An Open-Label, Randomised, Phase 4 Study of Continuing Sodium Zirconium Cyclosilicate (SZC) after Discharge in Participants with Chronic Kidney Disease treated for Hyperkalaemia

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Main: To evaluate the efficacy of continuing SZC as part of the discharge medications, compared to SoC, in maintaining NK Secondary:To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC:1. in reducing the...

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON51555

Source
ToetsingOnline

Brief title
Continuing SZC after discharge study (CONTINUITY)

Condition

- Other condition

Synonym
CKD with HK

Health condition

Metabolism and nutrition disorders: Hyperkalaemia in patients with Chronic Kidney Disease

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: AstraZeneca

Intervention

Keyword: Chronic Kidney Disease, hyperkalaemia, Sodium Zirconium Cyclosilicate (SZC)

Outcome measures

Primary outcome

• Endpoint: Occurrence (yes/no) of NK (K+ between 3.5 and 5.0 mmol/L,

inclusive) at 180 days post-discharge.

Secondary outcome

1. Endpoint: Time to first occurrence of all-cause hospital admissions or ED

visits with HK as a contributing factor, use of rescue therapy for HK, or

all-cause death at any time post-discharge up to 180 days.

2. Endpoint: Time to first occurrence of any component of all-cause hospital

admission or ED visit, both with HK as a contributing factor, at any time

post-discharge up to 180 days.

3. Endpoint: Number of all-cause hospital admission or ED visit both with HK as

a contributing factor, at any time post-discharge up to 180 days..

4. Endpoint: Time to first occurrence of RAASi down-titration (including

discontinuation) at any time post-discharge up to 180 days.

5. Time to first occurrence of hospital admission or ED visit, both with HK as

a contributing factor at any time post-discharge up to 180 days.

6. Number of hospital admission or ED visits, both with HK as a contributing

factor at any time post discharge up to 180 days.

Study description

Background summary

Hyperkaliemia is a potentially life-threatening electrolyte disorder and is primarily caused by renal dysfunction leading to reduced excretion of K+. The incidence of HK in CKD patients has been reported to range between 7.7% and 73%. In a study of approximately 36,000 patients with an estimated glomerular filtration rate (eGFR) < 60 ml/min per 1.73 m2, HK was associated with increased all-cause mortality.
Because HK can induce or worsen cardiac arrhythmias, it is associated with significantly increased mortality.

Treatment of severe HK is then a medical emergency but it should be followed by continuous long-term treatment to prevent recurrence. So far, the common practice for managing chronic HK is focused on eliminating HK predisposing factors. Patients are then advised to reduce high K+ intake in diets but also to withdraw or reduce medications known to raise K+ levels.

Maintaining the use of these beneficial medications (renin-angiotensin-aldosterone system inhibitors (RAASi), for example,) while implementing various strategies to control K+ balance is desirable and could be obtained by long-term use of K+ binders.
A treatment of up to 12 months with SZC utilising a dose titration scheme with the starting dose of 5 or 10 g daily, titrated to a maximum of 15 g daily or a minimum of 5 g every other day, was effective in maintaining NK in the majority of subjects in a long-term study (Spinowitz et al, 2019). However, in the US, only 0.1% of patients with a HK-related inpatient stay received a binder at discharge (Davis et al, 2019).

Hyperkalaemia is reported in less than 5% of the population, worldwide (Lederer and al, 2020), but may affect up to 10% of hospitalised patients (Rossignol et al, 2016). In addition to clinical consequences, HK is associated with increased health care costs and healthcare resource utilisation (HRU). (protocol section 2.2)

Study objective

Main:
To evaluate the efficacy of continuing SZC as part of the discharge medications, compared to SoC, in maintaining NK

Secondary:
To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC:
1. in reducing the incidence of the composite outcome of all-cause hospital admissions or ED visits with HK as a contributing factor, or all-cause death, or use of rescue-therapy for HK.
2. in reducing the incidence of all-cause hospital admissions or ED visit with HK as a contributing factor.
3. in reducing the number of all-cause hospital admissions or ED visits with HK as a contributing factor.
4. in reducing the risk of renin angiotensi-aldosterone system inhibitors (RAASi) down-titration (including discontinuation).
5. in reducing the incidence of hospital admissions or ED visits with HK as a contributing factor.
6. in reducing the number of hospital admissions or ED visits with HK as a contributing factor.

Study design

This is a Phase 4, randomised, controlled, open-label, parallel group, multicentre study in participants with CKD treated for HK, whilst admitted to the hospital. There will be 3 phases:
• The in-hospital phase
- screening visit
- The Inpatient phase
- clinical phase:
- baseline visit: correction treatment with SZC will be initiated.
- discharge visit: randomisation to one of the 2 parallel arms.
• The outpatient phase: treated with either SZC, as per local label, or SoC as per local practice for 180 days.
• The follow-up phase: end of study visit 7 days after end of treatment

Intervention

All participants will be treated with SZC as per local label (correction and maintenance treatment) during the in-hospital phase. The duration of in-hospital phase will be 2 to 21 days post-enrolment; medical monitor*s approval may be sought for allowing longer duration hospital stays for specific participants.
At discharge, participants who are NK (K+ between 3.5 and 5.0 mmol/L, inclusive) and have been started on a maintenance dose for SZC will be randomised in a 1:1 ratio to one of the following arms and subsequently enter the outpatient phase:
• Arm A: Participants discharged with SZC, as per local label, to manage HK until end of outpatient phase
• Arm B: Participants discharged with SoC, as per local practice, to manage HK

until end of the study.
Note: Participants intended to receive a K-binder at discharge (as per the site routine medical practice) will not be randomised and will be discontinued from the study. Still, it is allowed that participants randomised into Arm B have any K-binder prescribed at Day 7 post-discharge (or after Day 7 post-discharge) to treat confirmed HK or in case there is an increase in K+ level since discharge that, in the investigator*s opinion, requires therapy.

The duration of outpatient phase will be approximately 180 days.
After the outpatient phase, participants will enter into the follow-up phase which will last 7 days. Study drug will be discontinued for participants in Arm A. These participants will be treated as per local practice (SoC). Participants in Arm B will continue SoC treatment.

The total study duration for each participant will then be approximately 6 months.

Study burden and risks

In the hospital:
- Screening visit
- baseline visit
- Treatment: 14 days in the hospital, with SZC for stabilizing potassium values.

At home:
Return to hospital 4 times for visit
Being called at home four times for a check-up

Type of examinations:
- physical examination
- ECG
- assess side effects
- blood collections, 5-9.5 mL per visit
- urine collection/handing in for pregnancy testing (if applicable)

Contacts

Public
Astra Zeneca

- -
Södertälje 151 85
SE
Scientific

Astra Zeneca

- -
Södertälje 151 85
SE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1 Must be 18 years of age or older, at the time of signing the informed consent
2 Admitted to hospital (inpatient care; directly or from ED)
3 With:
- diagnosed CKD (any stage)
or
- eGFR <90 ml/min/1.73 m2 at, or within 3 months of, study screening, based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al, 2009). Note: Race/ethnicity should not be included in CKD-EPI equation calculation.
4 Local laboratory K+ measurement within 24 hours of baseline visit (visit 2), where result is either:
• Hyperkalaemic as defined by site's local practice and K+ <= 6.5 mmol/L
• Or, normokalaemic: K+ between >= 3.> 5.0 and <= 5.0 mmol/L, where patient started and is receiving treatment for this episode of HK
5 Male or female
6 Capable and willing of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in the protocol.

Exclusion criteria

1 Hospitalisation for an acute cardiovascular event within 12 weeks prior to screening
2 Unable to take oral SZC drug mix
3 -
4 With a life expectancy of less than 6 months
5 Any medical condition (including active, clinically significant infection) that, in the opinion of the investigator or sponsor, may pose a safety risk to the participant not suitable for inclusion
6 QT interval corrected by the Fridericia method (QTcF) > 550 msec
7 History of QT prolongation associated with other medications that required discontinuation of that medication
8 Congenital long QT syndrome
9 Clinically significant arrythmias as judged by the investigator
10 Ongoing treatment with SZC or patiromer before current ED visit/hospital admission (ongoing treatment with other K-binders before current ED visit/hospital admission is allowed).
Note: Initiation of SZC or patiromer during the current ED visit/hospitalisation preceding enrolment is allowed.
11 Chronic haemodialysis or peritoneal dialysis or the recipient of or scheduled date for a kidney transplant. Note: Emergency/unscheduled haemodialysis to treat HK during the current ED visit/hospitalisation preceding enrolment is allowed.
12 Participation in another clinical study with an investigational medical product (IMP) administered during the month before screening.
13 Known hypersensitivity to SZC or any of the excipients of the product
14 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)
15 Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements
16 Previous randomisation in the present study
17 For women only: Women of child-bearing potential (WOCBP; ie, those who are not chemically or surgically sterilised or who are not postmenopausal) who are not willing to use one of the methods of
contraception described hereafter, or who are not stable on the contraception method for the last one month, from the time of signing the informed consent throughout the study and 7 days after the last
dose
(a) Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, transdermal
(b) Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, implantable
(c) Intrauterine device
(d) Intrauterine hormone-releasing system

(e) Bilateral tubal occlusion
(f) Vasectomised partner (vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP participant and that the vasectomised partner has received medical assessment of the surgical success
(g) Sexual abstinence: it is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
18 For WOCBP only: Women who have a positive pregnancy test at screening OR women who are breastfeeding.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	12-08-2022
Enrollment:	50
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Lokelma
Generic name:	Sodium zirconium cyclosilicate

Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	17-11-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-04-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-08-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-09-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-10-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-01-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	31-03-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-12-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	31-01-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2021-003527-14-NL
CCMO	NL79268.042.21