dog from the afternoon of Day 3 through Day 7. There were no adverse effects on hematology or coagulation parameters but treatment was associated with increases in serum sodium, chloride and calcium and an ~90% decrease in urinary potassium concentration when compared to pre-treatment values. Urinary sodium concentration was also increased in 1 M and both F and urinary nitrogen concentration was decreased in 1M and both F. **Conclusion: a dose of 1300 mg ZS-9 /kg administered three times a day was considered suitable for use in 14-day toxicity studies in Beagle dogs.**
14250-10/ GLP - Yes	Dog (beagle) M/2 F/2	0, 325, 650, 1300[1,3] Oral in food	14 days + 10-day recovery	-	*Motrality*: No. *Electrocardiographic Examinations*: ZS-9 treatment had no adverse effect on heart rate, PR, QRS or QT intervals. *Clinical observations* : With the exception of white material in feces noted in one M and one F dog in Group 2 (325 mg/kg/dose) and in all dogs in Groups 3 and 4 (≥ 650 mg/kg/dose) ZS-9 had no adverse effect on clinical signs. *Serum Chemistry*: At 325 mg/kg/dose, BUN was increased and chloride was decreased in M. At 650 mg/kg/dose, LDH was increased and triglyceride was decreased in F, and cholesterol was increased in M; at >650 mg/kg dose, creatinine and magnesium were increased and glucose and chloride were decreased in F, and phosphorus and the albumin/globulin ration were decreased in M. At the 1300 mg/kg/dose magnesium and AST were increased and potassium was decreased in F and sodium, globulin LDH and AST were increased in M. A dose-related decrease in serum potassium was observed in M, but failed to reach significance. *Hematology* : A statistically significant increase in WBC was observed in Group 4 M compared to control. This finding was considered to be incidental as the magnitude of the change was well within normal values, was below the pre-test value, was not dose related and did not occur in females. A statistically significant reduction in PT was observed in all treated M compared to control. This finding was considered incidental as the magnitude of the change was well within normal values, was similar to the pre-test values for these animals, was not dose related and did not occur in F. *Urinalysis*: On Day 13, a statistically significant increase in pH was

Study ID	Species/ Sex/ Number/ Group	Dose (mg/kg b.w.)/ Route/	Duration	NOAEL (mg/kg/ day)	Major findings
					observed in all treated M and in Group 2 and Group 4 F. There was a significant, dose dependent increase in urinary sodium concentration in M and F in Groups 2, 3 and 4 and a dose related decrease in urinary potassium and urea nitrogen concentration. The decrease in urinary potassium concentration reached statistical significance in Group 3 M and Group 4 M and F and statistically significant reductions in urea nitrogen concentration were observed in Group 4 M and F. *Necropsy Findings*: There were no abnormal external findings in any animal on Day 14 necropsy. Internal findings consisted of mottled lungs in a Group 1 M, an enlarged spleen, mottled lungs and red fluid in the stomach of a Group 3 F, spleen-like tissue collected from the mesentery with the lymph node of another Group 3 F , bright yellow fluid in the stomach of a Group 4 M and an enlarged spleen in a Group 4 F. At the Day 24 recovery necropsy, one Group 1 F , and one Group 4 F , were thin. Internally, the Group 4 F had clear fluid in abdominal cavity. *Histopathology*: Microscopically minimal to mild focal and/or multifocal inflammation was observed in the kidneys of treated animals. The renal lesions of both sexes had similar incidence and severity at 650 and 1300 mg/kg/dose and were less frequent and severe at 325 mg/kg/dose. In some dogs the inflammation was unilateral rather than bilateral and in some cases was associated with inflammation in the urinary bladder and origin of the ureter. Taken together these observations suggest that factors other than direct renal injury, such as alterations in urine composition of ZS-9 treated dogs may have resulted in increased susceptibility to subclinical urinary tract infections, even though no microorganisms were observed in these tissues. Results of Day 13 urinalysis data, with elevated pH in all treated groups compared to control are also consistent with, but not diagnostic of, a urinary tract infection. In recovery animals the inflammation was completely resolved in F and partly resolved in M suggesting that whatever the cause of the inflammation it was reversible following cessation of dosing. A number of other spontaneous lesions commonly observed in young dogs were also diagnosed but were not considered to be test article related. **Conclusion: As aresult of the microscopic findings no NOAEL was established in this study.**
1959-001/ GLP - No	Dog (beagle) F/3	$0^{1,3}$, $100^{1,3}$, $100^{3,4}$, 100^{3}, $600^{1,3}$,	14 days	**1 - NOEL -** 100 mg/kg tid for sodium	*Mortality*: No. *Clinical observations*: There were no adverse test article-related clinical findings observed during this study. White material, presumed to be the test article and/or the potassium supplement, was frequently observed in

Study ID	Species/ Sex/ Number/ Group	Dose (mg/kg b.w.)/ Route/	Duration	NOAEL (mg/kg/ day)	Major findings
		600+KCl[1,3], 600[4,3], 600[3], 50[5,3] Oral in food		zirconium cyclosilicate and ZS-9 with or without screening at 5 µm. **2- NOAEL -** 600mg/ kg/ dose for sodium zirconium cyclosilicate or ZS-9 supplemented with potassium.	the feces of the three dogs in Group 3 treated with ZS-9 + K. All other reported clinical findings were considered incidental to treatment and are commonly found in dogs of this age and strain under normal laboratory conditions. *Clinical Chemistry*: No clinically meaningful differences or test article-related effects were identified among clinical chemistry analytes in any treatment group. *Urinalysis*: There was a statistically significant increase urinary pH compared to Control in animals treated with 600 mg/kg/dose of screened or unscreened ZS-9 that was not observed at the 100 mg/kg/dose or in animals treated with 600 mg/kg/dose of screened and protonated ZS-9 or 50 mg/kg/dose of sodium bicarbonate. Mean urinary pH in these animals increased from 5.33 to ~7.67 on Day 7 and from 5.83 to 7.733 on Day 13. The lack of effect on urinary pH in animals treated with 600 mg/kg/dose of protonated ZS-9 (ZS-9SP) suggests that the increase in the urinary pH in animals treated with the higher dose of sodium loaded ZS-9 (ZS-9 and ZS-9S) was a result of gastrointestinal hydrogen absorption. On Days 7 and 13 the fractional excretion of sodium was increased relative to pre-dose intervals in all groups including controls. Animals receiving 600 mg/kg/dose ZS-9, ZS-9 + K, and ZS-9S tended to have increases that were slighter greater (up to 116% relative to controls) than those seen in other treatment groups or among the control animals. Significant decreases in the fractional excretion of potassium, relative to Control, were observed in animals treated with 600 mg/kg/dose ZS-9, ZS-9S, ZS-9SP, and 100 mg/kg/dose ZS-9S on Days 7 and 13. On Days 7 and 13 the fractional excretion of chloride was mildly increased relative to pre-dose intervals in all groups including controls. Animals receiving 600 mg/kg/dose ZS-9 and ZS-9S tended to have mild decreases in the fractional excretion of chloride (up to 49%) relative to controls. On Days 7 and 13 urea nitrogen/ creatinine ratio was mildly increased relative to predose intervals in all groups including controls. There were mild decreases in urea nitrogen/creatinine ratios on Days 7 and 13 in animals receiving 600 mg/kg/dose ZS-9, ZS-9 + K, ZS-9SP, and ZS-9S relative to controls (up to 26%). *Microscopic:* Test article related microscopic findings were in all groups dosed at 600 mg/kg/dose and included minimal to mild mixed leukocyte infiltrates in the kidney sometimes associated with minimal to mild renal tubular regeneration, and occasionally minimal renal tubular degeneration/ necrosis, minimal mixed leukocyte infiltrates in ureter and /or urethra and minimal pyelitis in dogs dosed with ZS9 or ZS-9S. The presence of pyelitis

Study ID	Species/ Sex/ Number/ Group	Dose (mg/kg b.w.)/ Route/	Duration	NOAEL (mg/kg/ day)	Major findings
					and/or the mixed leukocyte infiltrates in the urethra and ureters in some dogs and random distribution of kidney findings are likely an indirect effect of the test article and, in the absence of the manifestation of clinically adverse effects (urine and serum chemistries, food consumption, weight gain and behavior), were not considered to be toxicologically adverse.
1959-007/ GLP - Yes	Dog (beagle) M/3-6 F/3-6	0[3], 100[3], 300[3], 1000+K[3], 1000[3], 1000[2] Oral in food	28 days + 21-day recovery	1 - For sodium zirconium cyclosilicate - 300 mg/kg tid or 1000 mg/kg qd; 2 - For sodium zirconium cyclosilicate supplemented with potassium 1000 mg/kg tid.	*Mortality*: No. *Clinical observations* : There were no adverse test article-related clinical findings observed during this study. *Clinical Pathology*: At the Week 2 and Week 4 collections, both sexes receiving 1000 mg/kg tid had minimal increases in serum pH that were associated with minimal increases in bicarbonate (HCO_3) (up to 1.2-fold), relative to controls. Minimal increases in tCO_2 (up to 1.2-fold) were also present in these treatment groups. Similar changes were also noted at the Week 2 collection in males receiving 1000 mg/kg + KCl tid, and at the Week 4 collection in females receiving 1000 mg/kg + KCl tid. There were no test article-related effects among hematology endpoint parameters in either sex at any interval. *Clinical Chemistry*: Dose-related changes in mean clinical chemistry parameters included decreases in serum potassium, phosphorous, and aldosterone, a mild to moderate increase in mean urine volume with associated decreases in specific gravity and osmolality, a dose-related reduction in the mean fractional excretion of urinary potassium (FE: K) and a slight increase in mean urine pH. There was a tendency for mean serum bicarbonate to be minimally increased in both sexes receiving 1000 mg/kg TID that corresponded to a mild increase in mean serum pH relative to controls. In most treatment groups, there was a mild to moderate increase in the mean fractional excretion of sodium (FE: Na), relative to control groups but these were not associated with meaningful changes in mean serum sodium. All changes were reversible following a 21-day recovery period. Mild increases in FE: K and fractional excretion of chloride (FE: Cl) were noted in both sexes receiving potassium supplemented ZS (1000 mg/kg + KCl; TID) relative to controls and were considered secondary to KCl supplementation. In three F at the 1000 mg/kg tid dose serum potassium was decreased by up to 1.8 mmol/l over the dosing period. These same animals also had increased alanine aminotransferase (ALT) and aspartate transaminase (AST) values at Weeks 2 and/or 4. No elevations in ALT/AST were observed in high dose animals that remained within the normokalemic range or in high dose animals supplemented with potassium suggesting that the elevations may have been a secondary response to the hypokalemia. *Microscopic:* Test article-related microscopic findings present in the adrenal

Study ID	Species/ Sex/ Number/ Group	Dose (mg/kg b.w.)/ Route/	Duration	NOAEL (mg/kg/ day)	Major findings
					glands included increased intracytoplasmic lipid vacuolation in cells of the zona glomerulosa in all groups of ZS-treated animals given daily ZS doses ≥ 900 mg (300, 1000 + KCl, and 1000 mg/kg/dose tid, and 1000 mg/kg sid) and an increased incidence of cystic degeneration in the zona glomerulosa in M and F given 1000 mg/kg tid. These changes were attributed to the decrease in aldosterone production. Kidneys from animals given 1000 mg/kg tid had multifocal areas in the medulla and cortex with a spectrum of tubular and interstitial degenerative and inflammatory changes that included vacuolation/degeneration of tubules or vacuolation/degeneration of tubules with concomitant expansion of the interstitium by inflammatory cells (primarily lymphocytes, macrophages, and/or fibroblasts). Some animals had dilation of tubules with attenuation of tubular epithelium and one hypokalemic F animal in this group also had hemorrhage, hyperplasia of transitional epithelium lining the renal pelvis, and increased neutrophils in addition to the other inflammatory cells in the interstitium. These renal findings are consistent with changes described in the kidneys of animals with prolonged decreased body potassium, and were prevented by potassium chloride supplementation.
1959-009/ GLP - Yes	Dog (beagle) F/3-6	0[3], 100[3], 300[3], 1000+K[3], 1000[3] Oral in food	28 days + 21-day recovery	**NOAEL -** 1000mg/kg/ tid for sodium zirconium cyclosilicate	*Mortality*: No. *Clinical observations* : There were no ZS-related clinical findings. *Clinical Pathology:* all F treatment groups administered ZS had minimal dose-dependent increases in bicarbonate (HCO_3, up to 1.1-fold) and tCO_2 (up to 1.1-fold), relative to controls. There were no test article-related effects among hematology parameters in any treatment group. At the Week 4 collection, minimal statistically significant decreases in sodium (2%) and chloride (2%), and a mild statistically significant increase in potassium (11%) were present in F administered 1000 mg/kg ZS tid relative to controls. *Electrocardiographic Examinations*: All animals were in sinus rhythm or sinus arrhythmia, both of which are normal rhythms in dogs. There was no effect of the oral administration of ZS on qualitative or quantitative ECG parameters. *Urine Chemistry*: • In the control group, FE:K increased by 40% at Week 2 and by 77% at Week 4. This increase was reversible, as FE:K decreased during the recovery period. • In the groups given ZS at 100 and 300 mg/kg tid, mean FE:K was little changed at Week 2 and had increased (35% and 15%, respectively) by Week 4. • In the group given ZS at 1000 mg/kg tid, mean FE:K had decreased by 46% at Week 2 but had nearly returned to the mean pre-test value by

Study ID	Species/ Sex/ Number/ Group	Dose (mg/kg b.w.)/ Route/	Duration	NOAEL (mg/kg/ day)	Major findings
					Week 4. There was little change in FE:K in this group during the recovery period. • In the group given ZS at 1000 mg/kg tid and KCl at 224 mg/kg tid, mean FE:K was substantially increased (>200%) at Weeks 2 and 4, which was considered secondary to KCl supplementation. There were also mild to moderate increases in the fractional excretion of sodium (FE: Na), relative to controls. These effects were most pronounced in females administered 1000 mg/kg + KCl TID (up to 188% increase), and indicated increased renal sodium excretion, however this increase was not associated with meaningful changes in serum sodium. There were no test article-related microscopic findings.
1959-008/ GLP - Yes	Dog (beagle) M/7-10 F/7-10	0^2, 300^2, 1000^2, 2000^2, 2000+KCl^2 Oral in food	270 days + 28-day recovery	***13-week NOAEL for M: 1000 mg/kg/day** ; ***13-week NOAEL for F:2000 mg/kg/day** ; ***39-week NOAEL for both sex: 1000 mg/kg/day** ;	*Mortality*: No. *Clinical observations* : After 13 weeks of dosing, there were no clinical findings related to ZS administration at any dose level. All observations recorded were considered typical of dogs of this age and strain. ZS-related clinical findings were observed between Weeks 17 and 31 in one F administered 300 mg/kg/day and one M and 5 F administered 2000 mg/kg/day without KCl supplementation and were attributed to hypokalemia, consistent with the expected pharmacology of the compound. These included decreased activity, inappetence, impaired limb function, ataxia, and rigid body. *Physical Examinations*: In M, all mean blood pressure measurements were broadly similar in all groups, including controls. In F at the end of the dosing period, mean systolic, diastolic and mean arterial blood pressure were 20-25%, 44-70%, and 27- 32% greater in all treated groups than in the control groups. The magnitude of the difference was unrelated to ZS dose level, and mean values in treated F groups were similar to mean values in all M groups, including controls. *Electrocardiographic Examinations*: There was no effect of the oral administration of ZS on qualitative or quantitative ECG parameters at the Week 13 interim or Week 39 terminal examinations. Recovery electrocardiographic examinations were therefore not conducted. *Clinical Pathology*: • Minimal reversible decreases in serum potassium in animals at 2000 mg/kg/day without KCl; • Minimal reversible increases in HCO_3 and tCO2 in animals receiving 2000 mg/kg/day without KCl; • Mild reversible decreases in aldosterone in animals receiving 2000 mg/kg/day without KCl; • Mild reversible increases in urine pH in animals receiving ≥1000 mg/kg/day and 2000 + KCl mg/kg/day;

Study ID	Species/ Sex/ Number/ Group	Dose (mg/kg b.w.)/ Route/	Duration	NOAEL (mg/kg/ day)	Major findings
					• Minimal increases in urine volume in animals at 2000 mg/kg/day with and without KCl; • Marked reversible decreases in renal potassium excretion in animals receiving ≥300 mg/kg/day without KCl; • Mild reversible increases in renal sodium excretion in M receiving ≥1000 mg/kg/day and F at ≥300 mg/kg/day with and without KCl; • A trend towards a minimal increase in calcium and phosphorous/creatinine ratios in animals receiving 2000 with or without KCl mg/kg/day. *Clinical Chemistry*: The only difference in the pattern of change that was potentially related to administration of ZS was a minimal decrease in mean serum potassium concentration in both sexes at 2000 mg/kg/day that was apparent by Week 6 and continued through Week 39 (up to -13% from baseline). All other mean and individual clinical chemistry values were considered within expected ranges for biological and/or procedure-related variation. At Weeks 13 and 39 in both sexes receiving 2000 mg/kg/day there were mild reductions in aldosterone (up to -41%) relative to controls. Trends towards reductions were also seen at Week 6 but were less substantial (up to -14%). Decreases in serum aldosterone were attributable to reductions in aldosterone biosynthesis secondary to test article-related decreases in serum potassium. *Urinalysis:* • Minimal to mild increases in urine pH at Weeks 2, 6, 13, 26, and/or 39 in both sexes receiving ≥ 1000 mg/kg/day, and 2000 + KCl mg/kg/day relative to controls. These differences occasionally reached statistical significance and appeared dose-related. The effects on urine pH had resolved by the recovery interval in both sexes. • A trend towards increased urine volume in animals receiving 1000 mg/kg/day, and 2000 mg/kg/day with or without potassium supplementation. *Urine Chemistry*: • A dose-related decrease in the fractional excretion of potassium (up to -91%) relative to controls at Weeks 2 through 39 at all dose levels. This finding was not observed in mg/kg/day supplemented with KCl. • A dose-related increase in the fractional excretion of sodium (up to +5.6-fold) at Weeks 2 through 39 in males at ≥ 1000 mg/kg/day and in females at all dose levels, relative to controls. • A trend towards a minimal increase in calcium and phosphorous/creatinine ratios in animals receiving 2000 with or without KCl mg/kg/day although this finding was inconsistently significantly

Study ID	Species/ Sex/ Number/ Group	Dose (mg/kg b.w.)/ Route/	Duration	NOAEL (mg/kg/ day)	Major findings
					different from controls. *Microscopic:* Microscopic findings observed in M and F treated with 2000 mg/kg/day included mild intracytoplasmic lipid vacuolation in cells of the zona glomerulosa of the adrenal glands and multifocal areas in the medulla and cortex of the kidneys with a spectrum of tubular and interstitial degenerative and inflammatory changes. These findings were consistent with prolonged potassium depletion and correlated with the hypokalemia observed in the affected animals. The incidence and grade of tubulointerstitial inflammation was similar after 13 or 39 weeks of administration, but there were additional renal changes (increased interstitial matrix and interstitial fibrosis) after 39 weeks of administration. At both time points, renal changes were less common and less pronounced in the kidneys of dogs supplemented with potassium, suggesting that potassium supplementation reduced the incidence and magnitude of this finding.

Repeat-dose toxicity studies in rats and dogs were conducted up to a maximum duration of 180-days and 270-days, respectively. The only effects of sodium zirconium cyclosilicate administration in either species were related to the intended pharmacodynamic activity of sodium zirconium cyclosilicate, which is to reduce potassium absorption from the GI tract. The effects reflected adaptive responses intended to maintain homeostasis, particularly adequate serum potassium concentration and adequate total body potassium stores. The primary adaptive response was to substantially reduce urine potassium excretion. Related secondary effects included decreased serum potassium and aldosterone concentrations, increased serum HCO^-_3 concentration, increased urine sodium excretion, and decreased urine hydrogen ion excretion (increased urine pH). Both rats and dogs tolerated chronic oral administration of sodium zirconium cyclosilicate at very high dose levels. Rats tolerated sodium zirconium cyclosilicate at up to the maximum feasible dose level of 2000 mg/kg tid (6000 mg/kg/day) for up to 26 weeks, and dogs tolerated sodium zirconium cyclosilicate at 1000 mg/kg/day for up to 39 weeks. These dose levels are equivalent to human dose levels of approximately 58 g/day (rats) and 32 g/day (dogs). In dogs, the pharmacodynamic effects of Sodium zirconium cyclosilicate became dose-limiting with chronic administration at very high dose levels due to the development of clinically significant hypokalemia and secondary degenerative and inflammatory changes in the kidneys and lipid vacuolisation in the adrenal cortex. Potassium supplementation helped reduce the incidence and/or magnitude of hypokalemia and its associated renal and adrenal effects.

Human equivalent dose (HED) calculations were prepared according to the Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. The summary of the safety margins for the NOAEL doses of sodium zirconium cyclosilicate in pivotal toxicology studies are presented below:

Species	NOAEL Animal dose	Multiplication factor[g]	Human Equivalent Dose	Dose for 60 Kg Body Weight	Safety Margin		
	(mg/kg/day)		(mg/kg/day)	(g)	30g	10g	5g
Rat	6000[a, b]	0.16	960	57.6	1.9	5.8	11.5
	2000[a]		320	19.2	0.6	1.9	3.8
Dog	1000[c, d]	0.54	540	32.4	1.1	3.2	6.5
	3000 + KCl[e]	0.54	1620	97.2	3.2	9.7	19.4
	2000 ± KCl[e]	0.54	1080	64.8	2.2	6.5	13
Rabbit	6000[f]	0.32	1,920	115.2	3.8	11.5	23

Source: data on file at ZS Pharma

a. Study 524020 (28-day Repeat dose toxicity study in rats)
b. Study 524942 (6 month Repeat dose toxicity study in rats)
c. Study 1959-007 (28- Day Repeat dose toxicity study in dogs)
d. Study 1959-008 (39-Week Repeat dose toxicity study in dogs)
e. Study 1959-008 (13 –Week data)
f. Study 496863 (Embryo-foetal Development study in rabbits)

The CHMP noted that quite a high percentage of the rats used in the toxicological studies had injuries during dosing. The applicant explained that the gavage dose administration is an invasive procedure and it was performed 3 times a day over a 12-hour period. The high incidence of oesophageal injury in studies conducted with ZS-9 was attributed to the differences in formulation pH with the commercial formulation.

The CHMP considered that even though overall mortality in the toxicological studies is increased, this finding has no major clinical impact.

Genotoxicity

Studies performed on testing the genotoxicity potential of sodium zirconium cyclosilicate are summarised in table below. The studies were conducted according to GLP principles.

Summary of genotoxicity studies with sodium zirconium cyclosilicate

Type of test / Study No. / GLP	Test system	Concentrations / Concentration range / Metabolising system	Results Positive / negative / equivocal
In Vitro: Reverse Mutation in Bacterial Cells (Ames test)[1] / 789296 / GLP - Yes	*Salmonella typhimurium* strains: TA1537, TA100, TA1535. *Escherichia coli*, strain WP2 uvrA$^-$	The test was performed with and without metabolic activation by rat liver enzymes (S9 mixture). 17 – 5000 µg/plate ± S9 3.13 to 100% DMSO Extract[2] +S9 3.13 to 75% DMSO Extract[2] –S9 Positive Controls: Sodium azide: sterile:water 9-Aminoacridine/2-Nitrofluorene: DMSO N-Ethyl-N-nitro-N-nitrosoguanidine: DMSO 2-Aminoanthracene: DMSO.	Negative.
In Vitro: Chromosome aberration test[1] / 789301/ GLP - Yes	Chinese Hamster Ovary Cells	78 – 5000 µg/mL +S9 39 – 156 µg/mL – S9 25 to 100% DMSO Extract[2] +S9 25 to 100% DMSO Extract[2] – Positive Controls: Cyclophosphamide (+ S9 mix): Ham's F-10/DMSO; Methyl methanesulphonate (– S9 mix): Ham's F-10/DMSO For Positive	Negative. Negative. Negative. Negative.
Micronucleus assay/ 524020/ GLP - Yes	Rat/Sprague Dawley M/5 F/5	Dose: 0, 900, 1000[3], 2000[3], 2000[4] mg/kg/day for 28 days. Cells Evaluated: Polychromatic erythrocytes (PCE).	No observed suppression of PCE/NCE ratio in the micronucleus test Negative.

1 - unprotonated form of sodium zirconium cyclosilicate (ZS-9);

2 - 100% DMSO = 100 µL;

3 - three times a day over a 12-hour period;

4 - once a day

Sodium zirconium cyclosilicate exhibited no genotoxic potential in an ICH-recommended battery of in vitro and in vivo studies. It was examined for mutagenic activity in a bacterial reverse mutation assay. The assays were conducted at concentrations of up to 5000 µg /plate, in the presence and absence of a metabolic activation system. Under these test conditions, ZS-9 did not exhibit any mutagenic activity in these assays. The ability of ZS-9 to induce chromosomal aberrations in Chinese hamster ovary (CHO) cells was also evaluated with and without metabolic activation. No significant increases in chromosomally aberrant cells were observed at any of the concentrations tested. Under the conditions of the assay, sodium zirconium cyclosilicate did not induce a significant increase in chromosomal aberrations in CHO cells. Sodium zirconium cyclosilicate was evaluated for *in vivo* clastogenic activity and/or disruption of the mitotic apparatus by quantifying micronuclei in polychromatic erythrocyte (PCE) cells in rat bone marrow mg Fe. Dose levels ranged from 900 to 2000 mg/kg/day for 28 days given as an oral administration.

In conclusion, sodium zirconium cyclosilicate exhibited no genotoxic potential in an ICH-recommended battery of in vitro and in vivo studies.

Carcinogenicity

No carcinogenicity studies have been performed. However, because sodium zirconium cyclosilicate is not systemically absorbed, and exhibited no genotoxic potential in an ICH recommended battery of in vitro and in vivo studies (ICH S2 [R1]), it is not considered to present a genotoxic hazard to humans.

Reproduction Toxicity

Reproductive toxicology studies in rats and rabbits were conducted according to GLP principles. The fertility and early embryonic development, embryo-foetal development, and pre- & post-natal development were studied following oral administration of sodium zirconium cyclosilicate. An overview of the results from reproductive and developmental toxicity studies in rats and rabbits are presented in the table below.

Summary of reproductive and developmental toxicity studies with Sodium zirconium cyclosilicate

Study type / Study ID / GLP	Species; Number / group	Route & dose	Dosing period	Major findings	NOAEL (mg/kg)
Male Fertility/ 524942/ GLP-Yes	Rat/ Sprague-Dawley (Cr1:CD ® BR)/ 40M	Oral/ 0, 333, 1000, 2000[1]	147 days	No sodium zirconium cyclosilicate treatment-related effects on mating performance, fertility, fecundity or sperm abnormalities at sodium zirconium cyclosilicate levels up to 6000 mg/kg/day, the maximum feasible dose tested.	6000 mg/kg/day for Male fertility
Fertility and Early Embryonic Development to Implantation / 496748 / GLP-Yes	Rat / Sprague-Dawley / 20F	Oral/ 0, 300, 1000, 2000[1]	14 days prior to mating through GD 16	Sodium zirconium cyclosilicate had no effect on maternal clinical signs, body weight, body weight gain, food consumption, maternal plasma sodium, potassium or chloride, estrous cycle length or mating and pregnancy performance. Fetal weight was unaffected by treatment with sodium zirconium cyclosilicate and there were no fetal visceral or skeletal abnormalities attributed to treatment with sodium zirconium cyclosilicate.	**F_0 Males:** treated females were mated with untreated males; **F_0 Females:** 2000 mg/kg tid (6000 mg/kg/day); **F_1 Litters:** 2000 mg/kg tid (6000 mg/kg/day);
Effects on Pre- and Postnatal Development, Including Maternal Function/ 496753/ GLP-Yes /	Rat /(Crl:CD ® Sprague Dawley)/ 24F	Oral/ 0, 300, 1000, 2000[1]	GD6 to LD-21	F_0 females: the only effect related to sodium zirconium cyclosilicate administration was pale feces in 7 rats at the 2000 mg/kg tid dose, which was attributed to excretion of the test article. Sodium zirconium cyclosilicate had no effect on body weight, body weight gain, food consumption, or plasma sodium, potassium and chloride concentrations. Sodium zirconium cyclosilicate also did not affect reproductive function (duration of gestation, F1 litter size, F1 pup weights) and did not produce findings	**F_0 Females:** 2000 mg/kg/tid (6000 mg/kg/day); **F_1 Males:** 2000 mg/kg/tid (6000 mg/kg/day); **F_1 Females:** 2000 mg/kg/tid (6000

Study type/ Study ID/ GLP	Species; Number / group	Route & dose	Dosing period	Major findings	NOAEL (mg/kg)
				detectable at necropsy. F_1 rats: there were no effects related to administration of sodium zirconium cyclosilicate to F_0 dams; i.e., no effects on survival, body weight, body weight gain, vaginal opening, preputial separation, performance on functional tests, or reproductive function (duration of gestation and F2 litter size) and no necropsy findings. F_2 pups, there were no effects related to administration of sodium zirconium cyclosilicate to F_0 dams. No necropsy findings.	mg/kg/day);
Rabbit Maternal Toxicity MTD/ 496858/ GLP-Yes /	Rabbit (New Zealand White)/ 3F	Oral/ 1000, 2000[1], 2000[2]	GD6 – GD18	Light colored feces observed in unmated females, which was attributed to excretion of the test article. Sodium zirconium cyclosilicate had no effect on clinical signs, body weight gain, food consumption, or plasma sodium, potassium and chloride concentrations. Sodium zirconium cyclosilicate also had no effect on pregnancy performance when administered at dosages of up to 6000 mg/kg/day on GD 6-18, inclusive.	**Conclusion:** a suitable series of dose levels for use on the subsequent Developmental Toxicity Study in Rabbits was considered to be 0, 500, 1000 and 2000 mg/kg/tid.
Effects on Embryofetal Development/ 496863/ GLP- Yes /	Rabbit (New Zealand White)/ 20F	Oral/ 500, 1000, 2000[2]	GD6 – GD18	In dams: sodium zirconium cyclosilicate had no effect on clinical signs, body weight, body weight gain, food consumption, plasma sodium, potassium and chloride concentrations, or pregnancy performance. In fetuses: no abnormalities were attributed to treatment with sodium zirconium cyclosilicate.	**F_0 Females:** 2000 mg/kg/dose (6000 mg/kg/day) (the highest dose of test article tested); **F_1 Litters:** 2000 mg/kg/dose (6000 mg/kg/day) (the highest dose of test article tested.

[1] – three times a day; [2] – once a day; GD – Gestation day; LD – Lactation Day; M – Male; F – Female

Sodium zirconium cyclosilicate did not affect reproductive function in rats of either sex at up to the maximum feasible dose level of 6000 mg/kg/day, which is equivalent to a human dose level of approximately 62 g/day. When administered to pregnant rats and rabbits at up to 6000 mg/kg/day, sodium zirconium cyclosilicate did

not affect maintenance of pregnancy or fetal development. The rabbit 6000 mg/kg/day dose is equivalent to a human dose of ~115 g/day based on a 60 kg body weight. When administered to pregnant rats from the first trimester of pregnancy through the end of lactation at up to 6000 mg/kg/day, sodium zirconium cyclosilicate did not affect pregnancy, parturition, or the development of offspring.

Toxicokinetic data

Toxicokinetic evaluation was included into the repeat-dose toxicity studies.

Local Tolerance

The dermal sensitization potential of sodium zirconium cyclosilicate was evaluated in a GLP-compliant study performed in Hartley-derived albino guinea pigs. Ten male and 10 female guinea pigs were topically treated with 100% ZS once per week, for 3 consecutive weeks. Following a 2-week rest period, a challenge was performed whereby the 20 test and 10 previously untreated (naïve) challenge control guinea pigs were topically treated with 100% ZS. A α-hexylcinnamaldehyde (HCA) positive control group consisting of 10 HCA test and 10 HCA control guinea pigs was included in this study. Based on the results of this study, sodium zirconium cyclosilicate (ZS) is not considered to be a contact sensitizer in guinea pigs, as the criterion for sensitization (dermal scores ≥ 1 in at least 15% of the test animals) was not met. The results of the HCA positive control study demonstrated that a valid test was performed and indicated that the test design would detect potential contact sensitizers. Sodium zirconium cyclosilicate elicited no dermal irritation in guinea pigs following topical administration at the maximum feasible dose (0.3 g), and is therefore not considered to be a dermal sensitizer.

Other toxicity studies

No other toxicology studies were conducted with sodium zirconium cyclosilicate.

2.3.5. Ecotoxicity / environmental risk assessment

A specific environmental risk assessment (ERA) has been performed for Lokelma oral powder for suspension, which contains the completely insoluble drug substance, sodium zirconium silicate, and no excipients.

Table: Summary of main study results

Substance (INN / Invented Name): Sodium zirconium cyclosilicate			
CAS-number (if available): 242800-27-7			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …		Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		not B
	BCF		not B
Persistence	DT50 or ready biodegradability		not P
Toxicity	NOEC or CMR		not T
PBT-statement :	The compound is not considered as PBT		

Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)		µg/L			Not applicable
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 or …	K_{oc} =			Not applicable
Ready Biodegradability Test	OECD 301				Not applicable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = $DT_{50, sediment}$ = $DT_{50, whole\ system}$ = % shifting to sediment =			Not applicable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC		µg/L	Not applicable
Daphnia sp. Reproduction Test	OECD 211	NOEC		µg/L	Not applicable
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC		µg/L	Not applicable
Activated Sludge, Respiration Inhibition Test	OECD 209	EC		µg/L	Not applicable
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	Not applicable
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			Not applicable

According to the applicant, the action limit of 0.01 µg/L is not applicable for sodium zirconium cyclosilicate, which will be excreted into the sewage system with patient stools. After entering the sewage system, sodium zirconium cyclosilicate is expected to be retained in the sewage treatment plant by filtering and sedimentation, and disposed of in landfill or by incineration. Where disposed of in landfill, the stability and the complete insolubility of sodium zirconium cyclosilicate will cause it to remain localised. If any sodium zirconium cyclosilicate enters the terrestrial environment outside of landfill sites by limited spreading of sewage sludge on agricultural land, no adverse environmental effects would be expected given its dilution within the terrestrial compartment and since sodium, zirconium and silicon are all common elements in the environment.

Furthermore, it can be concluded that there are no impurity concerns for the sewage treatment plant and other aquatic compartments including surface water, taking into account environmental exposure to sodium zirconium cyclosilicate from the use of Lokelma.

2.3.6. Discussion on non-clinical aspects

The non-clinical profile of sodium zirconium cyclosilicate has been evaluated in a programme of pharmacology and toxicology studies that conformed to current regulatory guidance and scientific standards, with pivotal safety studies conducted in compliance with GLP regulations.

From the data provided, it is evident that the ion exchange activity of ZS is selective for small monovalent ions such as sodium, hydrogen, potassium and ammonium over divalent cations such as calcium and magnesium. Based on in vitro studies using simulated gastric and intestinal fluids, sodium zirconium cyclosilicate-related potassium exchange is likely to be limited in the stomach and will occur throughout the gastrointestinal tract, with equilibrium occurring quite rapidly. As expected from its ion exchange activity, its administration to rats and dogs decreased the urinary excretion of potassium and increased the faecal excretion of potassium in a dose-related manner. These effects were accompanied by changes in urinary excretion of urea (decreased) and sodium (increased) and faecal excretion of urea (increased) and sodium (decreased). Both rats and dogs tolerated chronic oral administration of sodium zirconium cyclosilicate at very high doses, which resulted in excretion of light-coloured faeces due to the excretion of sodium zirconium cyclosilicate. Rats tolerated sodium zirconium cyclosilicate at up to the maximum feasible dose level of 2000 mg/kg tid (6000 mg/kg/day) for up to 26 weeks. Dogs tolerated sodium zirconium cyclosilicate at up to 1000 mg/kg/day for up to 39 weeks. These dose levels are equivalent to human dose levels of approximately 62 g/day (rats) and 32 g/day (dogs) assuming a 60 kg body weight.

Upon request of the CHMP, the applicant provided data on in-vitro interaction of ZS-9 with hot fluids and a selection of beverages. The effect of temperature on the integrity and potassium exchange of sodium zirconium cyclosilicate was discussed and the applicant submitted data from a study investigating the effect of temperature on the integrity and potassium exchange of sodium zirconium cyclosilicate. It was demonstrated that both the structural integrity and potassium exchange capacity of ZS-9 and sodium zirconium cyclosilicate are stable at temperatures <150 °C.

Hence, the dynamic nature of the ion exchange and the thermal stability data indicate that the in vivo performance of ZS will not be affected by type of beverage or hot fluids consumed in conjunction with administration of ZS, however, considering the volume of liquid recommended for taking Lokelma in the proposed SmPC and the need to take the medication quickly before the powder settles, it is not advisable to use hot fluids which might burn the throat and oesophagus. Consequently, when taking the medicine, only the use of water is advised in the Product Information.

The only effects of sodium zirconium cyclosilicate administration in either species were related to its ion exchange activity, which reduced potassium absorption from the GI tract. ZS is insoluble and thus, not systemically absorbed to a significant extent. The effects seen in animals reflected adaptive responses intended to maintain homeostasis in animals that were healthy and that had normal potassium stores; specifically, responses aimed at maintaining adequate serum potassium concentration and total body potassium stores. The primary adaptive response was to substantially reduce urine potassium excretion. This generally was adequate to maintain serum potassium concentration at a lower level but within the normal range (except on a few occasions in dogs at the highest dose level of 2000 mg/kg, equivalent to a human dose of ~65g/day). Related secondary effects included decreased serum aldosterone concentrations, increased serum HCO3- concentration, increased urine sodium excretion, and decreased urine hydrogen ion excretion (manifested as increased urine pH). In rats, these effects were relatively mild and not considered adverse even at the maximum feasible dose level of 6000 mg/kg/day. In dogs, the pharmacodynamic effects of ZS became dose limiting with chronic administration at very high dose levels due to the development of

clinically significant hypokalaemia. In dogs (but not rats), chronic administration of ZS resulted in degenerative and inflammatory changes in the kidneys and lipid vacuolisation in the adrenal cortex, both of which were considered to be secondary to hypokalaemia. Potassium supplementation helped reduce the incidence and/or magnitude of hypokalaemia and its associated renal and adrenal effects. The hypokalaemia also reversed rapidly following cessation of dosing.

Sodium zirconium cyclosilicate exhibited no genotoxic potential in an ICH-recommended battery of in vitro and in vivo studies, and is thus not considered to present a genotoxic hazard to humans. Sodium zirconium cyclosilicate also produced no hyperplastic or pre-neoplastic findings in chronic toxicity studies in rats and dogs at a human equivalent dose of ~65g/day and because of this, the lack of systemic absorption and the absence of genotoxic potential, sodium zirconium cyclosilicate is considered unlikely to present a carcinogenic hazard to humans. Sodium zirconium cyclosilicate did not affect reproductive function in rats of either sex at up to the maximum feasible dose level of 6000 mg/kg/day, which is equivalent to a human dose level of ~ 62 g/day. When administered to pregnant rats and rabbits at up to 6000 mg/kg/day, sodium zirconium cyclosilicate also did not affect maintenance of pregnancy or fetal development. When administered to pregnant rats from the first trimester of pregnancy through the end of lactation at up to 6000 mg/kg/day, sodium zirconium cyclosilicate did not affect pregnancy, parturition, or the development of offspring. Sodium zirconium cyclosilicate elicited no dermal irritation in guinea pigs following topical administration at the maximum feasible dose (0.3g), and is therefore not considered to be a dermal sensitizer.

Based on the crystal phase composition of the batches used in the toxicology studies, the species in the pivotal non-clinical toxicology studies were exposed to higher levels of the crystalline phases than are present in the drug substance produced by the commercial manufacturing process. Thus, the potential toxicity of these phases has been appropriately studied, and is considered to be qualified as safe at the specified levels.

Sodium zirconium cyclosilicate is not expected to pose a risk to the environment.

Based on the results of the non-clinical pharmacology and safety studies in animals, oral administration of sodium zirconium cyclosilicate is expected to provide therapeutic benefit and to have a reasonable safety margin when used as directed to treat hyperkalaemia patients.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical data submitted in the application for the marketing authorisation of Lokelma are considered sufficient and although the CHMP identified several other concerns for clarification, the applicant satisfactorily addressed all. Therefore, the non-clinical data could be considered appropriate to support the clinical use of Lokelma for the treatment of hyperkalaemia in adult patients.

2.4. Clinical aspects

2.4.1. Introduction

The following main completed clinical studies (one phase 2 study, and three phase 3 studies) were presented to evaluate efficacy in the target population:

- for the acute lowering of S-K: two double-blind studies (study ZS-002 and acute phase of study EUZS-003) and one supportive study (acute phase of study ZS-004);

- for the maintenance of normokalemia: two pivotal studies (≤12 days in the subacute phase of study EUZS-003 and ≤28 days in the maintenance phase of Study ZS-004), one supportive long-term extension of study ZS-004 (≤11 months in study ZS-004E).

In addition, a long-term clinical study (Study ZS-005) is ongoing. During the procedure, the applicant presented results of phase 1 drug-drug interaction (DDI) study ZS-009.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Completed clinical studies of ZS

Study Identifier and Objective	Number of Study Centers Locations	Study Start Enrollment Status/Date Enrollment Planned/Actual	Study Design Control Type	Study and Control Drugs Dosage, Route, Regimen, and Duration	# of Subjects by Treatment Treated/ Completed	Gender Race[a] Mean Age (range)	Diagnosis Main Inclusion Criteria	Primary and Secondary Endpoints
EUZS-003 Efficacy and Safety	65 US, Australia, and South Africa	25 Nov 2012 Completed/ 29 Oct 2013 750 planned/ 754 randomized/ 753 treated in Acute Phase/ 543 treated in Subacute Phase	Two phase (Acute and Subacute), randomized, double-blind Subacute Phase design was randomized withdrawal for subjects who received ZS during Acute Phase Both phases were placebo controlled	**Acute Phase**				
				TID for 48 hours ZS 1.25 g ZS 2.5 g ZS 5 g ZS 10 g Placebo Administered orally, in conjunction with meals.	753 treated 154/150 141/137 157/152 143/140 158/157	M: 448 F: 305 W: 644 B: 87 O: 23 65.7 years[b] (22 – 93)	Mean of 3 i-STAT potassium values measured at 30-minute intervals between 5.0 and 6.5 mmol/L	*Primary:* Proportion of subjects who achieve normalization in S-K after 48 hours of treatment (ie, responders). *Secondary:* Exponential rate of change in S-K during initial 48 hours of treatment; Mean change and mean percent change in S-K at individual time points; Time to first decrease in S-K of 0.5 mmol/L; and Time to normalization of S-K (S-K 3.5 to 5.0 mmol/L). Proportion of subjects who achieve normalization in S-K after 24 hours of treatment.
				Extended Dosing (Subacute Phase, Randomized Withdrawal for Acute Phase ZS Subjects)				
				QD for 12 days Acute Phase ZS subjects: ZS 1.25 g ZS 2.5 g ZS 5 g ZS 10 g Acute Phase placebo subjects: ZS 1.25 g ZS 2.5 g Administered orally, in conjunction with meals.	447 treated 49/48 ZS: 41/38 PBO 54/52 ZS: 46/43 PBO 65/59 ZS: 68/66 PBO 63/61 ZS: 61/58 PBO 96 treated 46/44 ZS 50/49 ZS	M: 261 F: 186 W: 383 B: 49 O: 15 65.5 years[b] (22 – 93) M: 56 F: 40 W: 84 B: 11 O: 1 66.8 years[b] (27 – 88)	Completed Acute Phase and had an i-STAT potassium value between 3.5 and 4.9 mmol/L	*Primary:* Total number of days normokalemic (S-K 3.5 to 5.0 mmol/L). *Secondary:* Exponential rate of change in S-K over 12-day treatment interval; Time to relapse in S-K values (defined as return to original S-K baseline); Proportion of subjects who retained normal S-K (defined as S-K 3.5 to 5.0 mmol/L) at the end of the treatment; Mean change and mean percent change in S-K at other individual time points; and Time to an increase in S-K of 0.5 mmol/L.

Study Identifier and Objective	Number of Study Centers Locations	Study Start Enrollment Status/Date Enrollment Planned/Actual	Study Design Control Type	Study and Control Drugs Dosage, Route, Regimen, and Duration	# of Subjects by Treatment Treated/ Completed	Gender Race[a] Mean Age (range)	Diagnosis Main Inclusion Criteria	Primary and Secondary Endpoints
ZS-004 Efficacy and Safety	44 US, Australia, and South Africa	18 Mar 2014 Completed/ 08 Aug 2014 275 for Acute Phase and 232 for Maintenance Phase planned/ 258 treated in Acute Phase/ 237 treated in Maintenance Phase	Two phase (Acute and Maintenance) Acute Phase: single ZS treatment group, open-label Maintenance Phase: randomized, double-blind, placebocontrolled	**Acute Phase**				
				TID for 48 hours ZS 10 g Administered orally, just before meals.	258/251	M: 149 F: 109 W: 215 B: 37 O: 9 64.0 years (22 – 89)	Two i-STAT potassium values, measured 60 minutes apart, both ≤5.1 mmol/L and measured within 1 day of first ZS dose	*Secondary:* Exponential rate of change in S-K during initial 48 hours of treatment; Mean change and mean percent change in S-K at individual time points; Proportion of subjects who achieve normalization in S-K (3.5 to 5.0 mmol/L) after 24 and 48 hours of treatment; and Time to normalization of S-K.
				Extended Dosing (Maintenance Phase)				
				QD for 28 days ZS 5 g ZS 10 g ZS 15 g Placebo Administered orally, just before meals. Subjects who had i-STAT potassium values between 3.0 and 3.4 mmol/L were to have dosing reduced to QOD.	237 treated 45/40 51/44 56/49 85/75	M: 138 F: 99 W: 199 B: 32 O: 9 63.6 years[b] (22 – 89)	Completed Acute Phase and had an i-STAT potassium value between 3.5 and 5.0 mmol/L	*Primary Study Endpoint:* Model-based least squares mean of all available S-K values during Extended Dosing Study Days 8 to 29. *Secondary:* Number of normokalemic days during Extended Dosing Study Days 8 to 29; Mean change and mean percent change from Acute Phase and Extended Dosing baseline in S-K; Time to hyperkalemia (S-K ≥5.1 mmol/L); Time to relapse in S-K values (defined as return to original S-K baseline); Mean S-K intra-subject standard deviation calculated among subjects with ≥2 values on or after Extended Dosing Study Day 8; and Proportions of subjects who remained normokalemic at Extended Dosing Study Days 1, 2, 5, 8, 12, 15, 19, 22, 26, 29, and 35.

Study Identifier and Objective	Number of Study Centers Locations	Study Start Enrollment Status/Date Enrollment Planned/Actual	Study Design Control Type	Study and Control Drugs Dosage, Route, Regimen, and Duration	# of Subjects by Treatment Treated/ Completed	Gender Race Mean Age (range)	Diagnosis Main Inclusion Criteria	Primary and Secondary Endpoints
ZS-004E Long-term Efficacy and Safety	30 US, Australia, and South Africa	10 May 2014 Completed/ 14 Jul 2015 160 planned/ 2 treated in Acute Phase/ 123 treated in Extended Dosing	Long-term (up to 11 months), open-label, uncontrolled	**Acute Phase: TID for 24 or 48 hours** ZS 10 g Administered orally, in conjunction with meals.	2 treated/ 2 completed	M: 71 F: 52 W: 109 B: 11 O: 3 64.0 years (22 – 85)	Subjects who completed Study ZS-004 Extended Dosing Phase or who discontinued due to hypo- or hyperkalemia, and had a mean iSTAT potassium value between 3.5 and 6.2 mmol/L, inclusive, were eligible to participate. If the i-STAT potassium value was between 3.5 and 5.5 mmol/L, inclusive, at the end of Study ZS-004, the subject entered the Extended Dosing Phase and started open-label ZS at a dose of 10 g QD. If the i-STAT potassium value was > 5.5 mmol/L at the end of Study ZS-004, the subject entered an Acute Phase, where they received ZS 10 g TID for 24 (3 doses) or 48 hours (6 doses), depending on their daily i-STAT potassium measurement. Subjects who attained normokalemia (i-STAT potassium between 3.5 and 5.0 mmol/L, inclusive) after either 24 or 48 hours of treatment entered the Extended Dosing Phase.	*Primary Efficacy Endpoint:* Proportion of subjects with average S-K ≤ 5.1 mmol/L during Extended Dosing Phase Study Days 8 to 337, inclusive. *Secondary Efficacy Endpoint:* Proportion of subjects with average S-K ≤ 5.5 mmol/L during Extended Dosing Phase Study Days 8 to 337, inclusive.
				Extended Dosing: QD for up to 11 months ZS 10 g Dose could be adjusted in 5 g increments to a maximum of 15 g QD or a minimum of 5 g QOD based on i-STAT potassium values Administered orally, in conjunction with meals.	123 treated/ 79 completed			

Study Identifier and Objective	Number of Study Centers Locations	Study Start Enrollment Status/Date Enrollment Planned/Actual	Study Design Control Type	Study and Control Drugs Dosage, Route, Regimen, and Duration	# of Subjects by Treatment Treated/ Completed	Gender Race Mean Age (range)	Diagnosis Main Inclusion Criteria	Primary and Secondary Endpoints
ZS-009 Drug-drug interaction	1 US	26 December 2015 Completed 27 February 2016 193 enrolled/ 189 completed both study periods	Single-dose, open-label, one-sequence crossover 2 dosing periods 9 independent study cohorts	**Dosing period 1:** Single dose of the cohort drug (clopidogrel, dabigatran, glipizide, losartan, furosemide, atorvastatin, amlodipine, warfarin, or Levothyroxine) on study day 1 Administered orally with breakfast (levothyroxine 30 min before breakfast).	193 treated/ 192 completed	Overall M: 95 F: 98 W: 130 B: 54 O: 9 Within cohort groups: M: majority of the Dabigatran, Losartan, Atorvastatin, Warfarin, and Levothyroxine Cohorts. F: majority of the Clopidogrel, Glipizide, Furosemide, and Amlodipine Cohorts, W range: 44.4% to 79.2% Mean age range: 33.4 to 40.8 years.	Healthy adult subjects	The objective was to assess the effect of ZS on the pharmacokinetics of a single dose of clopidogrel, dabigatran, glipizide, losartan, furosemide, atorvastatin, amlodipine, warfarin, and levothyroxine in healthy subjects.
				Dosing period 2: Single dose of the same cohort drug + 10 g ZS on study day 1 Administered orally with breakfast (levothyroxine 30 min before breakfast).	190 treated/ 189 completed			

Abbreviations: B = Black or African American; CKD = chronic kidney disease; CSR = clinical study report; F = female; eGFR = estimated glomerular filtration rate; M = male; O = other race; QD = once daily; QOD = every other day; S-K = serum potassium; TID = 3 times daily; US = United States; W = White; ZS = sodium zirconium cyclosilicate [a]
Race categories are not mutually exclusive. Other includes Asian, American Indian or Alaska Native, and Native Hawaiian or other Pacific Islander.

Ongoing clinical studies of ZS

Study Identifier / Location / Status	Study Title / Objective	Study Design and Type of Control	Test Product, Dosage, Regimen, and Route of Administration	Total Number of Subjects Planned for Enrollment	Diagnosis of Subjects	Duration of Treatment
ZS-005/ US, Australia, South Africa, Germany, the Netherlands, and the United Kingdom/ Ongoing	A Phase 3, Multicenter, Multidose, Open-label Maintenance Study to Investigate the Long-term Safety and Efficacy of Sodium Zirconium Cyclosilicate (ZS), an Oral Sorbent, in Subjects with Hyperkalemia, Including a Randomized, Double-blind, Placebo-controlled, Withdrawal Study	Multicenter, multi-dose, open-label	ZS administered orally as a slurry/suspension in water. Acute Phase: ZS 10 g TID for 24, 48, or 72 hours (3 to 9 total doses) Extended Dosing (Maintenance Phase): Starting Dose: ZS 5 g QD, dose may be increased or decreased in increments/decrements of 5 g QD up to a maximum of 15 g QD or to a minimum of 5 g QOD dependent upon S-K. Randomized Withdrawal Study: Subjects randomized to either continue same ZS dose at time of Study Day 176 or placebo. No dose titration is allowed during the Randomized Withdrawal Study.	751 (open-label, extended dosing) 200 (randomized withdrawal) 751 enrolled as of 7 December 2015 751 dosed in Acute Phase and 746 dosed in Extended Dosing	Hyperkalemia (S-K values ≥ 5.1 mmol/L, Acute Phase); normokalemia (S-K values 3.5 to 5.0 mmol/L, inclusive, Extended Dosing)	Acute Phase: up to 72 hours; Extended Dosing: up to 12 months

Abbreviations: QD = once daily; QOD = every other day; S-K = serum potassium; TID = 3 times daily; US = United States; ZS = sodium zirconium cyclosilicate

2.4.2. Pharmacokinetics

The applicant did not perform conventional clinical pharmacology programme based on the facts that (1) non-clinical data from a mass balance study in rats demonstrated that there is no significant systemic absorption as would be expected for an insoluble material with this particle size; (2) as an insoluble, inorganic compound, ZS is not subject to enzymatic metabolism. However, measurements of Zr levels in urine and blood samples as a possible indicator of ZS absorption were performed in in vitro study TD14-008 and in clinical studies ZS-002, EUZS-003 and ZS-004. One study (Study BR-01519) provided an analysis of Zr concentrations from samples obtained in study ZS-004 using the validated bioanalytical methods. Also, open-label phase 1 pharmacodynamic clinical study (ZS-006) was conducted to characterize the potential effect of ZS 5 and 10 g QD doses on sodium and potassium excretion in healthy subjects.

The applicant presented bioanalytical report of the measurement of concentration of Zr in human urine and whole blood samples collected during clinical study ZS-004. Main characteristics of the method used (system suitability, carryover, selectivity, linearity, lower limit of quantitation, intra- and inter-assay precision and accuracy, dilution integrity, injection medium stability, freeze-thaw stability, long term frozen stability and stock solution stability) were validated before study, validation criteria were met and validation reports were included. Open-label phase 1 DDI clinical study (ZS-009) was conducted to determine effect of ZS on the pharmacokinetics of a single dose of 9 drugs in healthy subjects.

Absorption

Due to exposure to stomach acid, it was speculated weather some Zr or heavy metal impurities could be released from the crystal and subject to systemic absorption. Therefore an in vitro study (TD14-008) was conducted in which 13 different batches of ZS were sequentially incubated at 37 °C in USP simulated gastric fluid (pH 1.2) for 2 hours followed by USP simulated intestinal fluid (pH 6.8) for 20 hours. A total of 5 elements listed per USP <232> testing (chromium, copper, molybdenum, nickel and palladium) were detected in the SGF and simulated intestinal fluid supernatants, as well as Zr and aluminum. The amount of each element released was ≤ 1.0 µg/g ZS for aluminum, chromium, copper, molybdenum, nickel, and palladium, and remains well below the permissible daily exposure for these elements over the 5 to 30 g/day ZS dosing range. The average amount of Zr released per gram of ZS for batches manufactured at the 500 L and 200 L scale was 0.466 µg and 0.696 µg, respectively. One batch (RD011-9S) used in clinical study ZS-002 released 3.54 µg Zr/g ZS. The applicant explained that the potential amount of Zr exposure following oral administration of ZS at doses ranging from 5 to 30 g/day ranges from ~2.3 to 21 µg, which is <0.5% of the average daily Zr intake. ZS exchanges sodium and hydrogen for potassium, thus it is possible that some of the sodium released from the ZS crystal might be absorbed. Although no increase in urinary sodium excretion or clinically significant increases in serum sodium, blood pressure, or body weight were observed in the completed studies, sodium and potassium excretion was evaluated in a phase 1 pharmacodynamic study ZS-006. ZS did not increase urinary sodium output in this subject population and study conditions. Specific study evaluating the possible effect of gastrointestinal transit time with ZS is not deemed necessary.

Bioavailability study BR-01519: At selected sites of study ZS-004 in the US, whole urine and blood samples were collected and assayed for Zr levels at baseline, prior to administration of the first dose, and on maintenance phase study days 15 and 29, following ZS 10 g TID dosing in the acute phase. A total of 46 urine samples were analysed (placebo: 17; ZS 5 g QD: 9; ZS 10 g QD: 10; ZS 15 g QD: 10). Zr

concentrations were less than the lower limit of quantitation (LLOQ). Zr concentration in blood samples from the same subjects were at ≤ LLOQ of 10 ng/mL in all but 1 sample. The performed in-vitro release and clinical Zr levels in blood and urine analyses showed only minimal potential for systemic absorption. This is considered negligible.

Influence of food: In study ZS-002, ZS was administered TID in conjunction with meals (8 am, 12 noon and 6pm), except on study Day 1 when the first dose was administered ~90 minutes prior to breakfast. In studies EUZS-003 and ZS-004, the first dose of the acute phase was administered in conjunction with meal. The applicant explained that the effect of food can be assessed by comparing S-K decreases across studies at 1 hour after the first dose of ZS 10 g TID or placebo. Statistically significant difference from placebo at 1 hour after the start of dosing was observed in studies ZS-002 and EUZS-003 with the mean decrease from baseline of -0.11 for the ZS 10 g TID group in both studies. These results indicate that the effect of ZS is largely independent of food. Statistically significant mean decrease from baseline in S-K was also observed at 1 hour after the start of dosing in Study ZS-004. Larger (-0.23 mmol/L) mean reduction from baseline as compared to studies ZS-002 or EUZS-003 was explained with the higher starting S-K level in study ZS-004. The CHMP noted that formal interaction studies with food and diet were not performed. Form the safety and DDI perspective this is reasonable approach, however, from the efficacy perspective, the lack of influence is not so obvious. The impact of food is acknowledged (direct binding potassium in the food), thus impact of the S-K decreasing capacity would be expected to be higher if low potassium diet is used and the ZS capacity is directed more towards decrease in circulating S-K (removal form the systemic circulation) but not diminishing alimentary intake of S-K. On CHMP's request, the applicant explained that ZS would not be expected to induce hypokalaemia in subjects receiving low potassium diets based on its mechanism of action. The main impetus for the amount of potassium removed by ZS in vivo is the ionic potassium gradient in the gastrointestinal tract. When S-K level is high, ZS removes more potassium than when S-K level is lower, an effect that was consistently demonstrated in the ZS clinical studies.

The applicant was also asked to discuss the effect of drug-drug interactions, manifesting in an adverse effect (hypokalaemia, hyperkalaemia, and QTc change). The applicant conducted a Phase 1 study (Study ZS-009) to examine the potential for drug-drug interactions with ZS in vivo with 9 compounds that displayed significant in vitro changes in solubility in the presence of ZS. The final clinical study report for Study ZS-009 has been submitted during the procedure. In vivo, coadministration of ZS with 5 of the 9 compounds did not meet the bioequivalence criteria when coadministered with ZS. According to the applicant, all changes in pharmacokinetics are not clinically meaningful.

Distribution

As no relevant systemic absorption is expected, the formal distribution studies were not conducted and this is acceptable to the CHMP.

Elimination

No formal studies were conducted to examine the elimination or inter-conversion, PK of metabolites, genetic polymorphism, inter- and intra-variability in target, special populations, or to investigate the effect of gender, race, weight and age. Children < 18 years of age have not been studied; however, the pediatric development programme will be initiated upon the approval of ZS in treatment of adults. This is considered acceptable to the CHMP.

Dose proportionality and time dependencies

In acute phase, dose response for S-K was evaluated with ZS doses of 0.3 g, 3 g, and 10 g TID for 48 hours in study ZS-002 and doses of 1.25 g, 2.5 g, 5 g, and 10 g TID for 48 hours in study EUZS-003. For extended dosing in study EUZS-003, ZS demonstrated dose-dependent differences from placebo. A statistically significantly smaller mean increase in S-K from extended dosing baseline to extended dosing study day 12 was observed for ZS 10 g QD vs placebo (0.06 mmol/L vs 0.58 mmol/L). A similar trend was noted for ZS 5 g QD dosing (0.14 mmol/L vs. 0.24 mmol/L), although the difference was not statistically significant.

Special populations

No formal PK studies in special populations were performed. It is not expected that in special population the local GI kinetics would be different from the targeted population.

Pharmacokinetic interaction studies

In vitro drug-drug interaction studies were conducted to examine the effect of ZS on various compounds, including ACE inhibitors, ARBs, antacids, antibiotics, anticoagulants, antiepileptics, antimanics, antithrombotics, beta blockers, biguanidines, calcium channel blockers, cardiac glycosides, corticosteroids, diuretics, 3-hydroxy-3-methylglutarylcoenzyme A reductase inhibitors, immunosuppressants, NSAIDs, stimulant laxatives, phosphate binders, sulfonylureas, xanthine oxidase inhibitors, and thyroid replacement hormone. Drug products were evaluated using both standard USP compendial and Pharmacopeia Forum methods for dissolution, as well as physiologically relevant aqueous media (simulated gastric fluid, pH 4.5 sodium acetate buffer, and pH 6.8 phosphate buffer). When the USP dissolution media were used, no significant interactions were observed. When physiologically relevant dissolution media were used, the only significant findings were uptake of calcium and lithium by ZS in simulated gastric fluid and pH 4.5 acetate buffer. There was no significant effect of any of the drug products tested on the KEC of ZS. Thus, no contraindication of concomitant administration with ZS for any of the drug products tested is proposed.

Subgroup analyses from other ZS clinical studies demonstrated that efficacy and safety of ZS among subjects with concomitant use of rennin-angiotensin-aldosterone (RAAS) inhibitors was similar to that among all ZS-treated subjects. As changes in diet or initiation of or dose changes in medications that are known to increase S-K (e.g., RAAS inhibitors, potassium-sparing diuretics, mineralocorticoid-receptor antagonists) or decrease S-K (e.g., thiazide or loop diuretics) could potentially impact a subject's response to ZS, S-K should be monitored to determine appropriate dose adjustments to prevent hyperkalemia or hypokalemia. This is appropriately reflected in the SmPC. Following the analysis of all in-vitro drug interactions, the SmPC has been adequately updated to reflect these findings of possible interactions. The SmPC also informs the prescriber that there was a ~40% decrease in dabigatran systemic exposure when co-administered with ZS. However, no dose adjustment of dabigatran seems to be necessary when ZS is co-administered with dabigatran.

Pharmacokinetics using human biomaterials

Pharmacokinetic studies using human biomaterials have not been preformed and this is not considered to be of concern.

2.4.3. Pharmacodynamics

Mechanism of action

ZS is an inorganic cation exchange crystalline compound. The effect of ZS is based on the ability of cations (hydrogen and sodium), contained within its crystalline structure to freely exchange with other monovalent cations, potassium and ammonium, with high capacity and high selectivity. High affinity for potassium ions is not influenced by the presence of other cations such as calcium and magnesium. ZS ion-exchange properties and ion selectivity depends on its pore-openings size. The main factors to potentially affect the duration and potency of ZS at its site of action in the gut are potassium exchange capacity (KEC) as predicted by the crystalline structure of ZS, gastrointestinal motility (including the effect of food), and the gastric pH. It is assumed that ZS exerts its PD action throughout the entire GI tract through binding potassium in the food and in the intestinal fluid. The trapped potassium ions are excreted from the body via the faeces, resulting in lower absorption of potassium and lower S-K levels. Thus, the most direct PD measure of the potassium binding effect is the change in S-K levels, an objective clinical endpoint assessed in all clinical studies throughout the development programme. The mechanism of action is based on in-vitro studies, where potassium exchange capacity (KEC) was established to prove that ZS binds potassium.

Primary and Secondary pharmacology

The primary pharmacology was examined in a phase I study and in KEC investigations for several batches. In the phase I pharmacodynamic study ZS-006 healthy subjects on standard diet were enrolled. The following changes were observed: mean numerical decrease from baseline to the average over study days 7 and 8 was observed in both ZS 5g and 10g QD groups in urine sodium (-0.93 mmol/24 h and -5.47 mmol/24 h, respectively and decrease in urine potassium (-9.67 mmol/24 h and -21.17 mmol/24 h, respectively) that was statistically significant in ZS 10 g QD group (p = 0.0017), but not in ZS 5 g QD group (p = 0.0604). Secondary endpoints analyses revealed decrease in S-K (-0.059 mmol/L [p = 0.3591] and -0.247 mmol/L [p = 0.0014]) and increase in faecal potassium (363.998 mg [p = 0.0304] and 695.560 mg [p = 0.0021], respectively). This supports the concept that potassium, but not sodium is trapped in ZS and eliminated via GI, thus decreasing both S-K and urinary K. The mean reductions in S-K values were associated with mean dose-related reductions in urinary potassium excretion and by dose-related mean increases in faecal potassium in both dose groups, which is consistent with the known mechanism of action of ZS. The decreases in urinary potassium of ~379 and ~829 mg correspond to an in vivo KEC of 9.7 and 21.2 mEq potassium for the 5 g and 10 g doses of ZS, respectively.

2.4.4. Discussion on clinical pharmacology

The applicant did not perform conventional clinical pharmacokinetic investigations with zirconium cyclosilicate due to the facts that no significant systemic absorption would be expected based on non-clinical data and this was confirmed by the limited amount of Zr available determined in blood and urine. The analytical methods developed for determination of the active substance in biological fluids were acceptable and showed <1% of possible Zr absorption. There were no studies showing a difference in pharmacodynamics whether sodium zirconium cyclosilicate is administered with or without food.

The investigation of the mechanism of action of ZS is based on in vitro studies, where potassium exchange capacity (KEC) was established to prove that ZS binds potassium. Primary pharmacology was tested in a

phase 1 study (006), in KEC investigations and by analysing S-K changes in phase 2-3 clinical studies. Studies showed S-K decreasing effect via direct binding in GI tracts and thus, increased faecal potassium removal. Although in study 002 the effect started as soon as an hour after administering the dose of 10 g, a more pronounced effect is observed later with an acute effect in 48 hours. Secondary pharmacology was investigated in acute and extended phases of studies 002, 003 and 004. Small increases in bicarbonate and GFR and decreases in calcium were observed for acute phase; decreases in calcium and increase in sodium were observed in extended phase. In a clinical drug-drug interaction study conducted in healthy subjects co-administration of amlodipine, clopidogrel, atorvastatin, furosemide, glipizide, warfarin, losartan, or levothyroxine did not result in clinically meaningful drug-drug interactions and no dose adjustments are required. The SmPC also informs the prescriber that there was a ~40% decrease in dabigatran systemic exposure when co-administered with ZS. However, no dose adjustment of dabigatran seems to be necessary when ZS is co-administered with dabigatran.

2.4.5. Conclusions on clinical pharmacology

The CHMP considered that the applicant conducted sufficient studies in order to investigate the clinical pharmacology of ZS. There are no measures necessary to address the issues related to pharmacology in the post-marketing setting. The SmPC includes adequate information informing the prescribing physicians about the correct use of Lokelma including its potential for drug-drug interactions and their management in clinical practise.

2.5. Clinical efficacy

2.5.1. Dose response studies

The applicant provided a Phase 2, first in human, multicenter, prospective, randomized, placebo-controlled, double-blind dose escalating study report in subjects with mild hyperkalemia in CKD and moderate kidney dysfunction. Study sites were located at 9 sites in the US. A total of 90 subjects were randomized to cohorts of escalating ZS doses (0.3, 3, and 10 g) or placebo (2:1), administered TID with meals. Safety and tolerability were assessed by an independent Data Safety Monitoring Board after completion of each cohort, before escalation to the next dose level was allowed.

The acute lowering of S-K level was also assessed in 2 pivotal double-blind, placebo-controlled studies (study ZS-002 and acute phase of study EUZS-003) and 1 supportive open-label, single ZS treatment group study (acute phase of study ZS-004). Studies ZS-003 and ZS-004 are discussed in section 2.5.2.

Study ZS-002: The applicant provided a phase 2, first in human, multicentre, prospective, randomised, placebo-controlled, double-blind dose escalating study report in subjects with mild hyperkalaemia in CKD and moderate kidney dysfunction. Study sites were located at 9 sites in the US. A total of 90 subjects were randomized to cohorts of escalating ZS doses (0.3, 3, and 10 g) or placebo (2:1), administered TID with meals. Safety and tolerability were assessed by an independent Data Safety Monitoring Board after completion of each cohort, before escalation to the next dose level was allowed. Main inclusion criteria : adult subjects, ability to have repeated blood draws with: S-K of 5.0-6.0 mmol/L at screening; GFR 40-60 mL/min (after completion of Cohort 1 and 27 of 36 subjects in Cohort 2, the protocol was amended to broaden the GFR criteria to 30-60 mL/min. Eligible subjects in a double-blind dose-escalating fashion (3

separate cohorts), were to be randomized to receive escalating doses of ZS (0.3 g, 3 g, and 10 g) or placebo, administered TID daily with meals.

The primary objectives were to evaluate the safety, tolerability, and efficacy of 3 ZS doses TID administered for 48 hours to subjects with moderate CKD and mild hyperkalemia. The doses (0.3, 3, and 10 g) were selected based on the in vitro finding that ZS was ~10 times more effective than SPS in exchanging potassium cations in the presence of physiological levels of magnesium and calcium, and to define the dose-response relationship. The secondary objectives were to identify the optimal dose for the subsequent studies, evaluate the effect of ZS on BUN, on other electrolytes, on various biomarkers for kidney damage, on urinary excretion of sodium, potassium, urea nitrogen, and 24-hour creatinine clearance. The primary efficacy endpoint was the difference in the exponential rate of change in S-K levels during the initial 48 hours of study drug treatment between placebo- and ZS-treated subjects. A total of 90 subjects (38 females, 52 males) with CKD (mean GFR on Study Day 0 = 45.4 mL/min, range: 30 to 62 mL/min) and hyperkalaemia (mean screening S-K [per central laboratory] = 5.16 mmol/L, range: 4.6 to 6.0 mmol/L) were randomized to treatment in the study. Among all subjects, the mean age was 71.1 years (range: 42 to 96 years) and most were white (98%).

ZS met the predefined primary endpoint of exponential decrease in S-K from baseline to 48 hours at the 10 g TID dose (mean maximal reductions of 0.43 mmol/L; $p < 0.0001$) and the 3 g TID dose (mean maximal reductions of 0.92 mmol/L, $p = 0.048$), see table below. ZS 0.3 g TID did not result in a significant S-K reduction.

Statistical Model of Serum Potassium (mmol/L) Exponential Rate of Change to 24 Hours and 48 Hours – ITT Treat Population

Endpoint	Solution for Fixed Effects						
	Effect	Dose (g) TID	Estimate[a]	Standard error	DF	t-Value	Pr > |t|
24 Hours	Intercept		1.61766	0.008414	89	192.25	< 0.0001
	Time		-0.00228	0.000633	86	-3.60	0.0005
	Time*Dose	ZS 0.3	-0.00035	0.001166	86	-0.30	0.7661
	Time*Dose	ZS 3.0	-0.00169	0.000932	86	-1.81	0.0737
	Time*Dose	ZS 10	-0.00143	0.000932	86	-1.53	0.1293
	Time*Dose	Placebo	0				
48 Hours	Intercept		1.61196	0.008095	89	199.13	< 0.0001
	Time		-0.00096	0.000298	86	-3.21	0.0019
	Time*Dose	**ZS 0.3**	-0.00045	0.000555	86	**-0.81**	**0.4198**
	Time*Dose	**ZS 3.0**	-0.00089	0.000444	86	**-2.01**	**0.0480**
	Time*Dose	**ZS 10**	-0.00256	0.000444	86	**-5.77**	**< 0.0001**

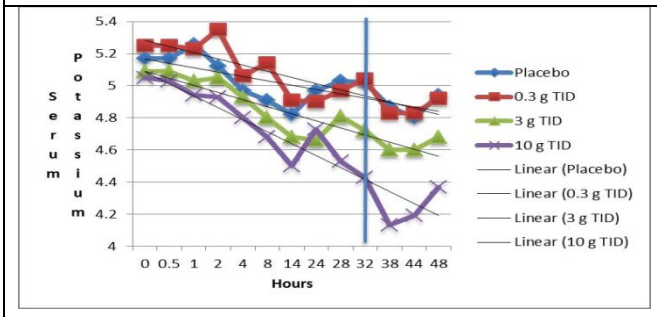
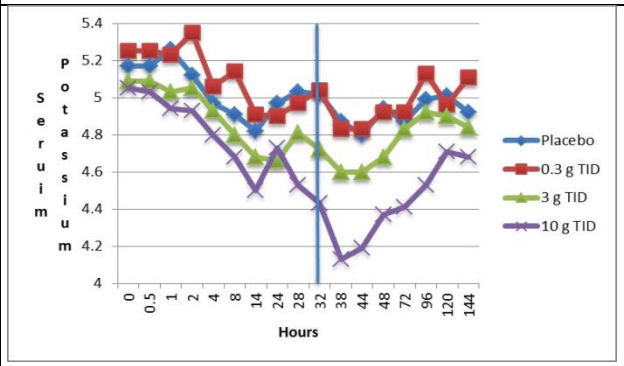
	Time*Dose	Placebo	0				

Abbreviations: ITT = intent-to-treat; TID = three times daily; ZS = zirconium silicate

[a] The exponential rate of decline from baseline to 48 hours of treatment was modeled as $S(t) = S(0) \exp(-\beta t)$ where β is the exponential rate of decline using a longitudinal model.

The S-K lowering effect started immediately, with statistically significant reductions vs. placebo 1 hour after the first ZS 10 g TID dose (p = 0.044), see figure below.

Serum Potassium over Initial 48 Hours and 7 days– ITT Population, Study ZS-002

Over 48 hours	Over 7 days
	

During Study Day 2 (from 28 to 48 hours post first study dose), statistically significantly greater mean reductions in S-K values were observed at all time points in the ZS 10 g TID dose group vs. placebo ($p \leq 0.001$), and this reduction continued for 2.5 days after the last dose of study drug (p = 0.005 at Study Day 4 and p = 0.003 at Study Day 5). Mean maximal reductions (-0.66 mmol/L) occurred 38 hours into the study, 4 hours after the 6th dose of ZS 10 g TID: a > 1 mmol/L drop in S-K was observed in 41.7% of ZS 10 g TID subjects had vs. 3.4% of placebo subjects.

Dose-dependent responses were also demonstrated with other S-K assessments with the maximal effect at the ZS 10 g TID dose:

- The time to first S-K decrease of 0.5 mmol/L was statistically significantly reduced with the ZS 10 g TID dose vs. placebo (p = 0.042), with a modest reduction observed with the ZS 3 g TID dose and generally no difference was observed for the ZS 0.3 g TID dose. There were no statistically significant differences between placebo and the lower ZS dose (0.3 g and 3 g) groups.
- Following the 4th dose, 58.3% of ZS 10 g TID subjects achieved a ≥ 0.5 mmol/L decrease in S-K vs. the 17.2% in placebo group (p = 0.004). At 48 hours, after 6 doses, 33.3% of ZS 10 g TID subjects had achieved a ≥ 1.0 mmol/L decrease in S-K vs. 6.7% in placebo group (p = 0.016).
- Time to normalization of S-K levels (3.5 to 4.9 mmol/L) was also dose-dependent and statistically significantly faster in the ZS 10 g TID vs. the placebo group (p = 0.040). S-K levels had normalized in all 24 ZS 10 g TID subjects after 48 hours of treatment so they did not need to extend the treatment. In contrast, 30% (9/30) of subjects in the placebo group received study drug treatment beyond the initial 2 days.

The reduction in S-K levels was accompanied by a similar reduction in urinary potassium excretion, with a 23% reduction in urinary potassium excretion observed from baseline to Study Day 2 at the10 g TID dose ($p < 0.002$ vs. placebo). There were no statistically significant reductions in urinary potassium excretion between the 2 lower ZS doses and placebo.

2.5.2. Main studies

Study ZS-003: A Phase 3, multicentre, two-phase, multi-dose, prospective, randomized, double-blind, placebo-controlled study to investigate the safety and efficacy of ZS, an oral sorbent, in subjects with mild to moderate hyperkalaemia

ZS-004: A phase 3 multicentre, multi-phase, multi-dose, prospective, randomized, double-blind, placebo-controlled maintenance study to investigate the safety and efficacy of ZS, an oral sorbent, in subjects with hyperkalaemia

Methods, study participants and treatments

Study EUZS-003 was a phase 3, multicentre, prospective, randomised, placebo-controlled, double-blind, dose-ranging study in subjects with mild to moderate hyperkalaemia. Study sites were located at 65 sites in the United States, Australia, and South Africa. A total of 754 subjects were randomized to the 48-hours Acute Phase of whom 543 subjects followed in ≤12-days Subacute Phase (Extended Dosing). Study EU-004 was a phase 3, multicentre, prospective, randomized, placebo-controlled, double-blind, dose-ranging study in subjects with hyperkalaemia. Study sites were located at 44 sites in the United States, Australia, and South Africa. A total of 258 subjects were treated in the outpatient, open-label Acute Phase, of whom 237 achieved normokalaemia (S-K 3.5-5.0 mmol/L) and were randomized to Extended Dosing.

In both pivotal studies, adult subjects (<18 years) of both genders with an ability to have repeated blood draws were included. Potassium requirements: In study EUZS-003, the mean i-STAT potassium of 5.0-6.5 mmol/L on Study Day 0; Study ZS-004: Two consecutive i-STAT potassium values, measured 60 min. apart, both ≥5.1 mmol/L and measured within 1 day of the first ZS dose on Acute Phase Study Day 1.

Both pivotal studies exclusion criteria included pseudohyperkalaemia signs and symptoms, such as haemolysed blood specimen, history of severe leucocytosis or thrombocytosis; cardiac arrhythmias that required immediate treatment; diabetic ketoacidosis; dialysis; treatment with resins, calcium acetate, calcium carbonate, or lanthanum carbonate, within the last 7 days. Study 003 included also the following conditions as exclusion criteria: receiving insulin, but stable dose not established; HIV positive, except subjects enrolled at sites in South Africa; treatment with lactulose, rifaximin, or other non-absorbed antibiotics for hyperammonaemia within the last 7 days.

In study EUZS-003, eligible subjects were randomised in a 1:1:1:1:1 ratio to receive double-blind treatment with 1 of 4 doses of ZS (1.25 g, 2.5 g, 5 g, and 10 g) or placebo, administered TID for the initial 48 hours (acute phase), followed by a randomized dose of ZS (1.25 g, 2.5 g, 5 g, and 10 g) or placebo administered QD for 12 days (subacute phase). For subacute phase, normokalaemic subjects were randomized to 1 of the 4 active doses in a 1:1 ratio for the same acute phase dose QD and placebo QD, whereas subjects who received placebo in the Acute Phase were randomized to receive either 1.25 g or 2.5 g of ZS administered QD in Subacute Phase. During the acute phase (study days 1 and 2), all randomized subjects received study drug TID with meals. All subjects who completed the acute phase and had i-STAT

potassium values within the normal range (3.5 to 4.9 mmol/L) on the morning of study day 3 were to enter into the subacute phase (extended dosing) during which study drug was to be administered QD with breakfast. All subjects were to continue the treatments they were on upon admission into the study.

In study ZS-004, eligible subjects were enrolled in the study and treated on an outpatient basis. In the open-label acute phase, subjects were treated with ZS 10 g TID for the initial 48 hours (6 doses). Subjects who achieved normokalemia during the acute phase were randomized in a double-blind manner in a 4:4:4:7 ratio to 1 of 3 doses of ZS (5 g, 10 g, or 15 g) or placebo administered QD for a further 28 days (maintenance phase, or extended dosing). An additional week of safety follow-up after the last dose day extended the study to a total of 35 days. During the acute phase, all enrolled subjects received study drug TID for 2 days (a total of 6 doses). On each day, the first dose was to be administered at the site and the second and third doses were to be taken at home just before lunch and the evening meal, respectively. Subjects with i-STAT potassium values ≥ 6.1 mmol/L on day 1 at the 4-hour post dose 1 received the second dose of study drug 4 hours after the first dose. If the i-STAT potassium value was > 6.2 mmol/L or met any of the ECG stopping criteria at the 90-minute post dose 2 time point, the subject was to be discontinued from the study. All subjects who completed the acute phase and had i-STAT potassium values within the normal range (3.5 - 5.0 mmol/L) on the morning of acute phase study day 3 were to be randomized into the maintenance phase. Study drug was administered QD at the site in the morning on maintenance phase study days 1 (acute phase study day 3), 2, 5, 8, 12, 15, 19, 22, and 26; on all other days, subjects were to take study drug at home, just before breakfast. Subjects who developed i-STAT potassium values between 3.0 and 3.4 mmol/L, inclusive, during the maintenance phase, were to have study drug dosing reduced from QD to every other day (QOD) for the remainder of the study.

The primary efficacy endpoint in study EUZS-003 for the acute phase was % of subjects achieving normokalaemia after 48 hours of therapy. For the subacute phase, it was the cumulative number of days remaining normokalaemic during the 12 days of therapy for subjects on subacute therapy and randomized withdrawal, separately calculated for the 4 acute phase active treatments. In study ZS-004, the primary efficacy endpoint was the model-based least squares mean (LSMEAN) of all available S-K values during maintenance phase study days 8 to 29. The secondary efficacy endpoints for the maintenance phase included the number of normokalaemic days during maintenance phase study days 8 to 29; mean change and mean % change from acute phase baseline in S-K and from maintenance phase baseline in S-K; time to hyperkalaemia (S-K ≥ 5.1 mmol/L); time to relapse in S-K values.

In study EUZS-003, 1433 subjects were screened for entry into the study, and 679 of these failed to meet the entry criteria, primarily due to average i-STAT values not within the acceptable range (628 subjects). Among the 754 subjects randomized in the acute phase of the study, 158 were randomized to placebo, 154 to ZS 1.25 g TID, 141 to ZS 2.5 g TID, 158 to ZS 5 g TID, and 143 to ZS 10 g TID. Majority of subjects in each study group completed the acute phase of the study (range: 96.2 to 99.4%). A total of 18 subjects (including subject who was never dosed) prematurely discontinued from the study, of them 4 ZS and 1 placebo treated subjects due to hyperkalaemia. Study ZS-004. Overall, 425 subjects were screened for entry into the study. Of these, 167 failed to meet the entry criteria, primarily due to average i-STAT values not within the acceptable range (160 subjects), and were not enrolled in the study. The 258 subjects enrolled in the open-label acute phase of the study were treated with ZS 10 g TID. Of them, 7 subjects prematurely discontinued; 5 due to withdrawal of consent and 2 due to hyperkalaemia (i-STAT potassium values of 6.3 mmol/L, 90 minutes after the second dose of ZS on acute phase study day 1).

The applicant claimed that demographic characteristics in the study 003 were generally similar among the acute phase treatment groups at baseline: mean age ranged from 65.2 to 66.2 years, majority of subjects

in each of the treatment groups were male (range: 53.9% to 64.5%) and white (range: 83.9% to 88.7%). The greatest proportions of subjects had baseline S-K values (per central laboratory) ≤ 5.3 mmol/L (range: 49.4% to 65.7%). The most common aetiology of elevated S-K within each of the acute phase treatment groups (subjects could have multiple aetiologies) was CKD (based on eGFR < 60 mL/min, ~75%; range: 71% to 80%). Other aetiologies of elevated S-K included use of RAAS inhibitor medication (~67%; range: 63.1% to 70.8%), and diabetes mellitus (~60%; range: 56.6% to 61.1%). At baseline of the acute phase of study ZS-004, mean age was 64.0 years, the majority of the subjects were male (57.8%) and white (83.3%). Baseline S-K values (per central laboratory) were < 5.5 mmol/L for 46.1% of subjects, ≥ 5.5 to < 6.0 mmol/L for 38.8% of subjects, and ≥ 6.0 mmol/L for 15.1% of subjects. The most common aetiologies of elevated S-K (subjects could have had multiple aetiologies) were use of RAAS inhibitor medication (69.8%), CKD (based on eGFR < 60 mL/min, 69.4%), and diabetes mellitus (65.9%). The demographic and other baseline characteristics of the maintenance phase were generally similar to those noted for the acute phase: among the treatment groups, mean age ranged from 61.5 to 64.9 years, the majority of the subjects were white (range: 80.0 to 86.3%). The proportions of male subjects tended to be higher in the ZS 15 q QD group (71.4%) compared with the placebo (51.8%) and the lower ZS dose (5 g QD: 60.0%; 10 g QD: 52.9%) groups. Greater proportions of subjects in the ZS 15 g QD group had HF, CKD (based on eGFR < 60 mL/min) and diabetes mellitus vs. placebo group. Almost all of the subjects in study 004 (97.3%) enrolled in the acute phase. The most common types of medications included agents acting on the renin-angiotensin system (66.7%), drugs used in diabetes (62.4%), and lipid-modifying agents (57.4%). Almost all of the subjects in each treatment group of study 004 (range: 94.6 to 100%) randomized in the maintenance phase reported the use of medication, the most commonly agents acting on the renin-angiotensin system (range: 57.1 to 70.6%), drugs used in diabetes (range: 55.6 to 72.5%), and lipid modifying agents (range: 51.1 to 62.7%).

Objectives

Study EUZS-003. The primary objective was to perform a controlled evaluation of the safety and efficacy of 4 ZS TID doses (1.25 g, 2.5 g, 5 g, and 10 g) for 48 hours in the Acute Phase for subjects with mild to moderate hyperkalemia at baseline.

The secondary objectives were: (1) to evaluate the safety and efficacy of ZS QD for 12 additional days in a Subacute Phase; (2) to assess the robustness of efficacy in normalizing S-K (Acute Phase), and maintaining normalized S-K (Subacute Phase); (3) to evaluate the effect of ZS on other electrolytes.

Study ZS-004. The primary objective was to evaluate the safety and efficacy of 3 ZS QD doses for 28 days in maintaining normokalemia in subjects achieving normokalemia following 2 days of acute therapy for subjects with hyperkalemia at baseline.

The secondary objectives were: (1) to evaluate the safety and efficacy of the ZS 10 g TID dose administered for 48 hours in the Acute Phase in subjects with hyperkalemia; (2) to assess the robustness of efficacy with ZS treatment for normalizing S-K (Acute Phase), and maintaining normalized S-K; (3) to evaluate the effect of ZS on other electrolytes.

Outcomes/endpoints

Study EUZS-003: The primary efficacy endpoint for the acute phase was % of subjects achieving normokalaemia after 48 hours of therapy (i.e., responders); for the subacute phase was the cumulative

number of days remaining normokalaemic during the 12 days of therapy for subjects on subacute therapy and randomized withdrawal, separately calculated for the 4 acute phase active treatments (excluding acute phase placebo). Secondary efficacy endpoints for the acute phase included the exponential rate of change in S-K values during the initial 48 hours of study drug treatment, S-K change from baseline at all time points, time to first decrease in S-K of 0.5 mmol/L, time to normalization of S-K (3.5 to 5.0 mmol/L), and proportion of subjects who achieved normalization in S-K values by time point. Secondary efficacy endpoints for the Subacute Phase included exponential rate of change in S-K values during the 12 days, time to relapse in S-K values (return to original S-K baseline value), proportion of subjects within each treatment group who retain normal S-K values (3.5 to 5.0 mmol/L) at the end of study, S-K change from baseline at all time points, and time to an increase in S-K values of 0.5 mmol/L.

Study ZS-004: The primary efficacy endpoint was the model-based least squares mean (LSMEAN) of all available S-K values during maintenance phase study days 8 to 29. The secondary efficacy endpoints for the maintenance phase included (1) number of normokalaemic days during Maintenance Phase Study Days 8 to 29; (2) mean change and mean % change from Acute Phase baseline in S-K and from Maintenance Phase baseline in S-K; (3) time to hyperkalaemia (S-K ≥ 5.1 mmol/L); (4) time to relapse in S-K values (return to original Acute Phase S-K baseline value); (5) mean S-K intra-subject standard deviation calculated among subjects with ≥ 2 values on or after Maintenance Phase Study Day 8; and (6) proportion of subjects who remained normokalaemic at Maintenance Phase Study Days 1, 2, 5, 8, 12, 15, 19, 22, 26, 29, and 35. The secondary efficacy endpoints for the Acute Phase included (1) exponential rate of change in S-K values during the initial 48 hours of treatment; (2) mean change and mean % change from baseline in S-K values at all measured time intervals post dose; (3) proportion of subjects who achieved normokalaemia during the Acute Phase at 24 and 48 hours after start of dosing; and (4) time to normalization in S-K values (3.5 - 5.0 mmol/L).

Sample size

Study EUZS-003: Sample size for the exponential rate of change during the Acute Phase was calculated using the program for sample size calculation of a random slopes model with parameters estimates based on Study ZS-002 data. When the model was fit to the ZS-002 data, with time measured in days, the variance of the intercept was 0.00802, the variance of the slope was 0.00130 and the covariance was -0.00045, the residual variance was 0.00473. Based on these parameters, there was 90% power to detect a difference in slopes of 0.0183/day. On the log potassium scale, this was a reduction of 1.83%/day. For the percentage normokalaemic at the end of the Acute Phase, any 20% absolute gain after 48 hours in the percentage with normokalaemic control from placebo control to any ZS dose could have been detected with at least 90% power for a two-sided test with 0.05 Type I error. For the subacute phase, it was estimated that at least 100 of the 150 treated Acute Phase subjects would achieve normokalaemia for each ZS dose group. With the parameters above, there was a 90% chance of detecting a difference in slopes of 0.0205/day. On the log potassium scale, this was a slope of 2.05%/day. For the Subacute Phase, it was projected that there was at least 80% power to detect a 0.6 effect size (based on a 3-day difference with a 5-day standard deviation) for cumulative days normokalaemic.

Study EUZS-004: The sample size was based on the mean S-K during Maintenance Phase Study Days 8 through to 29. To optimize the comparison of 3 active doses vs. placebo, the placebo group had 1.73 × the number of subjects per active dose. A 4:4:4:7 allocation best approximated the optimum Dunnett's allocation. A sample size of 232 Maintenance Phase subjects (49 per active dose and 85 placebo controls) had 90% power and 5% Type 1 error for a 2-sided hypothesis test to detect a mean 0.3 mmol/L advantage

for Maintenance Phase Study Days 8 through 29 for any active dose vs. placebo using a pre-specified closed testing order (highest to lowest dose); a mean 0.3 mmol/L decrease represents a meaningful advantage between any dose and placebo for a pooled 0.5 standard deviation. The sample size also had 90% power and 5% Type I error to detect a mean 4-day increase in days normokalaemic between any dose and placebo over the 28-day Maintenance Phase for a pooled 6-day standard deviation.

Randomisation

Study EUZS-003: Each subject was randomized once and received the Acute Phase randomization and the separate Subacute Phase randomization. For the Acute Phase, subjects were randomly allocated to 1 of 4 doses of ZS or placebo for the Acute Phase in a 1:1:1:1:1 ratio. Subjects entering the Subacute Phase were already randomized in a 1:1 ratio to either the same dose of ZS or placebo control QD while subjects receiving placebo in the Acute Phase were randomized to receive ZS at either the 1.25 g or 2.5 g QD. All randomizations were assigned in a double-blind fashion using the kit number based on the randomization.

Study ZS-004: Acute Phase was open-label. During the Maintenance Phase, subjects were randomly allocated by the IWRS to 1 of 3 doses of ZS (5 g, 10 g, and 15 g) or placebo in a 4:4:4:7 ratio. All randomizations were assigned in a double-blind fashion using the kit number based on the randomization. The randomization code was held by Sharp Clinical Packaging, which was not associated with the clinical management of the study.

Blinding (masking)

Studies EUZS-003, maintenance phase in ZS-004 were double blind; acute phase in study ZS-004 was open-label.

Statistical methods

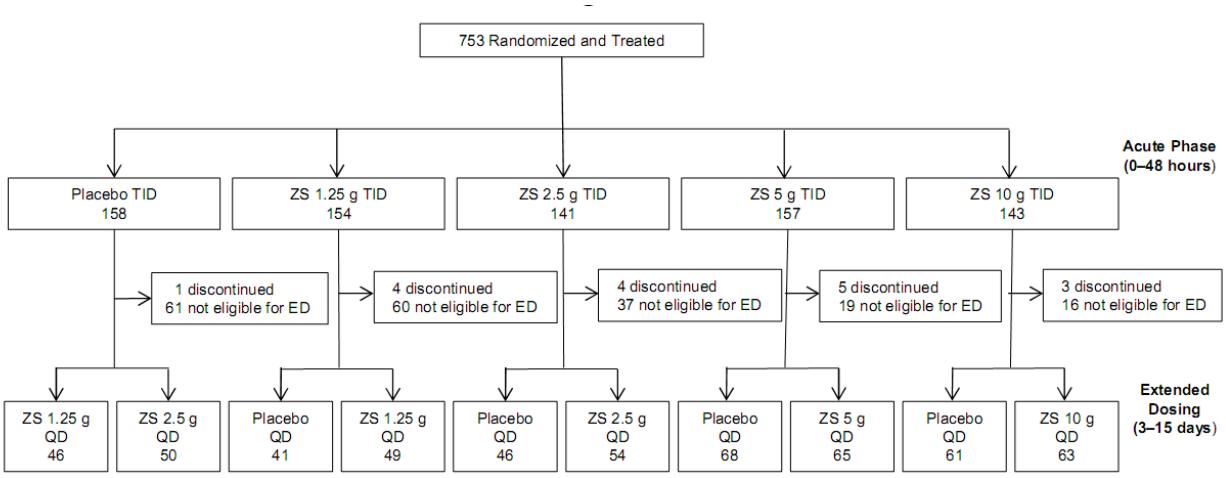
Statistical methods: the primary efficacy population of each study was the ITT population. In the acute phase the ITT population included: (1) for study EUZS-003: all subjects who were randomized, received TID study drug, and had S-K measurements after 48 hours of treatment, (2) for study ZS-004: all subjects who received TID study drug, and had a post-baseline S-K measurement during the first 48 hours after start of dosing. In the extended dosing the ITT population included: (1) for study EUZS-003, all randomized subjects who received QD study drug and had a post-baseline S-K measurement during extended dosing (subacute phase); (2) for study ZS-004, all randomized subjects who received QD study drug and had at least 1 S-K measurement on or after extended dosing (maintenance phase) Study Day 8.

Results

Participant flow

Study EUZS-003: Overall, 1433 subjects were screened for entry into the study, and 679 of these failed to meet the entry criteria, primarily due to average i-STAT values not within the acceptable range (628 subjects). Among the 754 subjects randomized in the Acute Phase of the study, 158 were randomized to placebo, 154 to ZS 1.25 g TID, 141 to ZS 2.5 g TID, 158 to ZS 5 g TID, and 143 to ZS 10 g TID. Majority of subjects in each study group completed the Acute Phase of the study (range: 96.2 to 99.4%). A total of

18 subjects (including subject who was never dosed) prematurely discontinued from the study, of them 4 ZS and 1 placebo treated subjects due to hyperkalemia.Participant flow in Study EUZS-003 is depicted in the figure below.



Study ZS-004: Overall, 425 subjects were screened for entry into the study. Of these, 167 failed to meet the entry criteria, primarily due to average i-STAT values not within the acceptable range (160 subjects), and were not enrolled in the study. The 258 subjects enrolled in the Open-Label acute phase of the study were treated with ZS 10 g TID. Of them, 7 subjects prematurely discontinued; 5 due to withdrawal of consent and 2 due to hyperkalaemia (i-STAT potassium values of 6.3 mmol/L, 90 minutes after the second dose of ZS on Acute Phase Study Day 1). Of the 251 subjects who completed the Acute Phase, 240 were eligible to enter the Maintenance Phase. Among the 11 subjects who were ineligible to enter the Maintenance Phase, 2 had i-STAT potassium values < 3.5 mmol/L (3.2 and 3.4 mmol/L), 9 had i-STAT potassium values ≥ 5.1 mmol/L. Three eligible subjects did not enter Maintenance Phase due to consent withdrawal, investigator's decision and ECG withdrawal criteria. Thus, 237 subjects entered Maintenance phase; of them, 85 were randomized to placebo, 45 to ZS 5 g QD, 51 to ZS 10 g QD, and 56 to ZS 15 g QD.

Recruitment

Study EUZS-003 recruitment was initiated in November 2012 and completed in October 2013. Study ZS-004 recruitment was initiated in March 2014 and completed in August 2014.

Conduct of the study

Study EUZS-003: 11 subjects had major protocol deviations based on blinded data review: Acute Phase: not fasting for the baseline S-K value (1 placebo subject), not fasting for Study Day 3 S-K value (1 ZS 1.25 g TID subject), dosed while S-K > 7.0 mmol/L (1 ZS 1.25 g TID subject), received incorrect study drug (1 ZS 5 g TID subject), received SPS within 7 days (1 ZS 10 g TID subject), and < 80% dosing compliance (1 ZS 10 g TID subject). Subacute Phase: i-STAT potassium value did not qualify for Subacute Phase (1 ZS 1.25 g TID/Placebo subject and 1 Placebo/ZS 1.25 g QD subject) and received incorrect study drug (2 ZS 5

g TID/5 g QD subjects and 1 ZS 5 g TID/Placebo subject). The Applicant explained that small number of subjects who had major protocol deviations would have no impact on the overall efficacy and safety results of the study.

Study ZS-004: Deviations are not summarised and provided by individual patient data only. The Applicant explained that deviations noted during the study included mistiming or omission of study procedures or deviations in study drug dosing. All subjects met the inclusion/exclusion criteria of the study.

Baseline data

Study EUZS-003: The applicant claimed that demographic characteristics in the study 003 were generally similar among the Acute Phase treatment groups at baseline: mean age ranged from 65.2 to 66.2 years, majority of subjects in each of the treatment groups were male (range: 53.9% to 64.5%) and White (range: 83.9% to 88.7%). The greatest proportions of subjects had baseline S-K values (per central laboratory) ≤ 5.3 mmol/L (range: 49.4% to 65.7%). The most common etiology of elevated S-K within each of the Acute Phase treatment groups (subjects could have multiple etiologies) was CKD (based on eGFR < 60 mL/min, ~75%; range: 71% to 80%). Other etiologies of elevated S-K included use of RAAS inhibitor medication (~67%; range: 63.1% to 70.8%), and diabetes mellitus (~60%; range: 56.6% to 61.1%). The demographic and other baseline characteristics in the Study 003 Subacute Phase ITT Population were generally similar to that noted for the Acute Phase ITT Population. The demographic and other baseline characteristics of the Maintenance Phase were generally similar to those noted for the Acute Phase.

Study ZS-004: At baseline of the Acute Phase, mean age was 64.0 years, the majority of the subjects were male (57.8%) and White (83.3%). Baseline S-K values (per central laboratory) were < 5.5 mmol/L for 46.1% of subjects, ≥ 5.5 to < 6.0 mmol/L for 38.8% of subjects, and ≥ 6.0 mmol/L for 15.1% of subjects. The most common etiologies of elevated S-K (subjects could have had multiple etiologies) were use of RAAS inhibitor medication (69.8%), CKD (based on eGFR < 60 mL/min, 69.4%), and diabetes mellitus (65.9%). While predefined primary efficacy population was ITT population, and all efficacy analyses were conducted with this population, all the baseline data is provided for the safety population.

Numbers analysed

Subject disposition and reasons for withdrawal in the Acute Phase of Study EUZS-003

Disposition, n (%)	Placebo	ZS 1.25 g TID	ZS 2.5 g TID	ZS 5 g TID	ZS 10 g TID
Randomized	158	154	141	158	143
Treated	158 (100)	154 (100)	141 (100)	157 (99.4)	143 (100)
Completed Acute Phase	157 (99.4)	150 (97.4)	137 (97.2)	152 (96.2)	140 (97.9)
Discontinued Acute Phase	1 (0.6)	4 (2.6)	4 (2.8)	6 (3.8)	3 (2.1)
Adverse event	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)	1 (0.7)
Consent withdrawn	0 (0.0)	1 (0.6)	1 (0.7)	4 (2.5)	0 (0.0)
Subject compliance	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Sponsor's decision	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Hypo- or hyperkalemia	1 (0.6)	1 (0.6)	3 (2.1)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)[a]	0 (0.0)

Abbreviations: TID = three times daily; ZS = sodium zirconium cyclosilicate [a]
family emergency.

Subject Disposition and reasons for withdrawal in Extended Dosing for Study ZS-004

Disposition, n (%)	Acute Phase Treatment: ZS 10 g TID			
	Maintenance Phase Treatment			
	Placebo	ZS 5 g QD	ZS 10 g QD	ZS 15 g QD
Randomized	85	45	51	56
Treated	85 (100.0)	45 (100.0)	51 (100.0)	56 (100.0)
Completed Maintenance Phase	75 (88.2)	40 (88.9)	44 (86.3)	49 (87.5)
Discontinued Maintenance Phase	10 (11.8)	5 (11.1)	7 (13.7)	7 (12.5)
Adverse event	0 (0.0)	3 (6.7)	0 (0.0)	1 (1.8)
Consent withdrawn	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
Subject compliance	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Investigator's decision	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)[a]
Sponsor's decision	2 (2.4)	0 (0.0)	2 (3.9)	1 (1.8)
Hypo- or hyperkalemia	3 (3.5)	0 (0.0)	3 (5.9)[b]	1 (1.8)
Met ECG withdrawal criteria	0 (0.0)	1 (2.2)	0 (0.0)	2 (3.6)
Other[c]	2 (2.4)	1 (2.2)	2 (3.9)	1 (1.8)

Source: Statistical Table 14.1.1

Abbreviations: QD = once daily; ZS = sodium zirconium cyclosilicate [a] The investigator decided to withdrawal the subject from the study due to pre-existing clinical status.

[b] One subject who prematurely discontinued due to hypokalemia subsequently died 4 days after last dose due to myocardial infarction.

[c] Placebo (1 subject had family emergency/gone for 1 month; 1 subject had to leave town), ZS 5 g QD (1 subject moving out of state), ZS 10 g QD (1 subject leaving for other residence; 1 subject hospitalized for treatment of cellulitis), and ZS 15 g QD (1 subject hospitalized due to dyspnea).

Outcomes and estimation

Study EUZS-003

Primary efficacy endpoints

In a Study 003 ZS met primary endpoints of (1) the percentage of normokalaemic subjects at 48 hours after the initial dose (acute phase) and (2) the total number of days maintaining normokalaemic control during the Subacute Phase: in the Acute phase analysis, the normal S-K values (3.5-5.0 mmol/L) were achieved at 48 hours for 86.4%, 77.6%, 67.9%, 51.3%, and 47.8% of subjects in the 10 g TID, 5 g TID, 2.5 g TID, 1.25 g TID, and placebo groups, respectively. The 10 g TID, 5 g TID, and 2.5 g TID doses of ZS were statistically significantly superior to placebo ($p < 0.0001$) (see table below).

Acute Phase: Percentage of Normokalaemic Subjects at 48 Hours –ITT Population of Study EUZS-003

	n/N (%) of Normokalemic Subjects					
	Placebo (N = 158)	ZS 1.25 g TID (N = 154)	ZS 2.5 g TID (N = 141)	ZS 5 g TID (N = 157)	ZS 10 g TID (N = 143)	p-value[a]

Baseline	39/158 (24.7)	28/154 (18.2)	31/141 (22.0)	32/157 (20.4)	41/143 (28.7)	0.2341
Study Day 3						
0 h pre-dose	75/157 (47.8)	77/150 (51.3)	**93/137 (67.9)*** **	**118/152 (77.6)*** **	**121/140 (86.4)*** **	< 0.0001

Abbreviations: h = hour; ITT = intent-to-treat; S-K = serum potassium; TID = three times daily; ZS = sodium zirconium cyclosilicate

*** = Statistically significant difference from placebo at the ≤ 0.001 level based on logistic regression model with factors for Acute Phase baseline S-K, Acute Phase baseline eGFR, etiology, and age.*

[a] *Kruskal-Wallis tests globally for a positive trend across all treatment groups.*

In the study 003 Subacute Phase ZS subjects, the total numbers of days normokalemic were statistically significantly greater in the ZS 10 g QD (10.2 vs. 8.2 days), 5 g QD (9.0 vs. 6.0 days), and 2.5 g QD (8.6 vs. 6.2 days) groups compared with their corresponding placebo controls (see table below).

Subacute Phase: Total Number of Days Normokalaemic – Acute Phase ZS Subjects - ITT Population, study EUZS-003

			p-value		
Total Days Normokalemic	**Subacute Phase Placebo QD**	**Subacute Phase ZS QD**	**Wilcoxon Rank Sum**	**Linear Regression[a]**	**Poisson Regression[b]**
Acute Phase ZS 1.25 g TID Subjects	(N = 41)	(N = 49)			
Mean (standard deviation)	7.6 (4.71)	7.2 (5.08)	0.6145	0.08772	0.7095
Median	7	7			
Minimum, maximum	0, 13	0, 13			
Acute Phase ZS 2.5 g TID Subjects	(N = 46)	(N = 54)			
Mean (standard deviation)	6.2 (4.78)	8.6 (4.55)	0.0096**	0.0075**	< 0.0001
Median	4	9.5			
Minimum, maximum	0, 13	0, 13			
Acute Phase ZS 5 g TID Subjects	(N = 68)	(N = 64)			
Mean (standard deviation)	6.0 (4.43)	9.0 (4.22)	0.0002***	0.0010***	< 0.0001
Median	4	10.5			
Minimum, maximum	0, 13	1, 13			
Acute Phase ZS 10 g TID Subjects	(N = 61)	(N = 63)			
Mean (standard deviation)	8.2 (4.64)	10.2 (3.96)	0.0338*	0.0050**	0.0010
Median	7	13			
Minimum, maximum	0, 13	1, 13			

Abbreviations: eGFR = estimated glomerular filtration rate; ITT = intent-to-treat; QD = once daily; S-K = serum potassium; TID = three times daily; ZS = sodium zirconium cyclosilicate

*, **, *** = Statistically significant difference from placebo at the ≤ 0.05, 0.01, or 0.001 levels, respectively.*

[a] *Linear regression model with factors for Acute Phase baseline S-K, Acute and Subacute Phase baseline eGFR, etiology, and age.* [b] *Poisson regression model with factors for Acute Phase baseline S-K, Acute and Subacute Phase baseline eGFR, etiology, and age.*

In Acute Phase placebo subjects, there was no statistically significant difference between the ZS 1.25 g QD and 2.5 g QD groups in the total number of normokalaemic days during the subacute phase.

Secondary endpoints

Acute Phase

The applicant stated that ZS met all of the predefined acute phase secondary endpoints. Mean baseline S-K values were comparable among the acute phase treatment groups, ranging from 5.26 to 5.37 mmol/L, with no statistically significant difference between any ZS dose group vs. placebo. The S-K lowering effect started immediately, with a statistically significant difference from placebo for the mean change from baseline at 1, 2 and 4 hours after the first 10 g, 5 g, and 2.5 d dose of ZS ($p = 0.009$, $p = 0.033$, and $p = 0.011$, respectively) (see table below). During study day 2 (from 24 to 48 hours), statistically significantly greater mean reductions in S-K values were observed at all time points in the ZS 10 g TID ($p < 0.001$), ZS 5 g TID ($p < 0.001$), and ZS 2.5 g TID ($p < 0.05$) dose groups vs. placebo (see Table 3.4.13). The largest mean decrease from baseline in S-K was at 48 hours after the first dose in all ZS TID groups: 10 g (-0.73 mmol/L), 5 g (-0.54 mmol/L), and 2.5 g (-0.46 mmol/L).

Acute Phase: Mean Change From Baseline in Serum Potassium (mmol/L) Over Initial 48 Hours – ITT Population, study EUZS-003

	Placebo (N = 158)	ZS 1.25 g TID (N = 154)	ZS 2.5 g TID (N = 141)	ZS 5 g TID (N = 157)	ZS 10 g TID (N = 143)
Baseline,[a] mean (SD)	5.30 (0.365)	5.37 (0.369)	5.35 (0.400)	5.31 (0.337)	5.26 (0.337)
Change From Baseline					
Study Day 1					
1 h Post 1st Dose	n = 158	n = 154	n = 141	n = 156	n = 143
Mean ± (SD)	0.01 (0.404)	-0.01 (0.360)	-0.08 (0.394)	-0.06 (0.413)	**-0.11 (0.361)****
Mean percent ± (SD)	0.09 (7.606)	-0.23 (6.732)	-1.37 (7.273)	-1.13 (7.791)	**-2.08 (6.873)****
2 h Post 1st Dose	n = 158	n = 154	n = 141	n = 155	n = 143
Mean ± (SD)	0.00 (0.423)	-0.04 (0.366)	-0.06 (0.499)	**-0.09 (0.355)***	**-0.18 (0.360)*****
Mean percent ± (SD)	0.03 (7.911)	-0.81 (6.813)	-0.99 (9.384)	**-1.71 (6.725)***	**-3.43 (6.779)*****
4 h Post 1st Dose	n = 158	n = 154	n = 141	n = 155	n = 143
Mean ± (SD)	-0.22 (0.429)	-0.28 (0.425)	**-0.34 (0.409)***	-0.31 (0.389)	**-0.37 (0.445)****
Mean percent ± (SD)	-4.05 (8.021)	-5.20 (7.842)	**-6.34 (7.460)***	-5.74 (7.283)	**-6.91 (8.249)****
Study Day 2:0 h (24 hours post dose)	n = 158	n = 152	n = 138	n = 153	n = 140
Mean ± (SD)	-0.18 (0.363)	**-0.28 (0.393)***	**-0.32 (0.390)*****	**-0.40 (0.375)*****	**-0.52 (0.364)*****
Mean percent ± (SD)	-3.40 (6.819)	**-5.14 (7.190)***	**-6.02 (7.099)*****	**-7.31 (6.942)*****	**-9.85 (6.693)*****
1 h Post 1st Dose	n = 157	n = 149	n = 138	n = 152	n = 140
Mean ± (SD)	-0.24 (0.484)	-0.27 (0.415)	**-0.38 (0.479)***	**-0.46 (0.440)*****	**-0.68 (0.437)*****
Mean percent ± (SD)	-4.42 (8.904)	-4.99 (7.717)	**-6.95 (8.910)***	**-8.62 (8.082)*****	**-12.70 (8.091)*****
4 h Post 1st Dose	n = 157	n = 151	n = 138	n = 153	n = 140
Mean ± (SD)	-0.22 (0.440)	-0.32 (0.449)	**-0.40 (0.462)*****	**-0.47 (0.465)*****	**-0.62 (0.420)*****

Mean percent ± (SD)	-4.08 (8.253)	-5.82 (8.187)	**-7.27 (8.405)*** **	**-8.63 (8.541)*** **	**-11.58 (7.645)*** **
Study Day 3:0 h (48 hours post dose)	n = 157	n = 150	n = 137	n = 152	n = 140
Mean ± (SD)	-0.25 (0.413)	-0.30 (0.404)	**-0.46 (0.398)*** **	**-0.54 (0.459)*** **	**-0.73 (0.496)*** **
Mean percent ± (SD)	-4.62 (7.751)	-5.44 (7.476)	**-8.48 (7.291)*** **	**-10.04 (8.333)*** **	**-13.76 (9.044)*** **

Abbreviations: h = hour; ITT = intent-to-treat; SD = standard deviation; TID = three times daily; ZS = sodium zirconium cyclosilicate

, **, * = Statistically significant difference from placebo at the ≤ 0.05, 0.01, or 0.001 levels, respectively, based on unpaired t-test comparing ZS group indicated versus placebo.*

[a] *Baseline was calculated by taking the mean of the screening time points (0 hour, 30 minutes, and 1 hour) averaged with the 0-hour time point on Study Day 1; all values used in the calculation were determined by the central laboratory.*

The 10 g, 5 g, and 2.5 g TID doses of ZS were statistically significantly superior to placebo for the exponential decrease in S-K over the initial 48 hours of treatment (-0.73 mmol/L, p < 0.0001, t-value: 11.40; -0.54 mmol/L, p < 0.0001, t-value: 6.55; and -0.46 mmol/L, p = 0.0009, t-value: 3.33, respectively), and over the initial 24 hours of treatment (study day 2: 0 hour; p < 0.0001, p < 0.0001, and p = 0.0315, respectively). Median time to a 0.5 mmol/L decrease in S-K values was 24.8 hours in the placebo group vs. 22.8, 23.5, 21.4, and 24.1 hours in the ZS 10 g, 5 g, 2.5 g, and 1.25 g TID groups, respectively; reduce in time was statistically significantly with the ZS 10 g (p < 0.0001), 5 g (p = 0.0137), and 2.5 g (p = 0.0067) TID doses vs. placebo. During acute phase time to normalization of S-K values (3.5 - 5.0 mmol/L) was statistically significantly reduced with the ZS 10 g TID dose vs. placebo (p = 0.0034), but not with the ZS 5 g, 2.5 g, or 1.25 g TID doses. Percentage of normokalemic subjects in each treatment group at various time points are summarised in the table below.

Acute Phase: Percentage of Normokalaemic Subjects – ITT Population, study EUZS-003

	n/N (%) of Normokalaemic Subjects					
	Placebo (N = 158)	**ZS 1.25 g TID (N = 154)**	**ZS 2.5 g TID (N = 141)**	**ZS 5 g TID (N = 157)**	**ZS 10 g TID (N = 143)**	**p-value[a]**
Baseline	39/158 (24.7)	28/154 (18.2)	31/141 (22.0)	32/157 (20.4)	41/143 (28.7)	0.2341
Study Day 1						
1 h Post 1st Dose	58/158 (36.7)	45/154 (29.2)	52/141 (36.9)	55/156 (35.3)	65/143 (45.5)	0.0730
2 h Post 1st Dose	54/158 (34.2)	46/154 (29.9)	49/141 (34.8)	55/155 (35.5)	**70/143 (49.0)***	0.0108
4 h Post 1st Dose	80/158 (50.6)	73/154 (47.4)	79/141 (56.0)	89/155 (57.4)	87/143 (60.8)	0.1337
Study Day 2						
0 h pre-dose	78/158 (49.4)	78/152 (51.3)	69/138 (50.0)	**100/153 (65.4)****	**108/140 (77.1)*****	< 0.0001
1 h Post 1st Dose	85/157 (54.1)	71/149 (47.7)	85/138 (61.6)	99/152 (65.1)	**115/140 (82.1)*****	< 0.0001
4 h Post 1st Dose	78/157 (49.7)	79/151 (52.3)	**85/138 (61.6)***	**101/153 (66.0)****	**119/140 (85.0)*****	< 0.0001
Study Day 3						
0 h pre-dose	75/157 (47.8)	77/150 (51.3)	**93/137 (67.9)*****	**118/152 (77.6)*****	**121/140 (86.4)*****	< 0.0001

Abbreviations: h = hour; ITT = intent-to-treat; TID = three times daily; ZS = sodium zirconium cyclosilicate

, **, * = Statistically significant difference from placebo at the ≤ 0.05, 0.01, or 0.001 levels, respectively, based on Fisher Exact test comparing ZS group indicated versus placebo.*

[a] *Kruskal-Wallis tests globally for a positive trend across all treatment groups.*

Subacute Phase

A statistically significantly ($p \leq 0.001$) smaller mean increase in S-K from subacute phase baseline to subacute days 2, 3, 6, and 12 was observed for ZS QD vs. placebo in subjects who received ZS 10 g TID in the Acute Phase (0.00 vs. 0.28 mmol/L; -0.06 vs. 0.37 mmol/L; 0.10 vs. 0.43 mmol/L; 0.06 vs. 0.58 mmol/L, respectively); for ZS 10 g TID difference was not significant at subacute days 1 and 18, for all other dosing groups difference was not significant at any time point. For the exponential rate of change in S-K values (1) over the 12-day treatment interval, the 10 g and 5 g QD doses of ZS were statistically significantly superior to placebo ($p < 0.0001$ and $p = 0.0083$, respectively); (2) over the first 5 days of the subacute phase, 10 g QD doses ($p < 0.0001$) were superior over placebo. There was no statistically significant difference between other ZS QD groups vs. placebo, or in acute phase placebo subjects in ZS 1.25 and 2.5 g QD groups.

In the study 003 time to first increase of ≥ 0.5 mmol/L in S-K during the subacute phase was statistically significantly later with ZS QD vs. placebo for subjects who received ZS 10 g TID (18 vs. 3 days) in the acute phase. Time to relapse in S-K values (return to acute phase S-K baseline value) was statistically significantly later with ZS QD vs. placebo for subjects who received ZS 5 g TID (6 vs. 2 days, $p = 0.0328$) and ZS 2.5 g TID (12 vs. 1 day, $p = 0.0061$), but not for the ZS 10 g QD (18 vs. 12 days; may be due to the extended effect of ZS dosing during the acute phase within the placebo group) and ZS 1.25 QD group (2 vs. 3 days). A statistically significantly greater proportion of subjects in the ZS 10 g and 5 g QD groups retained normal S-K values (3.5 - 5.0 mmol/L) at the end of treatment (subacute day 12) compared to their corresponding placebo groups, but not until the end of the subacute phase (subacute day 18); see table below.

Percentage of Subjects Who Retained Normal Serum Potassium Values at the End of Treatment and the End of the Subacute Phase – Acute Phase ZS Subjects - ITT Population, study EUZS-003

	n/N (%)Subjects		
	Subacute Phase Placebo QD	Subacute Phase ZS QD	p-value[a]
Acute Phase ZS 1.25 g TID Subjects			
Subacute baseline	32/41 (78.0)	39/49 (79.6)	1.0000
End of Treatment (Subacute Day 12)	32/38 (84.2)	24/48 (58.3)	0.0105
End of Study (Subacute Day 18, off drug)	30/41 (73.2)	29/49 (59.2)	0.1874
Acute Phase ZS 2.5 g TID Subjects			
Subacute baseline	35/46 (76.1)	50/54 (92.6)	0.0262
End of Treatment (Subacute Day 12)	20/43 (46.5)	33/52 (63.5)	0.1459
End of Study (Subacute Day 18, off drug)	30/46 (65.2)	35/54 (64.8)	1.0000
Acute Phase ZS 5 g TID Subjects			
Subacute baseline	55/68 (80.9)	57/64 (89.1)	0.2293
End of Treatment (Subacute Day 12)	32/66 (48.5)	45/60 (75.0)	0.0033
End of Study (Subacute Day 18, off drug)	37/68 (54.4)	37/64 (57.8)	0.7282
Acute Phase ZS 10 g TID Subjects			
Subacute baseline	59/61 (96.7)	57/63 (90.5)	0.2733
End of Treatment (Subacute Day 12)	33/58 (56.9)	50/61 (82.0)	0.0048

End of Study (Subacute Day 18, off drug)	37/61 (60.7)	39/63 (61.9)	1.0000

Abbreviations: ITT = intent-to-treat; QD = once daily; TID = three times daily; ZS = sodium zirconium cyclosilicate [a] *Fisher Exact test comparing ZS group indicated versus placebo.*

The applicant explained that superior efficacy of ZS 10 g TID vs. placebo in reducing S-K during the acute phase and of ZS 5 g and 10 g QD vs. placebo in maintaining S-K during the subacute phase was evident across a variety of subpopulation analyses, including subjects with diabetes mellitus, congestive heart disease, CKD, and concurrent use of RAAS inhibitor medication. During the Acute Phase, the difference between the ZS 10 g TID and placebo groups in the percentage of subjects with normalized S-K at 48 hours increased with higher baseline S-K values (from 28.1% with baseline S-K ≤ 5.3 mmol/L to 54.8% with baseline S-K > 5.5 mmol/L) and with lower baseline eGFR values (from 4.5% with baseline eGFR ≥ 60 mL/min/1.73 m^2 to 73.3% with baseline eGFR < 15 mL/min/1.73 m^2).

Study ZS-004

Primary efficacy endpoint

In Study 004 Subjects who achieved normokalaemia following ZS 10 g TID in the acute phase were randomized to 28 days of placebo, ZS 5 g, 10 g, or 15 g QD dosing during the maintenance phase. ZS met the primary efficacy endpoint of mean S-K value during Maintenance Phase Study Days 8 to 29 at all 3 doses of ZS (see table below). Each ZS group had a statistically significantly ($p \leq 0.0001$) smaller mean S-K value vs. placebo. The mean S-K value decreased with increasing dose of ZS (5.1, 4.8, 4.5, and 4.4 mmol/L for placebo, ZS 5 g, 10 g, and 15 g QD, respectively).

Mean S-K Between Maintenance Phase Study Days 8 and 29 - ITT Population, Study ZS-004

	Acute Phase Treatment: ZS 10 g TID			
	Maintenance Phase Treatment			
Statistic[a]	**Placebo (N = 82)**	**ZS 5 g QD (N = 45)**	**ZS 10 g QD (N = 50)**	**ZS 15 g QD (N = 54)**
Back-transformed from model				
Least squares mean	5.0603	4.7544	4.5081	4.3742
95% confidence interval	4.9646, 5.1578	4.6350, 4.8769	4.4005, 4.6184	4.2754, 4.4753
Log-transformed (as modelled)				
Least squares mean (standard error)	1.6214 (0.009681)	1.5591 (0.012906)	1.5059 (0.012260)	1.4757 (0.011595)
95% confidence interval	1.6023, 1.6405	1.5336, 1.5845	1.4817, 1.5300	1.4529, 1.4986
t-test p-value (ZS versus placebo)		0.0001	< 0.0001	< 0.0001

Abbreviations: eGFR = estimated glomerular filtration rate; ITT = intent-to-treat; QD = once daily; RAAS = reninangiotensin-aldosterone system; TID = three times daily; ZS = sodium zirconium cyclosilicate.

[a] The least squares means were derived from a mixed effect model of serial observations between Maintenance Phase Study Days 8 and 29 with a subject random effect and the following fixed effects: Maintenance Phase treatment group; Acute Phase baseline eGFR; Acute Phase and Maintenance Phase baseline serum potassium; age (< 55, 55-64, ≥ 65 years); and binary indicators for RAAS inhibitors use, chronic kidney disease, congestive heart failure, and diabetes mellitus. The observed margins option (option uses actual sample size ratio between treatment groups instead of assuming equal balance) and an unstructured variance covariance matrix were used.

Secondary endpoints

Acute Phase

In Study 004 ZS demonstrated statistically significant improvement from baseline in S-K with ZS 10 g TID over the first 48 hours of dosing (see table below). Based on Kaplan-Meier estimates, 84.3% of subjects had normalized S-K values at 24 hours after the first dose of ZS, and 97.6% of subjects had normalized S-K values at 48 hours after the first dose of ZS. The S-K lowering effect was rapid, with a statistically significant and clinically meaningful decrease from baseline noted at 1 hour after the first 10 g dose of ZS. The median time to normalization of S-K values during the acute phase was 2.17 hours after the first dose of ZS.

Subjects with higher starting S-K values demonstrated a greater mean decrease in S-K. As an example, subjects with a starting S-K ≥ 6.0 mmol/L demonstrated a mean decrease in S-K of -1.5 mmol/L at 48 hours after the first dose of ZS as compared with a mean decrease of -0.8 mmol/L in subjects with a starting S-K < 5.5 mmol/L. Similarly, subjects with a starting S-K ≥ 6.0 mmol/L demonstrated a mean reduction 2 hours after the first dose of ZS of -0.7 mmol/L as compared with the overall population where the mean reduction was -0.4 mmol/L.

Acute Phase: Overview of Results for Secondary Efficacy Endpoints - ITT Population, Study ZS-004

Time Point	Parameter	Estimate for ZS 10 g TID (N = 258)	P-value for H_0: Parameter = 0
24 hours after start of ZS dosing	Mean exponential rate of change	-0.00373	< 0.0001
	Mean (median) S-K change	-0.68 (-0.70)	< 0.0001
	Mean (median) S-K percent change	-12.03 (-12.50)	< 0.0001
	Percent normalized (KM estimate)	84.28	not applicable
	Percent normalized at 24 hours	66.1 (168/254)	not applicable
48 hours after start of ZS dosing	Mean exponential rate of change	-0.00324	< 0.0001
	Mean (median) S-K change	-1.05 (-1.10)	< 0.0001
	Mean (median) S-K percent change	-18.56 (-19.23)	< 0.0001
	Median time to normalization	2.17	not applicable
	Percent normalized (KM estimate)	97.62	not applicable
	Percent normalized at 48 hours	88.0 (221/251)	not applicable

Abbreviations: H_0 = null hypothesis; ITT = intent-to-treat; KM = Kaplan Meier; S-K = serum potassium; TID = three times daily; ZS = sodium zirconium cyclosilicate

Maintenance Phase

A statistically significant greater number of normokalaemic days during maintenance Phase Study Days 8 to 29 were observed for each ZS group vs. placebo. The mean number of normokalaemic days increased with increasing dose of ZS (13.4, 13.9, and 16.8 days for ZS 5 g, 10 g and 15 g QD, respectively) vs. 7.4 days for placebo (out of 22 days in total), see table below.

Maintenance Phase: Number of Normokalemic Days During Maintenance Phase Study Days 8

to 29 - ITT Population

Statistic[a]	Acute Phase Treatment: ZS 10 g TID Maintenance Phase Treatment Placebo (N = 82)	ZS 5 g QD (N = 45)	ZS 10 g QD (N = 50)	ZS 15 g QD (N = 54)
Mean (standard error)	7.4 (8.00)	13.4 (7.57)	13.9 (7.91)	16.8 (6.99)
95% confidence interval	5.6, 9.1	11.1, 15.6	11.6, 16.1	14.9, 18.7
t-test p-value (ZS versus placebo)		0.0001	< 0.0001	< 0.0001

Source: Statistical Tables 14.2.2.8.1 and 14.2.2.9.1

Abbreviations: ITT = intent-to-treat; QD = once daily; TID = three times daily; ZS = sodium zirconium cyclosilicate.

[a] Calculated assuming that the time interval between assessments was normokalemic only if both the beginning and end assessments for that time interval were normal S-K values. For example, if S-K was normal on Study Day 12, abnormal on Study Day 15, and normal on Study Days 19, 22, 26, and 29, a total of 6 days (Study Days 13, 14, 15, 16, 17, and 18) were considered abnormal in the calculation.

At maintenance phase study day 29/Exit, the proportion of subjects who remained normokalaemic was statistically significantly larger in the ZS 5 g QD, ZS 10 g QD, and ZS 15 g QD groups (71.1%, 76.0%, and 85.2% of subjects, respectively) than in the placebo group (47.6% of subjects) as depicted in table below.

Proportion of Subjects Who Remained Normokalaemic by Maintenance Phase Study Day - ITT Population, Study ZS-004

Maintenance Phase Study Day, n/N (%)	Acute Phase Treatment: ZS 10 g TID Maintenance Phase Treatment Placebo (N = 82)	ZS 5 g QD (N = 45)	ZS 10 g QD (N = 50)	ZS 15 g QD (N = 54)
Baseline	71/82 (86.6)	42/45 (93.3)	46/50 (92.0)	50/54 (92.6)
MP Study Day 2	68/81 (84.0)	42/45 (93.3)	45/49 (91.8)	51/54 (94.4)
MP Study Day 8	39/81 (48.1)	**32/45 (71.1)***	**41/50 (82.0)*****	**46/54 (85.2)*****
MP Study Day 12	32/80 (40.0)	**33/44 (75.0)*****	**37/47 (78.7)*****	**45/53 (84.9)*****
MP Study Day 15	35/80 (43.8)	**31/44 (70.5)****	**40/47 (85.1)*****	**43/52 (82.7)*****
MP Study Day 19	35/78 (44.9)	**32/43 (74.4)****	**37/47 (78.7)*****	**45/51 (88.2)*****
MP Study Day 22	34/77 (44.2)	**29/43 (67.4)***	**30/45 (66.7)***	**45/51 (88.2)*****
MP Study Day 26	36/74 (48.6)	**31/42 (73.8)***	**32/45 (71.1)***	**43/51 (84.3)*****
MP Study Day 29	37/73 (50.7)	26/39 (66.7)	**31/38 (81.6)****	**39/43 (90.7)*****
MP Study Day 29/Exit	39/82 (47.6)	**32/45 (71.1)***	**38/50 (76.0)****	**46/54 (85.2)*****

Abbreviations: ITT = intent-to-treat; MP = Maintenance Phase; n = number of subjects normokalemic; N = number of subjects evaluated; QD = once daily; TID = three times daily; ZS = sodium zirconium cyclosilicate.

Note: Subjects included in the Maintenance Phase Study Day 29 analysis had to have a serum potassium value measured within 1 day of their last dose of study drug.

**, **, *** p ≤ 0.05, 0.01, and 0.001, respectively (Fisher exact test).*

The mean change from the acute phase baseline to maintenance phase study Day 29/Exit was -0.44 mmol/L in the placebo group, -0.77 mmol/L in the ZS 5 g QD group, -1.10 mmol/L in the ZS 10 g QD group, and -1.19 mmol/L in the ZS 15 g QD group. Statistically significant differences from placebo were observed for all ZS groups from maintenance phase study day 2 to Day 26. Mean change from the

maintenance phase baseline to maintenance phase study day 29/Exit was 0.56 mmol/L in the placebo group, 0.25 mmol/L in the ZS 5 g QD group, 0.11 mmol/L in the ZS 10 g QD group, and -0.09 mmol/L in the ZS 15 g QD group. Statistically significant differences vs. placebo were observed (1) from maintenance phase study day 2 to day 26 for the ZS 15 g QD group, and (2) from maintenance phase study day 2 to day 22 for the ZS 5 g and 10 g QD groups. Time to hyperkalaemia (S-K ≥ 5.1 mmol/L) during the maintenance phase occurred later with continued ZS QD treatment than with placebo for subjects on ZS 5 g ($p = 0.0012$), ZS 10 g ($p < 0.0001$), and ZS 15 g QD ($p < 0.0001$). Median time to hyperkalaemia from the maintenance phase baseline was 7 and 14 days in the placebo and ZS 5 g QD groups, respectively; <50% of subjects in the ZS 10 g and 15 g QD groups had hyperkalaemia before the end of the maintenance phase, therefore, the median in these 2 groups was not reached.

Time to relapse (return to S-K value measured at acute phase baseline) during the maintenance phase was later with continued ZS QD vs. placebo for subjects who received ZS 5 g QD ($p = 0.0045$), ZS 10 g QD ($p = 0.0001$), and ZS 15 g QD ($p < 0.0001$). Median time to relapse from the maintenance phase baseline was 19 and 29 days in the placebo and ZS 5 g QD groups, respectively; <50% of subjects in the ZS 10 g QD and ZS 15 g QD groups had relapsed at the end of the Maintenance Phase, therefore, the median in these 2 groups was not reached.

Ancillary analyses

The consistency of ZS efficacy across subpopulations was assessed in Studies EUZS-003 and ZS-004 individually.

Acute Phase

Study EUZS-003: The ZS 10 g TID group had statistically significantly larger mean decreases than the placebo group in all demographic subpopulations tested (age <65 years/≥65 years; male/female gender; White/Black/Other race; and US/not US geographic region); in Black subjects (17 subjects in each treatment group) the treatment difference from placebo was almost double (-0.82 mmol/L) than for White subjects (-0.43 mmol/L). The ZS 10 g TID group had larger mean decreases vs. placebo with regards to baseline S-K (>5.5/5.4-5.5/≤5.3 mmol/L), eGFR (≥60/30 to <60/15 to <30/<15 mL/min/1.73 m2), concomitant diseases (diabetes mellitus, CKD, HF), and use of RAAS inhibitor medication; the treatment difference was statistically significant in all subpopulations, except for subjects with eGFR ≥ 60 mL/min/1.73 m2. The mean reduction at 48 hours in the ZS 10 g TID group increased with higher baseline S-K values (from -0.57 mmol/L with baseline S-K ≤ 5.3 mmol/L to -1.10 mmol/L with baseline S-K > 5.5 mmol/L; difference from placebo: -0.42 mmol/L and -0.68 mmol/L, respectively) and with lower baseline eGFR values (from -0.79 mmol/L with baseline eGFR 30 to < 60 mL/min/1.73 m2 to -1.03 mmol/L with baseline eGFR < 15 mL/min/1.73 m2; difference from placebo: -0.57 mmol/L to -0.86 mmol/L, respectively).

Study ZS-004: The ZS 10 g TID group had mean decreases in all demographic subpopulations (age, gender, race, and geographic region). The largest mean changes in S-K were observed in subjects who were Black (-1.28 mmol/L) or from outside the United States (-1.27 mmol/L). The ZS 10 g TID group had mean decreases in with regards to baseline S-K, eGFR, concomitant diseases, and use of RAAS inhibitor medication. The mean reduction in S-K at 48 hours increased with higher Acute Phase baseline S-K values (S-K ≥ 6.0: -1.49 mmol/L; S-K ≥ 5.5 to < 6.0: -1.19 mmol/L; S-K < 5.5: -0.78 mmol/L). Among subjects with baseline S-K values ≥ 6.0 mmol/L, statistically significant mean decreases from baseline in S-K were observed at all time points from 1 to 48 hours following ZS dosing.

Extended Dosing

Study EUZS-003*:* In Study 003 Extended dosing ZS 5g and 10 g QD group had smaller mean increases vs. placebo in all demographic subpopulations (age, gender, race, and geographic region), except for female subjects in ZS 5 g QD group: in ZS 5 g QD group, statistically significant mean differences were observed for males (0.06 vs. 0.30 mmol/L) and Black subjects (-0.30 vs. 0.29 mmol/L) vs. placebo. Overall difference from placebo was substantially larger for Black vs. White subjects (-0.59 vs. -0.04 mmol/L), and for males vs. females (-0.24 vs. 0.11 mmol/L). Black subpopulation had few (a total of 17) subjects. In ZS 10 g QD group, difference vs. placebo was statistically significant in all subpopulations except few subjects enrolled at sites outside the United States (8 subjects) and Blacks (16 subjects). The ZS 5 g QD group had smaller mean increases in S-K vs. placebo group all subpopulations with regards to baseline eGFR, S-K, concomitant diseases, and use of RAAS inhibitor medication, except for GFR ≥ 60 mL/min/1.73 m2; these differences were not statistically significant. The ZS 10 g QD group had smaller mean increases vs. placebo group in all subpopulations with regards to baseline eGFR, S-K, concomitant diseases, and use of RAAS inhibitor medication, except for subjects with eGFR < 15 mL/min/1.73 m^2 (0.87 vs. 0.46 mmol/L, respectively). The treatment difference was statistically significant in all subpopulations except for the few subjects with baseline S-K > 5.5 mmol/L (18 subjects) and with eGFR < 15 mL/min/1.73 m^2 (8 subjects).

Study ZS-004: mean change in S-K from Extended Dosing baseline to Extended Dosing Study Day 29/Exit with ZS 5 g, 10 g, and 15 g QD and placebo groups was summarised. The ZS 5 g, 10 g and 15 g QD group had smaller mean increases in S-K vs. placebo group in all demographic subpopulations (age, gender, race, and geographic region), except for other races in ZS 5 g QD group. In ZS 5 g QD group these differences were statistically significant for subjects enrolled at sites in the United States (0.17 vs, 0.47 mmol/L), Whites (0.20 vs. 0.53 mmol/L), Males (0.21 vs. 0.52 mmol/L), and subjects ≥ 65 years of age (0.36 vs. 0.69 mmol/L). In ZS 10 g QD group these differences were statistically significant in all subpopulations except for Blacks, other races, and subjects < 65 years of age. Differences between each ZS group and placebo were consistent across subpopulations with regards to baseline eGFR, Baseline S-K, Concomitant Diseases, and Use of RAAS Inhibitor Medication: smaller mean increases in S-K was observed in all ZS groups than with placebo group. In ZS 5 g group these differences were statistically significant for eGFR < 60 mL/min/1.73m, RAASi medication, Diabetes mellitus, Heart failure and CKD. In ZS 10 g group, also difference for Baseline S-K ≥ 6.0 mmol/L was statistically significant. In ZS 15 g group statistically significant difference was also observed for Baseline S-K ≥ 6.0 mmol/L and for Baseline S-K 5.5 to < 6.0 mmol/L; only difference with regards to Baseline S-K < 5.5 mmol/L was not statistically significant.

The Applicant concluded that ZS reduced S-K and maintained normokalaemia independently of the underlying cause of hyperkalaemia, demonstrating similar efficacy in subjects with CKD, heart failure, and diabetes mellitus, as well as in subjects receiving concomitant treatment with RAAS inhibitor medication. In addition, ZS demonstrated comparable efficacy across demographic subgroups, including age, gender, race, and geographic region.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of efficacy for trial EUZS-003

Title: A Phase 3, Multicenter, Two-phase, Multi-dose, Prospective, Randomized, Double-blind, Placebo-controlled Study to Investigate the Safety and Efficacy of ZS, an Oral Sorbent, in Subjects with Mild to Moderate Hyperkalemia		
Study identifier	**EUZS-003**	
Design	Subjects were randomized in a 1:1:1:1:1 ratio to receive double-blind treatment with 1 of 4 doses of ZS (1.25 g, 2.5 g, 5 g, and 10 g) or placebo, administered TID for the initial 48 hours (**Acute Phase**), followed by a randomized dose of ZS (1.25 g, 2.5 g, 5 g, and 10 g) or placebo administered QD for 12 days (**Subacute Phase**). For Subacute Phase, normokalemic subjects were randomized to 1 of the 4 active doses in a 1:1 ratio for the same Acute Phase dose QD and placebo QD, whereas subjects who received placebo in the Acute Phase were randomized to receive either 1.25 g or 2.5 g of ZS administered QD in Subacute Phase. Subjects were followed for 7 days after the last dose of study drug.	
	Duration of main phase (Acute Phase): Duration of Run-in phase: Duration of Extension phase (Subacute Phase):	2 days (Study Days 1 and 2) NA 12 days (Study Days 3 -14)
Hypothesis	Superiority against placebo	
Treatments groups	**Acute Phase**	
	ZS 1.25 g	ZS 1.25 g TID, N = 154 Duration: from baseline (BL) to 48 hours
	ZS 2.5 g	ZS 2.5 g TID, N = 141 Duration: from BL to 48 hours
	ZS 5 g	ZS 5 g TID, N = 157 Duration: from BL to 48 hours
	ZS 10 g	ZS 10 g TID, N = 143 Duration: from BL to 48 hours
	Placebo	Matching placebo TID, N = 158 Duration: from BL to 48
	Subacute Phase	
	Acute Phase ZS subjects	
	ZS 1.25 g	ZS 1.25 g QD, N = 49 Duration: from Study Day 3 to 14
	ZS 2.5 g	ZS 2.5 g QD, N = 54 Duration: from Study Day 3 to 14
	ZS 5 g	ZS 5 g QD, N = 65 Duration: from Study Day 3 to 14
	ZS 10 g	ZS 10 g QD, N = 63 Duration: from Study Day 3 to 14
	Placebo	Matching placebo QD, N = 216 Duration: from Study Day 3 to 14
	Acute Phase placebo subjects	
	ZS 1.25 g	ZS 1.25 g QD, N = 46 Duration: from Study Day 3 to 14
	ZS 2.5 g	ZS 2.5 g QD, N = 50 Duration: from Study Day 3 to 14

Endpoints and definitions	Primary endpoint	Efficacy	• f or the **Acute Phase**: % of subjects achieving normokalemia after 48 hours of therapy; • f or the **Subacute Phase**: cumulative number of days remaining normokalemic during the 12 days of therapy
	Acute Phase		
	Secondary endpoints	Efficacy	1. exponential rate of change in S-K values during the initial 48 hours 2. time to first decrease in S-K of 0.5 mmol/L 3. time to normalization of S-K (**3.5 to 5.0 mmol/L**) 4. proportion of subjects who achieved normalization in S-K values by time point.
	Subacute Phase		
	Secondary endpoints	Efficacy	5. exponential rate of change in S-K values during the 12 days, 6. time to relapse in S-K values, 7. proportion of subjects within each treatment group who retain normal S-K values (3.5 to 5.0 mmol/L) at the end of study.
Database lock	6 November 2013		

Results and Analysis

Analysis description	**Primary Analysis**
Analysis population and time point description	Intent to treat Acute Phase: BL-48 hours Subacute Phase: Subacute Phase Days 1 – 12

Descriptive statistics and estimate variability

Acute Phase

Treatment group	**ZS 1.25 g**	**ZS 2.5 g**	**ZS 5 g**	**ZS 10 g**	**placebo**
Number of subject	154	141	157	143	24.7
% of normokalemic subjects at BL	18.2	22.0	20.4	28.7	47.8
% of normokalemic subjects after 48 h	51.3	**67.9***	**77.6***	**86.4***	47.8

p-value ***< 0.0001*** (Kruskal-Wallis tests globally for a positive trend across all treatment groups)
* p-value ***≤ 0.001*** based on logistic regression model with factors for Acute Phase baseline S-K, Acute Phase baseline eGFR, etiology, and age.

Subacute Phase

Treatment group	**ZS 1.25 g**		**ZS 2.5 g**		**ZS 5 g**		**ZS 10 g**	
	PL	ZS	PL	ZS	PL	ZS	Pl	ZS
Number of subject	41	49	46	54	68	64	61	63
Total number of days normokalemic	7.6	7.2	6.2	8.6	6.0	9.0	8.2	10.2
SD	4.71	5.08	4.78	4.55	4.33	4.22	4.64	3.96
Wilcoxon Rank Sum	0.6145		0.0096**		0.0002***		0.0338*	
Linear Regression[a]	0.08772		0.0075**		0.0010***		0.0050**	

	Poisson Regression[b]	0.7095	< 0.0001	< 0.0001	0.0010
	*, **, *** = Statistically significant difference from placebo at the ≤ 0.05, 0.01, or 0.001 levels, respectively. a Linear regression model with factors for Acute Phase baseline S-K, Acute and Subacute Phase baseline eGFR, etiology, and age. b Poisson regression model with factors for Acute Phase baseline S-K, Acute and Subacute Phase baseline eGFR, etiology, and age.				
Analysis description	**Secondary analysis**				
	Acute Phase				
1. Exponential rate of change in S-K values during the initial 48 hours	Comparison groups	**1.25 g ZS*Time**			
	t-value	-0.67			
	S-K mmol/L	-0.00013			
	P-value	0.5037			
	Comparison groups	**2.5 g ZS*Time**			
	t-value	-3.33			
	S-K mmol/L	-0.00066			
	P-value	p = 0.0009			
	Comparison groups	**5 g ZS*Time**			
	t-value	-6.55			
	S-K mmol/L	-0.00127			
	P-value	<0.0001			
	Comparison groups	**10 g ZS*Time**			
	t-value	-11.40			
	S-K mmol/L	-0.00224			
	P-value	<0.0001			
2. Time to first decrease in S-K of 0.5 mmol/L	Comparison groups	**Placebo**			
	Median Time to 0.5 mmol/L Decrease (hours)	24.8			
	Wilcoxon-Gehan P-value				
	Comparison groups	**1.25 g ZS**			
	Median Time to 0.5 mmol/L Decrease (hours)	24.1			
	Wilcoxon-Gehan P-value	0.5278			
	Comparison groups	**2.5 g ZS**			
	Median Time to 0.5 mmol/L Decrease (hours)	21.4			
	Wilcoxon-Gehan P-value	0.0067			
	Comparison groups	**5 g ZS**			
	Median Time to 0.5 mmol/L Decrease (hours)	23.5			
	Wilcoxon-Gehan P-value	0.0137			
	Comparison groups	**10 g ZS**			
	Median Time to 0.5 mmol/L Decrease (hours)	22.8			
	Wilcoxon-Gehan P-value	<0.0001			
3. Time to normalization of	Comparison groups	**Placebo**			
	Median Time to normalization (hours)	4.0			

S-K	Wilcoxon-Gehan P-value	
	Comparison groups	**1.25 g ZS**
	Median Time to normalization (hours)	4.0
	Wilcoxon-Gehan P-value	0.3031
	Comparison groups	**2.5 g ZS**
	Median Time to normalization (hours)	3.8
	Wilcoxon-Gehan P-value	0.5592
	Comparison groups	**5 g ZS**
	Median Time to normalization (hours)	3.9
	Wilcoxon-Gehan P-value	0.4160
	Comparison groups	**10 g ZS**
	Median Time to normalization (hours)	1.1
	Wilcoxon-Gehan P-value	0.0034
4. Proportion of subjects who achieved normalization in S-K values by time point	Comparison groups	**Placebo**
	% Normalized at 24 Hours	49.4
	% Normalized at 48 Hours	47.8
	Comparison groups	**1.25 g ZS**
	% Normalized at 24 Hours	51.3
	% Normalized at 48 Hours	51.3
	Comparison groups	**2.5 g ZS**
	% Normalized at 24 Hours	50.0
	% Normalized at 48 Hours	67.9**
	Comparison groups	**5 g ZS**
	% Normalized at 24 Hours	65.4*
	% Normalized at 48 Hours	77.6**
	Comparison groups	**10 g ZS**
	% Normalized at 24 Hours	77.1**
	% Normalized at 48 Hours	86.4**
	p-value ***< 0.0001*** (Kruskal-Wallis tests globally for a positive trend across all treatment groups) at both 24 and 48 hours *, ** - p ≤0.01, or 0.001 levels, respectively, based onFisher Exact test comparing ZS group vs. placebo.	
	Subacute Phase (Acute Phase ZS subjects)	
5. Exponential rate of change in S-K values during the 12 days	Comparison groups	**1.25 g ZS*Time**
	t-value	0.80
	S-K mmol/L	0.00113
	P-value	0.4252
	Comparison groups	**2.5 g ZS*Time**
	t-value	0.20
	S-K mmol/L	0.00031
	P-value	0.8396
	Comparison groups	**5 g ZS*Time**
	t-value	-2.68
	S-K mmol/L	-0.00368

	P-value	0.0083	
	Comparison groups	**10 g ZS*Time**	
	t-value	-5.89	
	S-K mmol/L	-0.00844	
	P-value	<0.0001	
6. Time to relapse in S-K values	Comparison groups	**Placebo**	**ZS 1.25 g**
	Median Time to Relapse from Subacute Baseline (days)	3.0	2.0
	Wilcoxon-Gehan p-value	0.5121	
	Comparison groups	**Placebo**	**ZS 2.5 g**
	Median Time to Relapse from Subacute Baseline (days)	1.0	12.0
	Wilcoxon-Gehan p-value	0.0061	
	Comparison groups	**Placebo**	**ZS 5 g**
	Median Time to Relapse from Subacute Baseline (days)	2.0	6.0
	Wilcoxon-Gehan p-value	0.0328	
	Comparison groups	**Placebo**	**ZS 10 g**
	Median Time to Relapse from Subacute Baseline (days)	12.0	18.0
	Wilcoxon-Gehan p-value	0.4177	
7. Proportion of subjects within each treatment group who retain normal S-K values at the end of study.	Comparison groups	**Placebo**	**ZS 1.25 g**
	% of subjects	73.2	59.2
	p-value*	0.1874	
	Comparison groups	**Placebo**	**ZS 2.5 g**
	% of subjects	65.2	64.8
	p-value*	1.0000	
	Comparison groups	**Placebo**	**ZS 5 g**
	% of subjects	54.4	57.8
	p-value*	0.7282	
	Comparison groups	**Placebo**	**ZS 10 g**
	% of subjects	60.7	61.9
	p-value*	1.0000	
	Fisher Exact test comparing ZS group vs. placebo		

Summary of efficacy for trial EUZS-003

Title: A Phase 3 Multicenter, Multi-phase, Multi-dose, Prospective, Randomized, Double-blind, Placebo-controlled Maintenance Study to Investigate the Safety and Efficacy of ZS, an Oral Sorbent, in Subjects with Hyperkalemia	
Study identifier	**ZS-004**
Design	In the Open-label **Acute Phase** subjects were treated with ZS 10 g TID for the initial 48 hours (6 doses). Subjects who achieved normokalemia during the Acute Phase were randomized in a double-blind manner in a 4:4:4:7 ratio to 1 of 3 doses of ZS (5 g, 10 g, or 15 g) or placebo administered QD for a further 28 days (**Maintenance Phase**). Subjects who completed the Maintenance Phase Study Day 29 visit or who discontinued due to hypo- or hyperkalemia were able participation in an open-label extension study (ZS-004E). All study subjects who did not enter the extension study were to be followed for a total of 7 (± 1) days after the last dose of study drug.

	Duration of main phase (Maintenance Phase):				28 days	
	Duration of Run-in phase (Acute Phase):				2 days on ZS 10 g TID	
	Duration of Extension phase (Study ZS-004E):				11 months	
Hypothesis	Superiority against placebo					
Treatments groups	ZS 5 g		ZS 5 g QD, N = 45 Duration: Maintenance Phase BL - day 29/exit			
	ZS 10 g		ZS 10 g QD, N = 51 Duration: Maintenance Phase BL - day 29/exit			
	ZS 15 g		ZS 15 g QD, N = 56 Duration: Maintenance Phase BL - day 29/exit			
	Placebo		Matching placebo QD, N = 85 Duration: Maintenance Phase BL - day 29/exit			
Endpoints and definitions	Primary endpoint	Efficacy	Model-based least squares mean (LSMEAN) of all available S-K values during **Maintenance Phase** Study Days 8 to 29.			
	Secondary endpoints	Efficacy	1. number of normokalemic days during Maintenance Phase Study Days 8 to 29; 2. mean change and mean % change from Acute Phase baseline in S-K and from Maintenance Phase baseline in S-K; 3. time to hyperkalemia (**S-K ≥ 5.1 mmol/L**).			
Database lock	29 August 2014					

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	Intent to treat Maintenance Phase Study Days 8 to 29				
Effect estimate per comparison	Comparison groups	**Placebo**	**ZS 5 g**	**ZS 10 g**	**ZS 15 g**
	Number of subject	82	45	50	54
	Back-transformed from model LSMEAN	5.0603	4.7544	4.5081	4.3742
	95% CI	4.9646, 5.1578	4.6350, 4.8769	4.4005, 4.6184	4.2754, 4.4753
	Log-transformed (as modelled) LSMEAN (standard error)	1.6214 (0.009681)	1.5591 (0.012906)	1.5059 (0.012260)	1.4757 (0.011595)
	95% CI	1.6023, 1.6405	1.5336, 1.5845	1.4817, 1.5300	1.4529, 1.4986
	t-test p-value (ZS vs. placebo)		0.0001	< 0.0001	< 0.0001
Analysis description	**Secondary analysis**				

1. number of normokalemic days during Maintenance Phase Study Days 8 to 29	Comparison groups	**Placebo**	**ZS 5 g**	**ZS 10 g**	**ZS 15 g**
	Mean (days)	7.4	13.4	13.9	16.8
	95% CI	5.6, 9.1	11.1, 15.6	11.6, 16.1	14.9, 18.7
	t-test p-value (ZS vs. placebo)		0.0001	< 0.0001	< 0.0001
2.1. mean change and mean % change from Acute Phase BL to Maintenance Phase Day 29/exit in S-K	Mean change	-0.44	-0.77*	-1.10*	-1.19*
	SD	0.515	0.559	0.813	0.659
	Mean % change	-7.68	-13.85*	-19.28*	-21.06*
	SD	8.940	9.568	14.099	11.086
	*p ≤ 0.001 (Fisher exact test)				
2.2 mean change and mean % change from Maintenance Phase BL to Day 29/exit in S-K;	Mean change	0.56	0.25 *	0.11*	-0.09**
	SD	0.582	0.645	0.768	0.598
	Mean % change	12.97	6.12*	3.02**	-1.43**
	SD	13.116	4.424*	17.785	13.664
	*, ** p ≤ 0.01, 0.001, respectively (Fisher exact test)				

3. time to hyperkalemia (**S-K ≥ 5.1 mmol/L**), estimates were measured as Cox Proportional Hazards Model of Maintenance Phase Time-to-Hyperkalemia	Comparison groups	**ZS 5 g vs. placebo**
	Estimate	-0.768390
	Standard error	0.235358
	P-value	0.0011
	Comparison groups	**ZS 10 g vs. placebo**
	Estimate	-1.243381
	Standard error	0.269260
	P-value	<0.0001
	Comparison groups	**ZS 15 g vs. placebo**
	Estimate	-1.584343
	Standard error	0.277248
	P-value	<0.0001

Analysis performed across trials (pooled analyses and meta-analysis)

For the acute phase, the placebo and ZS 10 g TID groups are displayed from studies ZS-002, EUZS-003 and ZS-004; 10 g TID dose of ZS was evaluated in each of the studies, and it is the proposed dose for the acute treatment of hyperkalemia. For extended dosing, the placebo, ZS 5 g, 10 g QD, and 15 g QD groups are displayed. The placebo, ZS 5 g, and 10 g QD groups were evaluated in studies EUZS-003 and ZS-004. The 15 g QD dose of ZS was evaluated only in Study ZS-004. The inclusion and exclusion criteria were generally similar across each of the ZS studies. More than 90% and more than 86% of subjects completed treatment in each treatment group during extended dosing of studies EUZS-003 and ZS-004, respectively. According the applicant, effect of ZS was consistent across the studies: (1) in acute phase, rapid effect following ZS 10 g TID in lowering S-K was demonstrated, while (2) in extended dosing, sustained efficacy of ZS 5 g, 10 g, and 15 g QD doses was demonstrated.

Clinical studies in special populations

All pivotal studies involved subjects with CKD and in various age groups. The applicant performed studies in renally impaired population of several age groups. The analyses of these subgroups did not provide information about differences amongst these patients.

The applicant submitted a Paediatric Investigational Plan (PIP) for ZS to the paediatric development and the PDCO agreed to defer studies with ZS in children from birth to < 18 years of age with hyperkalaemia until the safety and efficacy of ZS in adults has been established and an adult dose and regimen is defined. In addition, age-appropriate oral and rectal formulations of ZS are under development for studies in paediatric subjects.

Supportive studies

Long-term efficacy has been assessed in the completed study ZS-004E and ongoing Study ZS-005. When the combined ZS exposure across studies ZS-004 and ZS-004E was added to the ZS exposure from study ZS-005, the overall extent of exposure as of 7 December 2015 was > 30 days for 634 subjects, > 90 days for 524 subjects, > 180 days for 360 subjects, > 270 days for 243 subjects, and > 360 days for 149 subjects. According the applicant, there has been no indication of loss of effect (tolerance) in study ZS-004E or ZS-005 and extended dosing with ZS for up to 11 months was effective in maintaining normokalaemia, see table below.

Extended Dosing Phase: Proportion of Subjects With Average Serum Potassium Values ≤ 5.5 mmol/L Across Extended Dosing Study Days 8 to 337 a (Study 004E)

Extended Dosing Phase	ZS QD (N = 121)		
	n/N	Proportion	95% Confidence Interval
ED Study Day 8	114/120	0.950	0.894, 0.981
ED Study Day 15	110/118	0.932	0.871, 0.970
ED Study Day 22	115/118	0.975	0.927, 0.995
ED Study Day 29	111/116	0.957	0.902, 0.986
ED Study Day 36	107/112	0.955	0.899, 0.985
ED Study Day 43	105/111	0.946	0.886, 0.980
ED Study Day 50	101/108	0.935	0.871, 0.974
ED Study Day 57	101/107	0.944	0.882, 0.979
ED Study Day 85	83/88	0.943	0.872, 0.981
ED Study Day 113	79/84	0.940	0.867, 0.980
ED Study Day 141	76/81	0.938	0.862, 0.980
ED Study Day 169	65/70	0.929	0.841, 0.976
ED Study Day 197	64/68	0.941	0.856, 0.984
ED Study Day 225	64/65	0.985	0.917, 1.000
ED Study Day 253	59/63	0.937	0.845, 0.982
ED Study Day 281	57/60	0.950	0.861, 0.990
ED Study Day 309	53/58	0.914	0.810, 0.971
ED Study Day 337	50/51	0.980	0.896, 1.000
ED Study Day 337/Exit	113/120	0.942	0.884, 0.976
	ED Study Days 8 to 337		
Average	120/120	1.000	0.970, 1.000
p-value[a]	< 0.0001		

Source: Statistical Table 14.2.1.2.1

Abbreviations: ED = Extended Dosing; ITT = intent-to-treat; n = number of subjects with S-K values ≤ 5.5 mmol/L; N = number of subjects evaluated; QD = once daily; S-K = serum potassium; ZS = sodium zirconium cyclosilicate.

Note: S-K assessments obtained more than 1 day after the last dose of study drug were not included in the analysis.

[a] P-value is from exact binomial test that the observed proportion of subjects with S-K ≤ 5.5 mmol/L is > 60%.

Across Extended Dosing Study Days 8 to 337, 88.3% (95% CI: 81.2%, 93.5%) of subjects had average S-K values ≤ 5.1 mmol/L, which is statistically significantly higher than the 50% null hypothesis. The least squares mean from a logistic regression analysis, which adjusted for baseline covariates, was 92.8% (95% CI: 84.7%, 96.8%). Results were consistent across subgroups defined by age and baseline presence of CKD, heart failure, diabetes mellitus, and RAAS inhibitor use. In addition, the proportions of subjects with S-K values ≤ 5.1 mmol/L were relatively constant among the Extended Dosing Phase time points, ranging from 77.1% to 87.5%.

The ongoing study ZS-005 is a phase 3, multicenter, multi-dose, open-label study to investigate the long-term safety and efficacy of ZS in subjects with hyperkalemia (i-STAT potassium values at entry ≥ 5.1 mmol/L). No CSR was provided for this study, only high level results of ongoing study. The open-label maintenance study contains an Acute Phase, in which subjects are dosed with ZS 10 g TID for 24 to 72 hours, followed by a long-term Extended Dosing period in which subjects are dosed with ZS starting at 5 g QD. During Extended Dosing, the ZS dose may be increased or decreased in increments/decrements of 5 g QD up to a maximum of 15 g QD or a minimum of 5 g QOD based on i-STAT potassium measurements.

In the randomized withdrawal study, subjects either continue on the same ZS dose they were receiving at the time of the Extended Dosing Study Day 176 visit (n = 100) or receive placebo (n = 100) for an

additional 28 days. No dose titration is allowed during the randomized withdrawal study. The randomized withdrawal component of the study has not yet started.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Four completed clinical studies (1 phase 2 studies, and 3 phase 3 studies) were presented to evaluate efficacy in the target population: (1) for the acute lowering of S-K: 2 studies (study ZS-002 and acute Phase of study EUZS-003) and 1 supportive study (acute phase of study ZS-004); (2) for the maintenance of normokalaemia: 2 pivotal studies (≤12 days in the subacute phase of study EUZS-003 and ≤28 days in the maintenance phase of study ZS-004) 1 supportive long-term extension of study ZS-004 (≤11 months in study ZS-004E).

Study ZS-002 was a Phase 2, first in human, multicenter, prospective, randomized, placebo-controlled, double-blind dose escalating study report in subjects with mild hyperkalemia in CKD and moderate kidney dysfunction. Treatment: Eligible subjects in a double-blind dose-escalating fashion (3 separate cohorts), were to be randomized to receive escalating doses of ZS (0.3 g, 3 g, and 10 g) or placebo, administered TID daily with meals. The primary objectives were to evaluate the safety, tolerability, and efficacy of 3 ZS doses TID administered for 48 hours to subjects with moderate CKD and mild hyperkalemia. A total of 90 subjects (38 females, 52 males) with CKD (mean GFR on Study Day 0 = 45.4 mL/min, range: 30 to 62 mL/min) and hyperkalemia (mean screening S-K [per central laboratory] = 5.16 mmol/L, range: 4.6 to 6.0 mmol/L) were randomized to treatment in the study.

Study EUZS-003 was a phase 3, multicenter, prospective, randomized, placebo-controlled, double-blind, dose-ranging study in subjects with mild to moderate hyperkalemia. Study sites were located at 65 sites in the United States, Australia, and South Africa. A total of 754 subjects were randomized to the 48-hours acute phase of whom 543 subjects followed in ≤12-days subacute phase (extended dosing), study EU-004 It was a phase 3, multicenter, prospective, randomized, placebo-controlled, double-blind, dose-ranging study in subjects with hyperkalemia. Study sites were located at 44 sites in the United States, Australia, and South Africa. A total of 258 subjects were treated in the outpatient, open-label acute phase, of whom 237 achieved normokalaemia (S-K 3.5-5.0 mmol/L) and were randomized to extended dosing.

In both pivotal studies, adult subjects (<18 years) of both genders, and with ability to have repeated blood draws were enrolled. Potassium requirements were: study EUZS-003: mean i-STAT potassium of 5.0-6.5 mmol/L on study Day 0; study ZS-004: two consecutive i-STAT potassium values, measured 60 min. apart, both ≥5.1 mmol/L and measured within 1 day of the first ZS dose on Acute Phase Study Day 1. Both pivotal studies exclusion criteria included (1) pseudohyperkalemia signs and symptoms, such as hemolyzed blood specimen, history of severe leukocytosis or thrombocytosis; (2) cardiac arrhythmias that required immediate treatment; (3) diabetic ketoacidosis; (4) dialysis; (5) treatment with resins (such as sevelamer acetate, SPS), calcium acetate, calcium carbonate, or lanthanum carbonate, within the last 7 days. In summary, the study designs of both pivotal studies (003 and 004) are appropriate to establish absolute effect and safe enough to avoid. The potassium content in the food was not regulated and nor was the impact of potassium content impacting concomitant medications, such as ACEI or diuretics. The concomitant medications were required to be continued. Even if this could be considered as a potential weakness of the study, the conditions are closer to real life and thus, the control of potassium in diet/concomitant therapy is acceptable to the CHMP.

In study EUZS-003, eligible subjects were randomized in a 1:1:1:1:1 ratio to receive double-blind treatment with 1 of 4 doses of ZS (1.25 g, 2.5 g, 5 g, and 10 g) or placebo, administered TID for the initial 48 hours (acute phase), followed by a randomized dose of ZS (1.25 g, 2.5 g, 5 g, and 10 g) or placebo administered QD for 12 days (subacute phase). There was a one-time randomization to assign the acute phase and the subacute phase if normalized S-K was achieved after completion of the acute phase. In the subacute phase, normokalaemic subjects were randomized to 1 of the 4 active doses in a 1:1 ratio for the same acute phase dose QD and placebo QD, whereas subjects who received placebo in the acute phase were randomized to receive either 1.25 g or 2.5 g of ZS administered QD in subacute phase; study ZS-004: in the open-label acute phase subjects were treated with ZS 10 g TID for the initial 48 hours (6 doses). Subjects who achieved normokalaemia during the acute phase were to be randomized in a double-blind manner in a 4:4:4:7 ratio to 1 of 3 doses of ZS (5 g, 10 g, or 15 g) or placebo administered QD for a further 28 days. An additional week of safety follow-up after the last dose day extended the study to a total of 35 days. In both pivotal studies patients received mainly two days acute phase dosages via TID regimen that was ranging from 1.25 TID to 10 g TID in Study 003 (with meals) and 10 g dose TID in Study 004 (it is understood, that “with meals”). For the maintenance phase, the dosage was administered QD for 12 (in Study 003) or 28 days (in Study 004). Maintenance phase in study 004 was designed enriching the population by responders excluding non-responders. The magnitude of the ineligible patients to enter maintenance phase is very limited (less than 5%). The magnitude of lowering dosages in study 004 (from QD to QOD regimen) was more pronounced: ~20% of patient in 10 g and 15 g dosages. This led to applicant to advise starting maintenance dose not with 1/3 of the two highest dosages but rather with only 5g QD. This is acceptable due to rigorous monitoring and clear titration scheme is proposed.

The primary objective in study EUZS-003 was to perform a controlled evaluation of the safety and efficacy of 4 ZS TID doses for 48 hours in the acute phase for subjects with mild to moderate hyperkalemia at baseline. The primary objective in study ZS-004 was to evaluate the safety and efficacy of 3 ZS QD doses for 28 days in maintaining normokalaemia in subjects achieving normokalaemia following 2 days of acute therapy for subjects with hyperkalemia at baseline. Thus, two primary objectives in two pivotal studies focus on two separate issues – acute hypokelaemic effect and maintenance of normokalaemic effect during a rather short term. This approach in the development is not seen as a usual in the development where one study is replicating another for acute hypokalemic effects. The primary efficacy endpoint in EUZS-003: (1) for the acute phase was % of subjects achieving normokalaemia after 48 hours of therapy; (2) for the subacute phase was the cumulative number of days remaining normokalaemic during the 12 days of therapy for subjects on subacute therapy and randomized withdrawal, separately calculated for the 4 acute Phase active treatments (excluding acute phase placebo). The primary efficacy endpoint in ZS-004 was the model-based least squares mean (LSMEAN) of all available S-K values during maintenance phase study (days 8 to 29). One of the secondary efficacy endpoints for the maintenance phase included number of normokalaemic days during maintenance phase study days 8 to 29. Thus, the two primary objectives were targeted with three main endpoints – one for acute phase in study 003 and two for maintenance phase in studies 003 and 004. This might be acceptable considering supportive secondary endpoints for acute phase from study 004. The scope of study and its objectives with endpoints do not interfere with statistical considerations and recommendations for phase III trial. The primary endpoint for maintenance therapy represents more a pharmacodynamic than clinical oriented, because the maintenance without maintenance is clinically questionable. Thus, the cumulative number of days normokalaemic where the subjects are normokalaemic were the advised primary endpoint that was followed and results were recalculated

Sample size for the exponential rate of change during the acute phase in EUZS-003 was calculated using the program for sample size calculation of a random slopes model with parameters estimates based on

study ZS-002 data. The sample size in EUZS-004 was based on the mean S-K during maintenance phase study days 8 through to 29. To optimize the comparison of 3 active doses vs. placebo, the placebo group had 1.73 × the number of subjects per active dose. A 4:4:4:7 allocation best approximated the optimum Dunnett's allocation. The randomization's specifications, conditions and procedure are appropriate for the trial. In studies EUZS-003 and 004, subsets of study sample analysis were built properly. In general, the statistical specifications were adequate. The multiplicity issue was approached properly. Missing data were treated properly.

Efficacy data and additional analyses

In study 002 ZS met the predefined primary endpoint of exponential decrease in S-K from baseline to 48 hours at the 10 g TID dose (mean maximal reductions of 0.43 mmol/L; $p < 0.0001$) and the 3 g TID dose (mean maximal reductions of 0.92 mmol/L, $p = 0.048$), while ZS 0.3 g TID did not result in a significant S-K reduction. The S-K lowering effect started immediately, with statistically significant reductions vs. placebo 1 hour after the first ZS 10 g TID dose ($p = 0.044$). During study day 2, statistically significantly greater mean reductions in S-K values were observed at all time points in the ZS 10 g TID dose group vs. placebo ($p \leq 0.001$), and this reduction continued for 2.5 days after the last dose of study drug ($p = 0.005$ at day 4 and $p = 0.003$ at day 5). Mean maximal reductions (-0.66 mmol/L) occurred at 38 hours of the study: a > 1 mmol/L drop in S-K was observed in 41.7% of ZS 10 g TID subjects had vs. 3.4% of placebo subjects. Dose-dependent responses were also demonstrated with other S-K assessments with the maximal effect at the ZS 10 g TID dose. Thus, three dosages (0.3, 3, and 10 g) were tested over placebo during 48 hours and two doses (3 and 10 g) were statistically superior over placebo in decreasing S-K. This was sufficient to proceed further in the development.

In study 003, ZS met primary endpoints of (1) the percentage of normokalaemic subjects at 48 hours after the initial dose and (2) the total number of days maintaining normokalaemic control during the subacute phase: in the acute phase analysis, the normal S-K values (3.5-5.0 mmol/L) were achieved at 48 hours for 86.4%, 77.6%, 67.9%, 51.3%, and 47.8% of subjects in the 10 g TID, 5 g TID, 2.5 g TID, 1.25 g TID, and placebo groups, respectively. The 10 g TID, 5 g TID, and 2.5 g TID doses of ZS were statistically significantly superior to placebo ($p < 0.0001$). In a study 003, subacute phase ZS subjects, the total numbers of days normokalaemic were statistically significantly greater in the ZS 10 g QD (10.2 vs. 8.2 days), 5 g QD (9.0 vs. 6.0 days), and 2.5 g QD (8.6 vs. 6.2 days) groups compared with their corresponding placebo controls.

In Study 004, subjects who achieved normokalaemia following ZS 10 g TID in the acute phase were randomized to 28 days of placebo, ZS 5 g, 10 g, or 15 g QD dosing during the maintenance phase. ZS met the primary efficacy endpoint of mean S-K value during the maintenance phase at all 3 doses. Each ZS group had a statistically significantly ($p \leq 0.0001$) smaller mean S-K value vs. placebo. The mean S-K value decreased with increasing dose of ZS (5.1, 4.8, 4.5, and 4.4 mmol/L for placebo, ZS 5 g, 10 g, and 15 g QD, respectively). A statistically significant greater ($p \leq 0.0001$) number of normokalaemic days during the maintenance phase were observed for each ZS group vs. placebo. The mean number of normokalaemic days increased with increasing dose of ZS (13.4, 13.9, and 16.8 days for ZS 5 g, 10 g and 15 g QD, respectively) vs. 7.4 days for placebo (out of 22 days in total).

This suggests that ZS might have an absolute hypokalaemic effect and might be beneficial for the mild to moderate hyperkalaemia if dosed at mild to moderate hyperkalemia level in 5 g to 10 g dosages in ~80% of patients. The proposed dosage to start with dose "up to 10 g" seems not entirely justified as the median time to normalization of S-K values (to 3.5 - 5.0 mmol/L) during first 48 hours was statistically significantly

reduced with the ZS 10 g TID dose vs. placebo, but not with the ZS 5 g, 2.5 g, or 1.25 g TID doses, that was 1.1 hours vs 3.9, 3.8, and 4.0 respectively. This is in disagreement with median time to 0.5 mmol/L decrease in S-K values that were statistically significantly different from placebo with the dosages ZS 10 g, 5 g, and 2.5 g TID dosages vs. placebo, but not with the 1.25 g TID dose. In the acute therapy, median time to normalization of S-K values (to 3.5 - 5.0 mmol/L) during first 48 hours was statistically significantly reduced with the ZS 10 g TID dose vs. placebo only but not with the ZS 5 g, 2.5 g, or 1.25 g TID, that were 1.1 hours vs 3.9, 3.8, 4,0, and 4,0 respectively. In addition, there was significant proportion of patients not achieving normokalaemia during first 24h. For the maintenance therapy the primary analysis in the study 003 subacute phase showed that the total numbers of normokalaemic days were statistically significantly greater in the ZS 10 g QD (10.2 vs. 8.2 days), 5 g QD (9.0 vs. 6.0 days), and 2.5 g QD (8.6 vs. 6.2 days) groups compared with their corresponding placebo controls. In the Study 004, median time to hyperkalemia from the maintenance phase baseline was 7 and 14 days in the placebo and ZS 5 g QD groups, respectively. This is useful information to address for the efficacy monitoring purpose. The applicant was also asked to summarise the data for relapses for various baseline S-K values before maintenance phase. Dose dependence in time to relapse was found with median time for 5 g dose ranging from 4 to 21 days depending on the baseline S-K values.

In Study 004, subjects who achieved normokalaemia following ZS 10 g TID in the acute phase were randomized to 28 days of placebo, ZS 5 g, 10 g, or 15 g QD dosing during the maintenance phase. ZS met the primary efficacy endpoint of mean S-K value during the maintenance phase at all 3 doses of ZS. Each ZS group had a statistically significantly ($p \leq 0.0001$) smaller mean S-K value vs. placebo. The primary efficacy analysis for the maintenance effect in study 003 incorporated both normokalaemic (24/49 for dose 1.25 g QD, 33/54 for dose 2.5 g QD, 40/64 for dose 5 g QD, and 50/63 for dose 10 g QD) and non-normokalsemic patient at the end of subacute phase. The proportions of subjects with S-K values ≤ 5.1 mmol/ ranged between 77.3% and 84.2% during the extended dosing phase (study 004E) time points up through study Day 239, with an average throughout study day 239 of 80.7%. The CHP asked the applicant to reanalyse the data for both pivotal studies and calculate the cumulative number of normokalaemic days where the subjects are normokalaemic for the entire primary endpoint time in subacute/maintenance phases. The additional analyses for studies 003, 004 and 004E showed dose dependent proportions of patients who remained normokalaemic during the entire subacute phases that were numerically higher as compared to placebo, i.e., ranging from ~30% to 49% as compared to 26% in placebo group in study 003 and ranging from 27% to 52% as compared to 12% in placebo group. The respective proportions of patients who remained normokalaemic during entire maintenance period of 1 year was ~16%. During CHMP assessment of these results, it was agreed to simplify the indication to “Lokelma is indicated for the treatment of hyperkalaemia in adult patients”. Several other changes were introduced into SmPC, such as posology scheme and mode of administration in order to bring clarity and to adequately inform the prescribers about the safe and efficacious use of Lokelma.

2.5.4. Conclusions on the clinical efficacy

The CHMP considers the clinical efficacy data submitted by the applicant are sufficient to conclude on a positive benefit/risk balance.

2.6. Clinical safety

Patient exposure

Safety data were analysed for the safety population, defined as all subjects who took at least 1 dose of study drug during the particular phase. The primary evaluation of safety is based on the data accumulated from the 4 completed Phase 2/3 studies. Data from Studies ZS-002, EUZS-003, and ZS-004 have been pooled to produce safety summaries. As of 7 December 2015 a total of 1,980 subjects (1760 patients and 220 healthy volunteers) have been exposed to at least 1 dose of ZS in the clinical program. Subject disposition data are presented by acute phase and extended dosing (see table below). The period of 48 hours up to 96 hours in Study ZS-002, 48 hours in Studies EUZS-003 and ZS-004, and 24 hours up to 72 hours in ongoing study ZS-005 is described as Acute Phase. Acute Phase was double-blind and placebo-controlled in Studies ZS-002 and EUZS-003, and open-label in Studies ZS-004 and ZS-005.

Exposure to ZS by study and by dose (all studies as of 7 December 2015)

	Phase 1 ZS QD						
Study, n	**5 g**					**10 g**	
ZS-006	15					15	
ZS-009						190	
	Phase 2 and 3 Acute Phase TID						
		ZS					
Study, n	**Placebo**	**0.3 g**	**1.25 g**	**2.5 g**	**3 g**	**5 g**	**10 g**
ZS-002	30	12			24		24
EUZS-003	158		154	141		157	143
ZS-004							258
ZS-004E							2a
ZS-005 (ongoing)							751
Totals	188	12	154	141	24	157	1176[a]
	Phase 3 Extended Dosing QD					O	
		ZS					
Study, n	**Placebo**	**1.25 g**	**2.5 g**	**5 g**	**10 g**	**15 g**	
EUZS-003	216	95	104	65	63		
ZS-004	85			45	51	56	
ZS-004E					123[b] (starting dose)		

ZS-005 (ongoing)				746 (starting dose)		
Totals	301	95	104	856	162[b]	56

Abbreviations: QD = once daily; TID = three times daily; ZS = sodium zirconium cyclosilicate

[a] *Two subjects who required Acute Phase dosing in Study ZS-004E are counted as part of the Acute Phase 10 g group for Study ZS-004 as all subjects in the Acute Phase received ZS 10 g TID.*

[b] *Of the 123 subjects in Study ZS-004E, 75 are counted as part of the Extended Dosing active dose groups for Study ZS-004.*

While ZS doses varied from 0.3 to 10 g in acute phase and from 1.25 to 15 g in extended dosing, the primary focus of the safety assessment is the comparison of ZS 10 g TID to placebo in the acute phase and ZS 5 g, 10 g, and 15 g QD to placebo during extended dosing. In the acute phase, 1101 subjects were treated (188 with placebo, 913 with ZS) mainly in studies ZS-002, EUZS-003, and ZS-004. For acute phase, extent of exposure was summarised by number of doses received; the majority of the subjects in each of the treatment groups received between 4 and 6 doses of study drug (94.7% placebo; 97.4% total ZS), see table below:

Acute Phase: Extent of Exposure (Safety Population of finished studies; Studies ZS-002, EUZS-003, and ZS-004)

Number of Doses Received, n	Placebo (N = 188)	ZS ≤ 3 g TID (N = 331)	ZS 5 g TID (N = 157)	ZS 10 g TID (N = 425)	Total ZS
≥1	188	331	157	425	913
1 to 3	1	6	4	9	19
4 to 6	178	320	153	416	889
7 to 9	6	4	0	0	4
10 to 12	3	1	0	0	1

Abbreviations: TID = three times daily; ZS = sodium zirconium cyclosilicate

A total of 1,273 subjects have received at least 1 dose of ZS during extended dosing (including ongoing study). Among subjects participating in the long-term exposure studies (ZS-004/ZS-004E combined and ZS-005), 765 have been treated for >1 month to 12 months, 432 for >180 days and 145 for >360 days with doses intended for clinical use. This exposure level is compliant with ICH guidance E1. For Extended dosing, extent of exposure was summarized by the number of days of treatment below.

Extended Dosing: Extent of Exposure (Safety Population; Completed Studies EUZS-003 and ZS-004 Pooled and ZS-004E, and Ongoing Study ZS-005 as of 7 December 2015)

Number of Days of Treatment, n		Starting Dose of ZS in Extended Dosing				Titration	Titration	
	Placebo[a]	≤2.5 g QD	5 g QD	10 g QD	15 g QD	ZS-004E 10 g QD	ZS-005 5 g QD	Total ZS
≥ 1	301	199	110	114	56	123[b]	746[C]	1273 (100%)
>30						113	652	765 (60.1%)
> 90						89	526	615(48.3%)
> 180						68	364	432 (33.9%)
> 270						61	247	308 (24.2%)
> 360						0	145	145 (11.4%)

Abbreviations: QD = once daily; TID = three times daily; ZS = sodium zirconium cyclosilicate

[a] *Following treatment with ZS TID during the Acute Phase.*

[b] *Of the 123 subjects in Study ZS-004E, 75 are already counted as part of the Extended Dosing active dose groups for Study ZS-004.*

[C] *Exposure data are incomplete for 1 subject in ongoing Study ZS-005; the subject is only included in the ≥ 1 day exposure category.*

Adverse events

The applicant stated that overall incidence of treatment-emergent adverse events (TEAEs) during the acute phase was comparable among the treatment groups (placebo 10.6%, ZS ≤ 3 g TID 12.4%, ZS 5 g TID 14.0%, ZS 10 g TID 10.4%). The only TEAE reported by ☐ 2.0% of sub diarrhea (2.1% in placebo group, 2.4% in the ZS ≤ 3 g TID group, 1.9% in ZS 5 g TID group, and 1.2% in ZS 10 g TID group). According the applicant, the overall incidence of gastrointestinal (GIT) disorders was comparable among the treatment groups (5.3% placebo; 3.6% ZS ≤ 3 g TID, 3.8% ZS 5 g TID, and 4.5%

ZS 10 g TID). The incidence of hypokalemia (a potential concern with any potassium-lowering drug) at the ZS 10 g TID dose was very low (0.7%; 3/425) in the acute phase, and all cases were classified as mild (S-K between 3.0 to 3.4 mmol/L). The only TEAEs considered related to study drug that were reported by ☐ 1% of subjects in any treatment group were diarrhea, nausea, and vomiting. The overall incidence of GIT disorders considered related to study drug was comparable among the treatment groups (3.2% placebo; 1.8% ZS ≤ 3 g TID, 3.2% ZS 5 g TID, and 2.1% ZS 10 g TID).

Only one subject reported TEAEs that were considered by the investigator to be severe. During extended dosing, the overall incidence of TEAEs was highest in the ZS 15 g QD group (44.6%), followed by the ZS 5 g QD (34.5%), ZS 10 g QD (31.6%), placebo (26.6%), and ZS ≤ 2.5 g QD (23.6%) groups. The applicant explained that increased incidence of TEAEs in ZS 15 g QD group was related with the higher frequency of events associated with general disorders and administration site conditions and those associated with infections and infestations. The overall incidence of related TEAEs was higher in the ZS 15 g QD group (see table below), which may be associated with the greater disease burden in this group. No clear dose-related trends were observed among the treatment groups for any specific type of event reported.

Extended dosing: related TEAEs Reported by ≥ 1.0% of subjects in any treatment group by SOC and PT (safety population; studies EUZS-003 and ZS-004)

		Starting dose of ZS in extensioN			
	Placebo[a] (N = 301)	≤ 2.5 g QD (N = 199)	5 g QD (N = 110)	10 g QD (N = 114)	15 g QD (N = 56)
Any Event, n (%)	16 (5.3)	5 (2.5)	8 (7.3)	7 (6.1)	6 (10.7)
System Organ Class Preferred Term, n (%)					
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)
Anaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)
Gastrointestinal disorders	7 (2.3)	3 (1.5)	5 (4.5)	3 (2.6)	2 (3.6)
Constipation	4 (1.3)	1 (0.5)	0 (0.0)	2 (1.8)	1 (1.8)
Diarrhoea	2 (0.7)	2 (1.0)	1 (0.9)	0 (0.0)	0 (0.0)
Dyspepsia	0 (0.0)	0 (0.0)	3 (2.7)	0 (0.0)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (1.8)
Vomiting	0 (0.0)	1 (0.5)	3 (2.7)	0 (0.0)	0 (0.0)
Infections and infestations	2 (0.7)	1 (0.5)	2 (1.8)	1 (0.9)	0 (0.0)
Urinary tract infection[b]					
All events	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)
Supported events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	2 (0.7)	0 (0.0)	0 (0.0)	1 (0.9)	1 (1.8)
Electrocardiogram QT prolonged	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (1.8)
Hypokalaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)

Abbreviations: QD = once daily; TID = three times daily; ZS = sodium zirconium cyclosilicate

[a] Following treatment with ZS TID during the Acute Phase.

[b] Preferred terms associated with urinary tract infections are presented for all reported events and reported events that were supported by urinalysis and/or urine culture results

During extended dosing in study ZS-004E, 82 (66.7%) subjects experienced at least 1 TEAE. Fourteen (11.4%) subjects had TEAEs considered related to study drug. Related AEs reported for more than one subject were muscle spasms (3 subjects; 2.4%), oedema peripheral (2 subjects; 1.6%), electrocardiogram QT prolonged (2 subjects; 1.6%), and hypomagnesaemia (2 subjects; 1.6%).

Ongoing study ZS-005 (as of 7 December 2015): During the acute phase, a total of 26 (3.5%) subjects reported at least 1 TEAE; the most common types of TEAEs reported were gastrointestinal disorders (9 subjects, 1.2%), including nausea, diarrhoea, constipation, and abdominal distension; hypertension was reported in 2 subjects (0.3%). All of the events that occurred during the acute phase were reported in < 1% of subjects. A total of 7 (0.9%) subjects reported at least 1 TEAE considered related to study drug including nausea (2 subjects), diarrhoea (2 subjects), constipation (1 subject), abdominal distension (1 subject), oedema peripheral (1 subject), hyperaesthesia (1 subject), and pruritus (1 subject). During extended dosing, a total of 398 (53.4%) subjects reported at least 1 TEAE, 1408 TEAEs in total. The most common events were hypertension (8.2%); events related to oedema (8.0%) (include oedema peripheral, oedema, pulmonary oedema, and generalized oedema); and constipation (5.0%). The incidence of these events did not show clear increases in proportions with increasing duration of exposure to ZS, as shown in table below.

Extended Dosing: Summary of treatment-emergent adverse events reported by ≥2.0% of subjects overall by system organ class and preferred term and by time (Safety Population; Ongoing Study ZS-005 as of 7 December 2015)

	Overall	Events Reported Up To		
	Events (N = 746)	6 months (N = 436)	9 months (N = 287)	12 months (N = 155)
System Organ Class Preferred Term, n (%)				
Any Event, n (%)[a]	398 (53.4)	203 (46.6)	150 (52.3)	73 (47.1)
Blood and lymphatic system disorders	37 (5.0)	14 (3.2)	8 (2.8)	6 (3.9)
Anaemia	28 (3.8)	11 (2.5)	7 (2.4)	5 (3.2)
Cardiac disorders	53 (7.1)	14 (3.2)	12 (4.2)	7 (4.5)
Cardiac failure congestive	15 (2.0)	4 (0.9)	3 (1.0)	2 (1.3)
Gastrointestinal disorders	117 (15.7)	55 (12.6)	41 (14.3)	24 (15.5)
Constipation	37 (5.0)	19 (4.4)	10 (3.5)	5 (3.2)
Nausea	32 (4.3)	15 (3.4)	13 (4.5)	6 (3.9)
Diarrhoea	26 (3.5)	10 (2.3)	9 (3.1)	7 (4.5)
Vomiting	22 (2.9)	9 (2.1)	9 (3.1)	5 (3.2)
General disorders and administration site conditions	90 (12.1)	55 (12.6)	37 (12.9)	21 (13.5)
Oedema peripheral	45 (6.0)	31 (7.1)	21 (7.3)	11 (7.1)
Oedema	16 (2.1)	7 (1.6)	3 (1.0)	2 (1.3)
Chest pain	16 (2.1)	6 (1.4)	5 (1.7)	1 (0.6)
Infections and infestations	146 (19.6)	82 (18.8)	68 (23.7)	37 (23.9)
Urinary tract infection	34 (4.6)	14 (3.2)	12 (4.2)	7 (4.5)
Upper respiratory tract infection	25 (3.4)	17 (3.9)	16 (5.6)	8 (5.2)
Nasopharyngitis	17 (2.3)	10 (2.3)	7 (2.4)	7 (4.5)
Pneumonia	17 (2.3)	6 (1.4)	7 (2.4)	2 (1.3)
Musculoskeletal and connective tissue disorders	60 (8.0)	38 (8.7)	32 (11.1)	16 (10.3)
Muscle spasms	20 (2.7)	11 (2.5)	10 (3.5)	3 (1.9)
Arthralgia	15 (2.0)	11 (2.5)	8 (2.8)	5 (3.2)
Nervous system disorders	43 (5.8)	22 (5.0)	22 (7.7)	16 (10.3)
Headache	15 (2.0)	9 (2.1)	9 (3.1)	8 (5.2)
Vascular disorders	78 (10.5)	41 (9.4)	34 (11.8)	18 (11.6)
Hypertension	61 (8.2)	34 (7.8)	28 (9.8)	14 (9.0)

[a] *Subjects reporting more than 1 event during Extended Dosing are counted only once in the total number of Subjects reporting any event.*

In extended dosing of the Study 005, 1332/1408 (94.6%) TEAEs were considered unrelated to study drug. In total, 76 (10.2%) subjects reported TEAEs considered related to study drug, the most commonly constipation (2.9%, 22 subjects), nausea (1.5%, 11 subjects), and oedema peripheral (1.2%, 9 subjects).

Based on study 005 analysis, the applicant changed safety profiling. The SmPC Section 4.8 was updated accordingly to the interim analysis of Study 005. This was challenged by CHMP due to lack of justification for each and every case of exclusion of adverse reaction reported by the investigator is provided. The applicant was asked to provide (1) thorough narrative analysis of the ADRs reported by investigators and (2) combine the events into syndromes (do the clustered safety specification). In response to that, the applicant explained the stepwise approach they took for the safety specification. In this respect volemia and potassium changes were encountered as safety signals as well as QTs changes. The applicant examined the signals generated by the investigators for possible gastrointestinal events (constipation, diarrhoea, abdominal pain/distension and nausea), possible hypersensitivity reactions (rash, pruritus, and dermatitis), and possible changes in serum electrolytes content (decreased or increased calcium and decreased magnesium). This approach is based either on the fact that findings are not essentially different form placebo controlled study results or due to fact that changes are common in this population (for diarrhoea, magnesium and calcium changes), low potential for this side effect (for calcium changes) or due to absence of clear mechanistic associations (for gastrointestinal events, such as constipation). The CHMP did not agree on this approach due to the incompleteness of the analysis and lack of data to exclude ADRs from the safety specification. Placebo controlled data are relevant to this discussion but do not override the value of clear observational findings of the investigators from the longer term, exposures and the class effects with other similar products. The deletions of observations are not justified also by clear alternative explanations for particular events such as increased/decreased calcium/magnesium supplementation, alternative reasons for GIT or hypersensitivity events. If this information had not been collected during long term study there is acknowledged difficulty to both either to exclude or to confirm the opinion of the investigator. Thus, the next study should be designed in such a way that these events would be assessed more specifically.

Therefore, before this information is available, the CHMP preferred to take more precautionary approach and requested inclusion of the possible ADRs into safety specification by statement in Section 4.8:Long term exposure (interim data): In an ongoing clinical trial with open label exposure of Lokelma up to 1 year in 751 subjects several events were reported as related by investigators: possible gastrointestinal events (constipation, diarrhoea, abdominal pain/distension and nausea), possible hypersensitivity reactions (rash, pruritus, and dermatitis), and possible changes in serum electrolytes content (decreased or increased calcium and decreased magnesium).“

In response to this position of CHMP, the applicant made an further analysis and provided additional justification about the uncertainty regarding possible changes in serum electrolytes content (decreased or increased calcium and decreased magnesium). For these changes specific patient confounding factors were provided, as well as in-vitro and in-vivo non-clinical data and thus, the electrolyte changes could be considered as not related for the time being. The alternative wording is reasonable to accept for the time being, until final analysis will be available. Thus, the alternative wording proposed for Section 4.8 of SmPC is acceptable: *“In an ongoing clinical trial with open label exposure of Lokelma up to 1 year in 751 subjects, the following events were reported as related by investigators: gastrointestinal events (constipation, diarrhoea, abdominal pain/distension, nausea and vomiting); and hypersensitivity reactions (rash, pruritus, and dermatitis). A causal relationship between these events and Lokelma has not been finally established.”*

Serious adverse event / deaths / other significant events

Among the completed phase 2/3 ZS studies, 2 deaths have been reported (0.2%; 2/1,009):

- in Study EUZS-003, 71-year-old male subject, treated with ZS 5 g in the Acute Phase (TID) and Extended Dosing (QD), died due to respiratory arrest on Study Day 4 (1 day after last ZS dose).
- in Study ZS-004, 60-year-old female subject, treated with ZS 10 g in the Acute Phase (TID) and Extended Dosing (QD), died due to myocardial infarction on Study Day 24 (4 days after last ZS dose).

No deaths were reported during long-term extension Study ZS-004E. Three deaths, 1 due to haemorrhagic cystitis, 1 due to interstitial lung disease, and 1 due to a severe cardiovascular event, were reported in long-term ongoing study ZS-005 up through 15 July 2015, Thus, the combined overall incidence of death across the ZS clinical program up through 15 July 2015 is 0.3% (5/1,592 subjects). All events were considered unrelated to the study drug.

Acute Phase: Studies ZS-002, EUZS-003, and ZS-004: None of the 913 subjects treated with ZS during acute phase dosing experienced a serious TEAE; one placebo subject experienced a serious TEAE of acute renal failure.

Extended dosing: Studies EUZS-003 and ZS-004: Twenty (4.2%, including the 2 deaths) of the 479 subjects treated with ZS during extended dosing experienced at least 1 serious treatment-emergent adverse event compared with 5 (1.7%) of 301 placebo subjects. During extended dosing, the overall incidence of serious TEAEs tended be higher among ZS-treated subjects in the 5 g and 15 g QD dose groups and comparable between placebo and subjects in the ZS 2.5 g and 10 g QD dose groups (1.7% in the placebo group, 3.0% in the ≤ 2.5 g QD group, 7.3% in the 5 g QD group, 2.6% in the 10 g QD group, and 5.4% in the 15 g QD group). The Applicant explained that no dose-response relationship was observed. None of the events by Preferred Term was reported in more than a single subject. The only serious TEAE considered possibly related to study drug was severe gastroenteritis in the placebo group.

Extended dosing: long-term Study ZS-004E: Twenty four (19.5%) of 123 subjects experienced serious TEAEs. Most serious adverse events were reported for a single subject; 2 (1.6%) subjects each experienced cardiac failure congestive, pneumonia, urinary tract infection, and chronic obstructive pulmonary disease. None of the serious TEAEs were considered related to study drug administration.

Other significant events:

Fluid overload and cardiac failure: Sodium (together with hydrogen) contained in the drug substance of ZS as a counter ion could be released from the crystal and might be absorbed as the drug exerts its effect in reducing levels of S-K. If sodium is absorbed, it could be associated with an increased risk of fluid overload in predisposed patients with severe heart failure or renal insufficiency, conditions which may be prevalent in patients with hyperkalemia. The applicant explained that no increase in urinary sodium has been observed with ZS administration, thus it is unlikely that sodium is being absorbed and thus is unrelated to the increased incidence of oedema-related events. During the acute phase of studies ZS-002, EUZS-003, and ZS-004, no subjects had a TEAE identified for inclusion in the cardiac failure broad SMQ; 4 ZS-treated subjects had TEAEs that were identified for inclusion in the haemodynamic oedema, effusions, and fluid overload SMQ. Two subjects (1 in the ZS ≤ 3 g TID group and 1 in the ZS 5 g TID group) had events of oedema and 2 subjects (1 in the ZS ≤ 3 g TID group and 1 in the ZS 10 g TID group) had events of oedema peripheral. TEAEs considering haemodynamic oedema, effusions, and fluid overload broad SMQ for

the pooled Extended Dosing analyses of Studies EUZS-003 and ZS-004, and for long-term study ZS-004E are summarized below.

Extended Dosing: Oedema-Related TEAEs Reported by Subjects in Pooled Studies EUZS-003 and ZS-004 and Study ZS-004E (Safety Population)

		Starting Dose of ZS in Extended Dosing				Titration
	Placebo[a] (N = 301)	≤ 2.5 g QD (N = 199)	5 g QD (N = 110)	10 g QD (N = 114)	15 g QD (N = 56)	ZS-004E (N = 123)
Any Event, n (%)	5 (1.7)	2 (1.0)	2 (1.8)	6 (5.3)	8 (14.3)	16 (13.0)
Preferred Term, n (%)						
Generalised oedema	0	0	0	0	2 (3.6)	0
Oedema	0	0	1 (0.9)	1 (0.9)	1 (1.8)	4 (3.3)
Oedema peripheral	5 (1.7)	2 (1.0)	0	5 (4.4)[b]	6 (10.7)	10 (8.1)[b]
Pulmonary oedema	0	0	1 (0.9)	0	0	2 (1.6)

Abbreviations: QD = once daily; TID = three times daily; ZS = sodium zirconium cyclosilicate [a]Following treatment with ZS TID during the Acute Phase, [b]One subject (4004-002) with a medical history of peripheral edema reported this event in Study ZS-004 and in Study ZS-004E.

In pooled studies EUZS-003 and ZS-004, 18 ZS-treated subjects and 4 placebo subjects had a total of 24 oedema-related events; 17/18 subjects were determined to be at risk for fluid overload-related events. A higher incidence was observed with the ZS 15 g QD dose (14.3%), with generally similar rates observed among the placebo (1.7%, 5 subjects), ZS ≤ 2.5 g QD (1.0%, 2 subjects), ZS 5 g QD (0.9%, 1 subject), and ZS 10 g QD (5.3%, 6 subjects) groups. All of the other events reported in this SMQ were considered mild or moderate in severity. One event of mild oedema peripheral reported in the ZS 10 g QD group (007-023) was considered probably related to study drug. More than half of the events (14 of 24 events) resolved without requiring study drug withdrawal and ~50% of the events required treatment, typically an adjustment in diuretic dosing. In study ZS-004E, 16 (13%) subjects had a total of 17 oedema-related events; 11/16 subjects were determined to be at substantial increased risk for fluid overload-related events. In Study ZS-004E (≤11 months of dosing), the overall rate of oedema-related events was slightly less than in the ZS 15 g QD group in Study ZS-004 (≤28 days of dosing), 13.0% *vs.* 14.3%, respectively. Overall, among the 33 (6.3%; 33/527) ZS-treated subjects who reported oedema-related adverse events during extended dosing in studies EUZS-003, ZS-004, and ZS-004E, 31 (93.9%) had events that were considered mild or moderate in severity, 19 (57.6%) required treatment for the event, 3 (9.0%) had an event that was serious, and 2 (6.1%) discontinued study drug due to the event.

In ongoing study ZS-005, as of 7 December 2015, a total of 83 (11.1%) subjects have reported adverse events associated with fluid overload and cardiac failure. The applicant was asked to address the long-term risk of hypervolemia. In response to that the applicant reviewed cases of subjects with fluid overload events and agreed on dose dependence on this event and credits the occurrence of oedema to comorbidities, which predispose to hypokalaemia. Hypervolemia is included in the SmPC of Lokelma, section 4.8.

Urinary tract infections: Non-clinical toxicology studies with the non-protonated form of ZS (ZS-9) showed an increase in urinary pH at the higher dosages, which was accompanied by urinary bladder inflammation in rats and minimal to mild mixed leukocyte infiltration in the kidneys of dogs that was associated with minimal to mild tubular regeneration and occasionally minimal tubular degeneration/necrosis and pyelitis. Renal findings in dogs were ameliorated by administration of potassium or the use of partially protonated

form of ZS-9. Thus, urinary tract infection was prospectively identified as an adverse event of special interest in the ZS clinical programme. The applicant noted that overall incidence of urinary tract infections is comparable to the incidence reported for this population in the literature.

Laboratory findings

The MAA recorded vital signs, haematology (hemoglobin, hematocrit, and white and red blood cells), serum chemistry (S-K, sodium, magnesium, calcium, phosphates, BUN, bicarbonates, pH, and eGFR), urine chemistry and ECG parameters during both acute and extension phase studies (Studies 003 and 004, as well as during extension study (004E). Number of AE were to be considered as AESI (AE observed during non-clinical development phase (increase in serum HCO3 and urine pH, decrease in BUN, signs of bladder and renal degeneration/inflammation) together with AE known for other similar products (hypomagnesaemia, hypocalcemia, constipation, poor gastrointestinal tolerability and electrolytes disturbances for sodium polystyrene sulfonate (SPS) and calcium polystyrene sulfonate (CPS). The clinical development program confirmed several findings, demonstrating a consistent dose-related increase in serum bicarbonate (approximately 10 to 15% increase from baseline with the 10 g and 15 g ZS doses; Study EUZS-003 and Study ZS-004) and a dose-dependent decrease in BUN (between 5 and 10% decrease from baseline with the 10 g ZS dose; Study EUZS-003 and Study ZS-004). There was also observed an increase in BUN in Study ZS-004E. The Applicant explained that in a patient population who tends to be acidotic and to have reduced kidney function, an increase in bicarbonate and companion decrease in BUN might be beneficial, although the clinical program was not designed to evaluate any improved outcome. This is agreed. The dose dependent QTc changes were observed during acute treatment phase (Study 003). In addition, number of withdrawals due to QTc changes was noticed during maintenance phase (Studies 004/004E). Although the view of the MAA could be shared that these are related to S-K decrease events more predictable risk management is needed. Relevant warnings were include into SmPC. The QTc changes were observed during both treatment phases dose dependently during acute phase (study 003) and leading to withdrawals. The applicant was asked to comment and justify the appropriateness of the ADR assignment process used. The applicant described their step-wise approach, which was reasonable to accept. Hyper- and hypokalaemia: although the applicant notes that there were no important dose-related trends for the proportions of the subjects who had other than efficacy related S-K post-baseline electrolytes values, there were clearly non-negligible proportion of patients (~20%) with abnormal S-K values (~6% (7/123) of confirmed hypokalsemia and 13% (16/123) hyperkalemia experiencing patients in Study 004E. Although dataset is representative only of a limited safety size, these findings highlights the need for more predictable risk management. Relevant warnings were added to the SmPC for the prescribing physicians.

Safety in special populations

All treatment-emergent adverse events (TEAEs) for the acute phase in studies ZS-002, EUZS-003, and ZS-004, and for extended dosing in studies EUZS-003, and ZS-004 are summarized by intrinsic and extrinsic factors. Data presented in this section are limited to those TEAEs reported for ≥ 2.0% of subjects in any treatment group for the pooled analyses of acute phase and extended dosing. For analysis, patients exposed to the proposed ZS doses for labelling (ZS 10 g TID for acute phase and ZS 5 g, 10 g, and 15 g QD for extended dosing) and placebo in safety population were taken.

Acute phase: The only TEAE reported by ≥ 2.0% of subjects in any treatment group was diarrhoea; no clinically important trend was apparent for the incidence of diarrhoea by any of the intrinsic (age, gender,

race, baseline weight, baseline serum potassium, CKD, heart failure, diabetes mellitus) or extrinsic (geographic region, use of RAAS inhibitors, use of diuretics) factors.

Age (< 65 years and ≥ 65 years): For extended dosing, notable differences between age groups for the ZS 15g QD dose included oedema peripheral (17.9% vs. 3.6%), generalized oedema (7.1% vs. 0%), and QT prolonged (7.1% vs. 0%), which were more commonly observed among subjects ≥ 65 years of age, whereas fatigue was more commonly observed among subjects < 65 years of age (7.1% vs. 0%).

	< 65 years of Age				**≥ 65 years of Age**			
		Starting Dose of ZS in Extension (QD)				**Starting Dose of ZS in Extension (QD)**		
	Placebo (N = 130)	**5 g (N = 53)**	**10 g (N = 51)**	**15 g (N = 28)**	**Placebo (N = 171)**	**5 g (N = 57)**	**10 g (N = 63)**	**15 g (N = 28)**
Any Event n (%)	39 (30.0)	16 (30.2)	17 (33.3)	11 (39.3)	41 (24.0)	22 (38.6)	19 (30.2)	14 (50.0)

Gender: For extended dosing, following ZS 5g QD dose, renal failure was more commonly observed in males (5.0%) than females (0%); events of renal failure were not observed in the ZS 10g or 15g QD groups. For the ZS 10g QD dose, urinary tract infection was more commonly observed in females (7.7%) than males (0%). In the ZS 15 g QD group, oedema peripheral (15.0% vs. 0%), diarrhoea (5.0% vs. 0%), nasopharyngitis (7.5% vs. 0%), electrocardiogram QT prolonged (5.0% vs. 0%), and generalized oedema (5.0% vs. 0%) were more commonly observed among males than females.

	Female				**Male**			
		Starting Dose of ZS in Extension (QD)				**Starting Dose of ZS in Extension (QD)**		
	Placebo (N = 123)	**5 g (N = 50)**	**10 g (N = 52)**	**15 g (N = 16)**	**Placebo (N = 178)**	**5 g (N = 60)**	**10 g (N = 62)**	**15 g (N = 40)**
Any Event, n (%)	33 (26.8)	17 (34.0)	19 (36.5)	5 (31.3)	47 (26.4)	21 (35.0)	17 (27.4)	20 (50.0)

Race (white, black, and other): For extended dosing, following the ZS 5g QD dose, urinary tract infection was more commonly observed among Black vs. White subjects (13.3% vs. 4.3%). In the ZS 15 g QD group, anaemia (33.3% vs. 0%), diarrhoea (22.2% vs. 0%), and generalized oedema (22.2% vs. 0%) were more commonly observed among Black than White subjects. Confirmed hypokalaemia, determined from S-K values in Study ZS-004, was also more commonly observed in Blacks (27.3%; 6 of 22 ZS-treated subjects) than in Whites (4.0%; 5 of 126 ZS-treated subjects). There were insufficient subjects of other races to allow for meaningful treatment group comparisons within race category.

	White				**Black or African American**				**Other**			
		Starting Dose of ZS in Extension (QD)				**Starting Dose of ZS in Extension (QD)**				**Starting Dose of ZS in Extension (QD)**		
	Placebo N = 251	**5 g N=93**	**10 g N = 99**	**15 g N = 46**	**Placebo[a] N = 36**	**5 g N = 15**	**10 g N = 13**	**15 g N = 9**	**Placebo N = 16**	**5 g N = 2**	**10 g N = 2**	**15 g N = 1**
Any Event n (%)	62 (24.7)	31 (33.3)	30 (30.3)	19 (41.3)	14 (38.9)	7 (46.7)	5 (38.5)	6 (66.7)	6 (37.5)	0 (0.0)	1 (50.0)	0 (0.0)

Baseline weight (<85 kg and ≥85 kg): In extended dosing, following the ZS 5g QD dose respiratory tract infection was more commonly observed among subjects <85 kg vs. ≥ 85 kg (5.4% vs. 0%). In the ZS 15 g QD group, fatigue (7.4% vs. 0%), generalized oedema (7.4% vs. 0%), and electrocardiogram QT prolonged (7.4% vs. 0%) were more commonly observed in subjects ≥ 85 kg than in subjects <85 kg.

	< 85 kg				≥85 kg			
		Starting Dose of ZS in Extension (QD)				Starting Dose of ZS in Extension (QD)		
	Placebo (N = 152)	5 g (N = 56)	10 g (N = 58)	15 g (N = 28)	Placebo (N = 147)	5 g (N = 54)	10 g (N = 54)	15 g (N = 27)
Any Event n (%)	44 (28.9)	18 (32.1)	16 (27.6)	7 (25.0)	36 (24.5)	20 (37.0)	20 (37.0)	17 (63.0)

Baseline serum potassium (< 5.5 mmol/L, 5.5 to < 6.0 mmol/L, and ≥ 6.0 mmol/L): In extended dosing, following the ZS 5g QD dyspepsia was more commonly observed among subjects with baseline S-K 5.5 - < 6.0 vs. < 5.5 mmol/L (8.8% vs. 1.4%). For the ZS 10g QD, hypertension was more commonly observed among subjects with baseline S-K 5.5 - < 6.0 mmol/L vs. < 5.5 (5.9% vs. 0%), whereas urinary tract infection was more commonly observed among subjects with baseline S-K < 5.5 mmol/L vs. 5.5 - < 6.0 (5.9% vs. 0%). For the ZS 15g QD, fatigue (8.3% vs. 0%) and nasopharyngitis (8.3% vs. 0%) were more commonly observed among subjects with baseline S-K of < 5.5 mmol/L than with 5.5 - < 6.0 mmol/L, whereas generalized oedema (7.7% vs. 0%) was more common among subjects with baseline S-K 5.5 - < 6.0 mmol/L than with < 5.5 mmol/L.

	< 5.5 mmol/L				5.5 to < 6.0 mmol/L				≥ 6.0 mmol/L			
		Starting Dose of ZS in Extension (QD)				Starting Dose of ZS in Extension (QD)				Starting Dose of ZS in Extension (QD)		
	Placebo N = 206	5 g N =69	10 g N = 68	15 g N = 24	Placebo N = 81	5 g N = 34	10 g N = 34	15 g N = 26	Placebo N = 14	5 g N = 7	10 g N = 12	15 g N = 6
Any Event n (%)	54 (26.2)	19 (27.5)	21 (30.9)	10 (41.7)	21 (25.9)	15 (44.1)	8 (23.5)	12 (46.2)	5 (35.7)	4 (57.1)	7 (58.3)	3 (50.0)

CKD at baseline (eGFR < 60 and ≥ 60 mL/min/1.73 m^2): For extended dosing, following ZS 5g QD, urinary tract infection was more commonly observed among subjects with eGFR < 60 vs. ≥ 60mL/min/1.73 m^2 (7.8% vs. 0%). For the ZS 10 g QD dose included oedema peripheral, which was more commonly observed among subjects with eGFR < 60 vs. ≥ 60 mL/min/1.73 m^2 (5.8% vs. 0%). For the ZS 15 g QD, anaemia (7.3% vs. 0%), oedema peripheral (12.2% vs. 6.7%), and nasopharyngitis (7.3% vs. 0%) were more commonly observed among subjects with eGFR < 60 vs. ≥ 60 mL/min/1.73 m^2. Subjects who experienced oedema and other manifestations of fluid overload tended to have lower eGFRs at baseline (< 30 mL/min/1.73m^2).

	< 60 mL/min/1.73 m^2				≥ 60 mL/min/1.73 m^2			
		Starting Dose of ZS in Extension (QD)				Starting Dose of ZS in Extension (QD)		
	Placebo (N = 213)	5 g (N = 77)	10 g (N = 86)	15 g (N = 41)	Placebo (N = 79)	5 g (N = 30)	10 g (N = 28)	15 g (N = 15)
Any Event n (%)	58 (27.2)	29 (37.7)	32 (37.2)	23 (56.1)	19 (24.1)	7 (23.3)	4 (14.3)	2 (13.3)

History of heart failure. Following ZS 5g QD, dyspepsia was more commonly observed among subjects with vs. without HF (6.7% vs. 1.5%). For ZS 15 g QD, hypertension (8.0% vs. 0%) and fatigue (8.0% vs. 0%) were more commonly observed among subjects with vs without HF.

History of diabetes mellitus: Following ZS 10 g QD, oedema peripheral was more commonly observed among subjects with vs. without diabetes (6.8% vs. 0%). For ZS 15 g QD, oedema peripheral (12.8% vs. 5.9%), influenza (5.1% vs. 0%), nasopharyngitis (7.7% vs. 0%), hypertension (5.1% vs. 0%), fatigue (5.1% vs. 0%), and diarrhoea (5.1% vs. 0%) were more commonly observed among subjects with vs. without diabetes.

Geographic region (US and outside the US): Following ZS 5 g QD, upper respiratory tract infection was more commonly observed among subjects outside the US (16.7%) than in US subjects (1.0%). For ZS 10 g QD, oedema peripheral was more commonly observed among US subjects (5.0%) than in those outside the US (0%). For ZS 15 g QD, anaemia (13.3% vs. 2.4%), diarrhoea (13.3% vs. 0%), influenza (13.3% vs. 0%), and nasopharyngitis (13.3% vs. 2.4%) were more commonly observed among subjects outside the US.

Use of RAAS inhibitors: Following ZS 10 g QD, oedema peripheral (8.6% vs. 2.5%) and urinary tract infection (8.6% vs. 1.3%) were more commonly observed among subjects not using RAAS inhibitors. For ZS 15 g QD, diarrhoea (6.1% vs. 0%), oedema peripheral (15.2% vs. 4.3%), influenza (6.1% vs. 0%), and nasopharyngitis (9.1% vs. 0%) were more commonly observed among subjects using RAAS inhibitors, whereas electrocardiogram QT prolonged (8.7% vs. 0%) and hypertension (8.7% vs. 0%) were more commonly observed among subjects not using RAAS inhibitors.

	RAAS Inhibitor Use				**No RAAS Inhibitor Use**			
		Starting Dose of ZS in Extension (QD)				**Starting Dose of ZS in Extension (QD)**		
	Placebo (N = 206)	**5 g (N = 71)**	**10 g (N = 79)**	**15 g (N = 33)**	**Placebo (N = 95)**	**5 g (N = 39)**	**10 g (N = 35)**	**15 g (N = 23)**
Any Event n (%)	59 (28.6)	25 (35.2)	24 (30.4)	17 (51.5)	21 (22.1)	13 (33.3)	12 (34.3)	8 (34.8)

Use of diuretics: Following ZS 5g QD, renal failure was more commonly observed among subjects using than not using diuretics (6.3% vs. 0%). For ZS 10g QD, dose included urinary tract infection was more commonly observed among subjects not using diuretics (5.7%) than in those using diuretics (0%). For ZS 15g QD, dose included anaemia (12.5% vs. 0%), fatigue (8.3% vs. 0%), generalized oedema (8.3% vs. 0%), and oedema peripheral (16.7% vs. 6.3%), and hypertension (8.3% vs. 0%) were more commonly observed among subjects using diuretics.

	Diuretic Use				**No Diuretic Use**			
		Starting Dose of ZS in Extension (QD)				**Starting Dose of ZS in Extension (QD)**		
	Placebo (N = 118)	**5 g (N = 48)**	**10 g (N = 44)**	**15 g (N = 24)**	**Placebo (N = 183)**	**5 g (N = 62)**	**10 g (N = 70)**	**15 g (N = 32)**
Any Event n (%)	37 (31.4)	22 (45.8)	16 (36.4)	13 (54.2)	43 (23.5)	16 (25.8)	20 (28.6)	12 (37.5)

Safety related to drug-drug interactions and other interactions

There are no additional specific safety data relevant to drug-drug interactions and other interactions.

Discontinuation due to adverse events

The applicant calculated that during the acute phase dosing, the incidence of TEAEs that led to premature discontinuation of study drug was similar between ZS- (0.7%; 6/913) and placebo-treated (0.5%; 1/188) subjects. No dose-response relationship was observed for the overall incidence (≤ 3 g TID: 0.9%; 5 g TID: 0.6%; and 10 g QD: 0.5%) or for any specific type of TEAE that led to premature discontinuation of study drug. During the extended dosing, 11/479 (2.3%) subjects treated with ZS experienced at least 1 TEAE that led to premature discontinuation of study drug *vs.* 1/301 (0.3%) of placebo subjects.

Post marketing experience

They are currently no post-marketing data on Lokelma, since the medicinal product is not authorised.

2.6.1. Discussion on clinical safety

Clinical safety data were gathered from five studies: 006, 002, 003, 004 and 004E. In addition, preliminary results were submitted from the ongoing study 005. In total, 913 patients in acute phase and 527 patients in extended phase were exposed to ZS. As of 7 December 2015, a total of 1,980 subjects (1760 patients and 220 healthy volunteers) have been exposed to at least 1 dose of ZS in the clinical programme.
Extended phase was investigated in double blind and placebo controlled studies 003 (for 12 days, 327 ZS vs 216 placebo patients) and study 004 (for 28 days, 152 ZS vs 85 placebo patients) and in open-label study 004E (for up to 11 months) and intermediate results of study 005.
The applicant recorded TEAE and ADRs therapy during acute and extension phase studies 003 and 004, extension study (004E) and intermediate data from ongoing study 005. The applicant claims that overall, TEAE incidences were not essentially different in ZS vs placebo groups in comparative studies during acute phase studies with exception of highest dose in extension phase studies. The higher proportions of TEAE in highest ZS group (15 g QD) in extension studies are likely to be associated with general disorders (mainly generalised and peripheral oedema). The overall ADR incidences were also comparable in ZS vs placebo groups in comparative studies (Studies 003 and 004) during acute phase studies (~ 2 to 3% vs ~3% in ZS vs placebo arms, respectively). There is no clear dose-related trends observed among the treatment groups for any specific type of event reported. The proportions of ADRs during long-term non-comparative data from study 004E and preliminary result from study 005 show rather similar qualitative findings with in ~11% of patients, represented mainly by oedema (~2%), muscle spasms (~2%), QT prolongation (~2%), and hypomagnesemia (~2%). Intermediate results from study 005 do not show new findings for the current intermediate evaluation. Furthermore, the applicant recorded deaths and serious TEAE during the acute and the extension phase studies (studies 003 and 004, as well as during long-term studies (004E and 005). Eight deaths are reported (1 in study 003, 1 in study 004 and 6 in study 005); none of them related to study drug by principal investigator. No of SAEs were reported for acute phases and higher proportions were reported for extended phases (4.2% vs 1.7%) but without clear tendencies in either ZS or placebo groups as well as no clear dose response can be observed. Rather high proportion (~20%) of subjects experienced SAEs in the long-term extension study (study 004E), some of them leading to withdrawals but without clear time dependence. Immunologic effects were not specifically tested.
The applicant recorded discontinuation events during both, the acute, and the extension phase studies (studies 003, 004, 004E) and concluded that during the acute phase dosing, the incidence of TEAEs that led to premature discontinuation of study drug was similar between ZS (0.7%; 6/913) and placebo-treated (0.5%; 1/188) subjects. No dose-response relationship was observed for the overall incidence or for any

specific type of TEAE that led to a premature discontinuation of study drug. Higher incidence in these 2 dose groups was possibly attributable to study ZS-004, where subjects randomised to the ZS 5 g and 15 g QD doses had a greater disease burden at baseline than subjects in the placebo and ZS 10 g QD dose groups.

From the safety database all the adverse reactions reported in clinical trials have been included in the SmPC.

2.6.2. Conclusions on the clinical safety

In summary, as there are no safety concerns and the long-term safety is defined based on sufficient safety population. Several methodological issues were raised for definitive representation of safety profile but these have been satisfactorily resolved mainly by defining the risk profile of the Lokelma in the PI and in the RMP. In addition, it is considered that the results of the study 005 will be presented post-marketing as the post-marketing commitment in the RMP.

2.7. Risk Management Plan

Safety concerns

Important identified risks	Hypokalaemia, Fluid overload
Important potential risks	Arrhythmia
Missing information	Long term use beyond one year, Use in pregnancy, Use in patients on dialysis, Use in patients with severe hyperkalaemia

Pharmacovigilance plan

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
ZS-005: A Phase 3 Multicenter, Multi-dose, Open-label Maintenance Study to Investigate the Long-term Safety and Efficacy of ZS (Sodium Zirconium Cyclosilicate), an Oral Sorbent, in Subjects With Hyperkalemia (category 3)	To generate open-label, long-term (up to 12 months) safety and tolerability data for ZS in subjects with hyperkalemia (serum potassium [S-K] ≥ 5.1 mmol/L).	Long term safety	Ongoing	Final study report Q3 2017

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hypokalaemia	Product labelling	Not applicable
Fluid overload	Product labelling	Not applicable
Arrhythmia	Product labelling	Not applicable
Long term use beyond one year	Product labelling	Not applicable
Use in pregnancy	Product labelling	Not applicable
Use in patients on dialysis	Product labelling	Not applicable
Use in patients with severe hyperkalaemia	Product labelling	Not applicable

Conclusion

The CHMP and PRAC considered that the risk management plan version 1 edition 4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the

requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The new EURD list entry will use the EBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The CHMP, based on the available data, considers sodium zirconium cyclosilicate to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Lokelma (sodium zirconium cyclosilicate) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Favourable effects

The main beneficial effect of Lokelma is the hyperkalaemia dose-related decreasing effect for the acute treatment of hyperkalemia that is achieved in mild to moderate hyperkalaemia:

- in more than two thirds of patients in acute phase during (84% in first 24h), when the therapy is started (either 2.5 or 5 or 10 g is started in TID regimen) and this response rate is higher than is seen in placebo group (in half of population). For patients who are still hyperkalaemic at 24 hours,

another 48 hours of ZS 10 g TID dosing should be given. This would restore normokalaemia in most of the remaining patients;

- may be maintained for longer period of time as compared to placebo (extended dosing with ZS (5 g QD, 10 g QD and 15 g QD) for up to 12 months was effective in maintaining normokalemia. Across Extended Dosing Study Days 8 to 337, 88.3% (95% CI: 81.2%, 93.5%) of subjects had average S-K values ≤ 5.1 mmol/L.).

These effects have a fast onset (in one to 4 few hours) and can be reasonably expected at 48 to 72 hours from the start of therapy. The GI tolerability seems promising as compared to general knowledge for other resins.

3.2. Uncertainties and limitations about favourable effects

The effects of Lokelma in more severe hyperkalaemia cases (>6.5 mmol/l) and when the urgent effect is needed, is not fully determined, as only a small number of such patients studied in the studies. Data on constant maintenance of the effect are limited for the long-term use. This is highlighted in the SmPC. The indication was simplified to state that Lokelma is used for treatment of hyperkalaemia, without specifying the acute or chronic phase. The ongoing study will resolve this uncertainty.

3.3. Unfavourable effects

During the use of Lokelma, GI ADRs were observed in 1 to 3% of subjects during the extended phase. They included mainly the constipation, vomiting, diarrhoea, dyspepsia, and nausea.

Hyperkalaemia (inefficiency, especially during long-term use) and hypokalaemia were also observed, suggesting a possible under- or over-dose. Of the 913 subjects treated with Lokelma during the acute phase, 4 (0.4%) developed a serum potassium below 3.5 mmol/L. Three of the subjects received 10 g TID and one 3 g TID. No other subject had a serum potassium below the lower limit of normal (< 3.5 mmol/L) during the Acute Phase dosing.

Events related to the QTc interval (electrocardiogram QT prolonged and long QT syndrome) were the most common cause of the premature discontinuation of study drug in both, acute and extended dosing in ZS-treated subjects. Electrocardiogram QT prolonged led to premature discontinuation of study drug in 4 ZS-treated subjects in study ZS-004.

Common events of muscle spasms and of oedema were also observed. Pooled analyses of extended dosing from studies ZS-003 and ZS-004 showed a higher incidence of oedema-related events that was observed with the 15 g QD dose (14.3%). Numerically smaller rates were observed in patients receiving placebo (1.7%, 5 subjects), 2.5 g QD (1.0%, 2 subjects), 5 g QD (1.8%, 2 subjects) and 10 g QD (5.3%, 6 subjects). In the acute phase, the incidence of oedema was lower at 0.4% (4 subjects). Over half of these cases resolved without treatment, the remaining resolved after change in medication, e.g. increase in diuretics dose.

3.4. Uncertainties and limitations about unfavourable effects

Limited data have been provided on the long-term safety profile from an ongoing study 005. The ongoing study will resolve this uncertainty. Interpretation of QTc changes is challenged, but the monitoring of the

safety is required as mentioned in the SmPC and this includes monitoring of hypokalaemia. The possibility of a local (non-systemic) uptake of small particles under long term treatment has not been established; however, based on the results of the available nonclinical and clinical studies, no clinical consequences are apparent.

3.5. Effects Table

Effects Table for Lokelma; indicated for the treatment of hyperkalaemia in adult patients, acute and extended use (data cut-off: 7 December 2015).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
nS-K (normokalemia)	Responders at 48 hours (acute effect)	%	10 g: 86.4 5 g: 77.6 2.5 g: 67.9	Pbo: 47.8	**(+/-)**: effect in severe hyperkalemia; **(+)**: PEP supported with SEP in Study 004	Study 003
	Maintenance • during D8 to D29 (22 days)	Days	15 g: 16.8/22 10 g: 13.9/22 5 g: 13.4/22	Pbo: 7.4/22	(SAWP PEP/FDA SEP) **(+/-):** effect for those remaining nS-K at the end & impact of confounding factors; The effect in severe hyperkalemia **(+):** supported with SEP in Study 004 (withdrawal effect)	Study 004
	• during D3 to D14		10 g: 10.2/12 5 g: 9.0/12 2.5 g: 8.6/12	10 g[1]: 8.2/12 5 g[1]: 6.0/12 2.5[1] g: 6.2/12		Study 003
Unfavourable Effects						
Acute phase	GI ADRs: Diarrhoea, nausea vomiting	%	10 g: 2.1 5 g: 3.2 ≤3 g: 1.8	3.2	**(+):** supported with high safety population size	Studies 002, 003 and 004
Extended phase	Any ADR (mainly GI) during 22 days	%	15 g: 10.7 10 g: 6.1 5 g: 7.3 >2.5 g: 2.5	5.3	(+/-): limited long-term safety *profiling* (<);	Studies 003 and 004
Long-term safety	Oedema, muscle spasms, QT prolongation	%	2% each			Study 004E
	Any ADR (mainly GI) during 12 months	%	8.9	No	(+/-): uncontrolled data; not interpretable AE; R for >QTc; > or < S-K; no final long-term Study 005 results available	Study 004E and 005

Abbreviations: ADR: treatment related adverse events; GI: gastrointestinal; nS-K: normokalaemia; Pbo: placebo; PEP: primary endpoint; Pts: patients; R: risk; SEP: secondary endpoint; S-K: serum potassium; (+): strengths; (+/-): uncertainties; (-): weakness; (>): increase or more; (<): decrease of less; (1): pre-randomization group.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The observed hyperkalaemia reducing effect of ZS is important for management of the condition in clinical practice. Untreated hyperkalaemia is deleterious to patient health and if not controlled, poses the risk of further worsening and development of life threatening complications. Current list of unfavourable effects is rather limited but indicates that the product is moderately risky and the adverse reactions can be adequately managed. The post-marketing study will provide further details.

3.6.2. Balance of benefits and risks

The acute effect in hyperkalaemia treatment is important as currently available therapies are not approved for such a broad spectrum of indications. Considering the favourable effect of Lokelma in lowering the serum potassium level and the reported unfavourable effects, the CHMP considered the benefit/risk balance positive and the risk minimisation measures adequate for the product's use.

3.7. Conclusions

The overall B/R of Lokelma is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Lokelma is favourable in the following indication:

Lokelma is indicated for the treatment of hyperkalaemia in adult patients (see section 4.4 and 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and

any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers sodium zirconium cyclosilicate to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.