# 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

Published: 02-04-2015
Last updated: 21-04-2024

Primary objective of this trial is to generate open-label, long-term (up to 12 months) safety and tolerability data for ZS in subjects with hyperkalaemia (S-K * 5.1 mmol/L)Secondary objectives:* To evaluate the portion of ZS-treated subjects in whom...

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Electrolyte and fluid balance conditions |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON43860

**Source**
ToetsingOnline

**Brief title**
ZS-005

### Condition

- Electrolyte and fluid balance conditions

**Synonym**
high potassium levels in blood; hyperkalemia

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** ZS Pharma Inc.
**Source(s) of monetary or material Support:** industry - pharmaceutical company

## Intervention

**Keyword:** Hyperkalemia, Long term safety & efficacy, Phase 3, Potassium absorption

## Outcome measures

### Primary outcome

The primary endpoints will be safety and tolerability as measured by adverse event reporting, vital signs, ECGs, physical examinations and safety laboratory measurements.

### Secondary outcome

Secondary endpoints include:

* The proportion of subjects with average S-K equal to or less than 5.1 mmol/l between Month 3 and Month 12;

* The proportion of subjects who maintain or achieve normal aldosterone values (normal range: 4.0 to 31.0 ng/dL) on ZS at Study Days 85, 176, 267 and 365.

* Change from Acute Phase and Maintenance Phase baselines in S-K levels at all measured Maintenance Phase study days.

* Change in serum-bicarbonate from Acute Phase baseline at all measured Maintenance Phase study days.

Exploratory endpoints include:

* Surrogate markers for possible effects on liver function (bilirubin, AST

and ALT)

* Other electrolytes and renal function parameters (calcium [total and ionized], magnesium, sodium, phosphate, creatinine and BUN).

* Hospitalization and emergency room visits;

* Non-protocol-specified doctor visits;

* Need for additional hyperkalaemia treatments to control serum potassium values;

* A binary composite endpoint defined to be 1 if any hospitalisation, emergency room visit, non-protocol-specified doctor visits, or any new hyperkalaemia treatments are initiated during the first 6 months of the Maintenance phase and 0 if otherwise;

* The proportion of subjects who can maintain normokalemia (defined as S-K between 3.5 and 5.0 mmol/L, inclusive) on ZS at Study Days 85, 176, 267, and 365;

* The proportion of subjects who can maintain S-K values between 3.5 and 5.5 mmol/L, inclusive, on ZS at Study Days 85, 176, 267, and 365;

* Surrogate markers for a possible kidney-preserving effect of ZS (eGFR by Modification of Diet in Renal Disease Study Group equation, urine protein, and urine albumin) as measured by UPCR and UACR.

# Study description

**Background summary**

Hyperkalaemia develops when there is excessive production (oral intake, tissue breakdown) or insufficient elimination of potassium. Insufficient elimination,

(which is the most common cause of hyperkalaemia) can be hormonal, pharmacological (treatment with ACE inhibitors or angiotensin-receptor blockers) or, most commonly, due to reduced kidney function.
Increased potassium values result in disturbance of cellular processes, finally resulting in impairment of neuromuscular, cardiac and gastrointestinal organ systems, responsible for the symptoms seen with hyperkalaemia like malaise, muscle weakness and cardiac arrhythmias like palpitations, bradycardia or tachycardia. Because of the potential for fatal cardiac arrhythmias, hyperkalaemia represents an acute emergency that must be immediately corrected.
Often, hyperkalaemia is detected during routine screening blood tests for a medical disorder or after complications have developed, such as cardiac arrhythmias. Diagnosis is established by serum potassium (S-K) measurements.
Treatment of hyperkalaemia depends on the S-K values. In case where S-K is between 5.0 and 6.5 mmol/L, acute treatment with a potassium-binding resin, combined with dietary advice and possibly modification of drug treatment. If S-K is above 6.5 mmol/L or if arrhythmias are present, emergency lowering of potassium and close monitoring in a hospital setting is mandated. Following treatments would typically be used:
* Sodium polystyrene sulfonate (SPS) is a resin that binds potassium in the intestine and increases faecal excretion, thereby reducing S-K values. However, as SPS has shown to cause intestinal obstruction and potential rupture, diarrhoea needs to be simultaneously induced, significantly reducing the palatability of the treatment. Even without the induction of diarrhoea, a substantial portion of patients complain from gastrointestinal symptoms such as constipation, abdominal pain, cramping, nausea and vomiting. In addition, SPS is non-specific and also binds calcium and magnesium, thereby increasing the risk of inducing hypocalcemia and/or hypomagnesaemia.
* Intravenous insulin (plus glucose) to shift potassium into the cells and away from the blood.
* Calcium supplementation. Calcium does not lower S-K values, but it reduces the risk for cardiac arrhythmias
* Administration of bicarbonate that stimulates an exchange of potassium for sodium, leading to stimulation of the sodium-potassium adenosine triphosphate enzyme
* Sever cases may require dialysis
The only pharmacological modality that actually increases elimination of potassium from the body is SPS. However, due to the need to induce diarrhoea, SPS cannot be administered on a chronic basis. Hence, there is a significant medical need for new and better treatment modalities for the acute as well as chronic treatment of hyperkalaemia

**Study objective**

Primary objective of this trial is to generate open-label, long-term (up to 12 months) safety and tolerability data for ZS in subjects with hyperkalaemia (S-K * 5.1 mmol/L)

Secondary objectives:
* To evaluate the portion of ZS-treated subjects in whom normokalaemia can be maintained over prolonged periods of time, using a dose range from 5 g every other day to 15 g once daily
* To evaluate the effect of ZS on various renal and bone biomarkers over prolonged periods of time, using a dose range from 5 g every other day to 15 g once daily.
* To evaluate the safety and tolerability of ZS consumed in ca. 40mL of water with no mandatory rinses and in ca. 180mL of water with two ca. 30mL rinses. (This only impacts centers in the USA. Patients outside the USA will continue to use 180 ml of water followed by two 30 ml rinses to consume their study medication).

**Study design**

This is a phase III, multi-centre, multi-dose, open-label maintenance study to investigator the long-term safety and efficacy of ZS (Sodium Zirconium Cyclosilicate), an oral sorbent, in subject with hyperkalaemia.

The study contains an Acute phase and a Maintenance phase. Patients with 2 consecutive i-STAT potassium values * 5.1 mmol/L will enter the Acute phase. During this phase patients receive ZS 10g tid for 24 to 72 hours, depending on the potassium values. Once normokalaemia is restored (values between 3.5 and 5.0 mmol/L), subjects will be enrolled in the Maintenance phase. Starting dose in this phase is 5 g once daily. Potassium will be measured weekly throughout the first month if study and every 4 weeks thereafter through month 12. During the Maintenance phase, the ZS dose may be increased or decreased in increments/decrements if 5g/day up to a maximum of 15 g/dag or a minimum of 5 g/ every other day. The i-STAT potassium values are used to check if dose adjustments are needed:
* Potassium value > 5.0 mmol/L while receiving 5g/ day or 5g/ every other day or > 5,5 mmol/L while receiving 10g/ day: increase ZS dosed in 5g/day increments to a maximum dose of 15 g/day;
* Between 3.0 and 3.4 mmol/L, inclusive: decrease ZS dose in 5g/day decrements to a minimum dose of 5g/every other day; if a subject*s i-STAT potassium value remains between 3.0 mmol/L en 3.4 mmol/L , inclusive, on the ZS 5g/ every other day dose, the subject will be withdrawn from the study and receive standard of care treatment.

Any time the ZS dose is adjusted, or a RAAS inhibitor or diuretic dose is adjusted or initiated, the subject will return to the site 7 (+/-1) days later for a potassium measurement and recording of adverse events and concomitant medications. There is no limit to the number of dose titrations allowed. The Medical Monitor may also request that subject's dose be adjusted based on the potassium value obtained from the central lab and if there is a significant discrepancy between the i-STAT potassium value.

## Intervention

Patients who meet the entry criteria start this study in the Acute phase for at least 24 hours and maximal 72 hours, depending if normokalaemia is restored (potassium values between 3.5 and 5.0 mmol/L). During the Acute phase patients are dosed with ZS 10g three times daily. Once normokalaemia is restored, subjects are enrolled in the Maintenance phase. If after 72 hours normokalaemia is not established, patients are taken off study and referred to standard care of treatment.
The Maintenance phase lasts up to 12 months. Starting dose in this phase is 5g ZS once daily. Based on the potassium values, this dose may be increased in increments/decrements of 5g/once daily to a maximum of 15g/ once daily or a minimum of 5g/ every other day. Adjustment of the dose is outlined in a dosing scheme. If a patient develops hypokalaemia (potassium < 3.0 mmol/L) or hyperkalaemia (potassium > 6.5 mmol/L) at any time during the Maintenance phase, the patient should be discontinued from the study and immediately receive appropriate medical treatment.

## Study burden and risks

Subjects who are eligible for participation in this study should have 2 consecutive i-STAT potassium values * 5.1 mmol/L. Patients enter the Acute phase for 24-72 hours in which it is investigated if normokalemia (i-STAT potassium between 3.5 and 5.0 mmol/L, inclusive) can be restored after treatment with the trial medication (total daily dose 30g). Treatment with ZS is extended for another 24 hours for those patients showing i-STAT potassium values * 5.1 mmol/L on Day 2 and 3.
The following assessments are performed during the Acute phase (day 1-4)
- Physical Examination (day 1)
- ECG (day 1 and 4)
- Vital Signs (day 1 and 4)
- Collecting blood potassium sample analysed by i-STAT (day 1 to 4)
- Haematology en and Clinical chemistry (day 1 and 4)
- Urinalysis (day 1 and 4)
- Urine pregnancy test for women of childbearing potential (day 1).

The day 4 assessments are only done on patients who do not qualify for the Maintenance phase on/before Acute phase Day 4 (except for potassium analysis on day 4).

During Maintenance phase, the patient is seen by the investigator on a weekly basis and every 4 weeks thereafter through Month 12. The following assessments are performed:
- Collecting blood potassium sample analysed by i-STAT (each visit to the clinic);
- Physical examination (at month 1 to 3, 6, 9, 12 and End of Study Visit);
- Vital signs (at month 1 to 3, 6, 9, 12 and End of Study Visit)

- ECG (at month 1 to 3, 6, 9, 12 and End of Study Visit)
- Haematology and Clinical chemistry (at month 1 to 3, 6, 9, 12 and End of Study Visit)
- Urinalysis (at month 3, 6, 9 and End of Study Visit)

The risks related to treatment with ZS come from a recently completed study. In this study there were more cases of swelling of the legs (also known as *edema*) in patients who received the highest dose of ZS (15 grams once daily) than in the placebo or lower dose groups.
The risks related to blood sampling are fainting, redness, pain, bruising, bleeding or infection at the puncture site. Risks related to ECG recording are: redness or itching caused by the sticky pads. Patients are also asked to fast at least 8 hours before sample collection. This might result in headache or light headedness.
It is hypothesized that ZS at doses between 5g every other day and 15 g once daily can restore and maintain normal S-K values (3.5 to 5.0 mmol/L, inclusive) on a chronic basis in subjects with hyperkalaemia as defined by S-K * 5.1 mmol/L with an acceptable safety and tolerability profile

# Contacts

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**Scientific**
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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

1). Provision of written informed consent.
2).18 years and older.
3). For all subjects enrolled outside Germany: Two consecutive i STAT potassium values, measured 60 (+/-15) minutes apart, both * 5.1 mmol/L and measured within 1 day before the first dose of ZS on Acute Phase Study Day 1.
For all subjects enrolled in Germany: Two consecutive i -STAT potassium values, measured 60 (+/-15) minutes apart, both * 5.1 mmol/L and * 6.5 mmol/l and measured within 1 day before the first dose of ZS on Acute Phase Study Day 1.
4). Ability to have repeated blood draws or effective venous catheterization.
5). For all subjects outside the European Union: Women of childbearing potential must have a negative pregnancy test within 1 day prior to the first dose of ZS on Acute Phase Study Day 1 and sexually active women of childbearing potential must be using 2 forms of medically acceptable contraception with at least one being a barrier method. Women who are surgically sterile or those who are postmenopausal for at least 2 years are not considered to be of childbearing potential.
For all subjects in the European Union: Women of childbearing potential must have a negative pregnancy test within 1 day prior to the first dose of ZS on Acute Phase Study Day 1 and sexually active women of childbearing potential must be using a highly effective medically acceptable contraception such as:
* combined or hormonal contraception associated with inhibition of ovulation;
* progesterone only hormonal contraception, associated with inhibition of ovulation;
* IUD (intrauterine device);
* IUS (intrauterine hormone-releasing system);
* bilateral tubal occlusion;
* vasectomised partner;
* sexual abstinence (true abstinence in line with the subjects preferred and usual lifestyle). Subjects practicing abstinence will agree to have a documented second acceptable method of birth control should they become sexually active during the course of study participation). Women who are surgically sterile or those who are postmenopausal for at least 2 years are not considered to be of childbearing potential.
Note: Controlled diabetic subjects are eligible for enrollment. Whenever possible, all blood draws collected before meals should be collected prior to insulin/insulin analog treatment.

## Exclusion criteria

1). Pseudohyperkalemia signs and symptoms, such as hemolyzed blood specimen due to

excessive fist clenching to make veins prominent, difficult or traumatic venipuncture, or history of severe leukocytosis or thrombocytosis.
2). Subjects treated with lactulose, Rifaximin, or other non-absorbed antibiotics for hyperammonemia within 7 days prior to first dose of ZS on Acute Phase Study Day 1.
3). Subjects treated with sodium polystyrene sulfonate (SPS; eg, Kayexalate®) or calcium polystyrene sulfonate (eg, Resonium) within 3 days prior to first dose of ZS on Acute Phase Study Day 1.
4). Subjects with a life expectancy of less than 12 months.
5). Subjects who are severely physically or mentally incapacitated and who, in the opinion of investigator, are unable to perform the subjects* tasks associated with the protocol.
6). Women who are pregnant, lactating, or planning to become pregnant.
7). Subjects with diabetic ketoacidosis.
8). Presence of any condition which, in the opinion of the investigator, places the subject at undue risk or potentially jeopardizes the quality of the data to be generated.
9). Known hypersensitivity or previous anaphylaxis to ZS or to components thereof.
10). Treatment with a drug or device within the last 30 days that has not received regulatory approval at the time of study entry.
11). Subjects with cardiac arrhythmias that require immediate treatment.
12). Subjects on dialysis.
13). Subjects randomized into the previous ZS-002, ZS-003, ZS-004, or ZS-004E studies.
14). Documented GFR < 15 mL/min within 90 days prior to study.
15). For Germany only: subjects presenting wiht QTc interval of 450 ms AND addtional risk factors for Torsade de pointes (e.g. heart failure or family history of long QT-syndrome) AND taking concomitant medications causing QT prolongation.
16). For Germany only: Patients who are committed to an institution by virtue of an order issued either by the judicial or the administrative authorities.
17). For Germany only: subjects who are dependents of either the Sponsor, Investigator or Institution
Note: Subjects who do not meet the criteria for entering the Acute Phase may be re-screened 2 more times during the study.

# Study design

## Design

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| Study phase: | 3 |
| Study type: | Interventional |
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 27-07-2015 |
| Enrollment: | 10 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | sodium zirconium cyclosilicate |
| Generic name: | sodium zirconium cyclosilicate |

# Ethics review

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| Approved WMO Date: | 02-04-2015 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 19-05-2015 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 17-06-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 24-06-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 20-07-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO | |

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|---|---|
| Date: | 07-08-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 22-03-2016 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 30-03-2016 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2014-004555-31-NL |
| ClinicalTrials.gov | NCT02163499 |
| CCMO | NL51330.018.14 |