AstraZeneca

Statistical Analysis Plan

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A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate a Potassium Normalization Treatment Regimen Including Sodium Zirconium Cyclosilicate (ENERGIZE)

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Study Statistician [redacted]

12 Nov. 2018
Date

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Global Product Statistician [redacted] 13 Nov 2018
Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
CI	Confidence Interval
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTMS	Clinical Trial Management System
ECG	Electrocardiography
ICF	Informed Consent Form
IP	Investigational Product
IPD	Important Protocol Deviation
ITT	Intention to Treat
MedDRA	Medical Dictionary for Regulatory Activities
PE	Physical Examination
SAE	Serious Adverse Event
SD	Standard Deviation
VS	Vital Signs
SZC	Sodium Zirconium Cyclosilicate

AMENDMENT HISTORY

Date	Brief description of change
	N/A

1. STUDY DETAILS

1.1 Study objectives

The primary objective in this study is to assess the effect of SZC vs placebo when added to insulin and glucose on the reduction of potassium at 4 hours after start of dosing.

Secondary objectives include the following:

- To assess the effect of SZC vs placebo when added to insulin and glucose on the response to therapy.
- To assess the effect of SZC vs placebo when added to insulin and glucose on the change in serum potassium at 1h and 2h after start of dosing.
- To assess the effect of SZC vs placebo when added to insulin and glucose on achieving normokalaemia.
- To assess the effect of SZC vs placebo when added to insulin and glucose on achieving S-K <5.5mmol/l and <6.0mmol/l.
- To assess the need for additional therapies for hyperkalaemia between SZC and placebo when added to insulin and glucose.

Safety objective is to characterize the safety of SZC when added to insulin and glucose.

In addition, there are several exploratory objectives to be considered as follows:

- To assess the effect of SZC vs placebo when added to insulin and glucose on the change in SK over time.
- To assess the effect between SZC and placebo when added to insulin and glucose on achieving normokalaemia.
- To compare the effect between SZC and placebo when added to insulin and glucose on achieving S-K <5.0mmol/l, S-K <5.5mmol/l and <6.0mmol/l.
- To assess the need for additional therapies due to hyperkalaemia between SZC and placebo when added to insulin and glucose.
- To assess the time and disposition of patients when leaving the treating department between SZC and placebo when added to insulin and Glucose.
- To compare the effect between SZC and placebo when added to insulin and glucose on duration of hospitalization.

1.2 Study design

The study is designed to determine if SZC 10g administered up to three times over 10h added to insulin and glucose in patients presenting with hyperkalaemia will prove to be tolerable and efficacious by performing a multicentre, international, randomized, double-blind, placebo-controlled, prospective, parallel-group study. The study will recruit patients with S-K ≥5.8 mmol/L. Eligible patients fulfilling all of the inclusion criteria and none of the exclusion criteria will be randomised in a 1:1 ratio to SZC or placebo. The study includes a single treatment visit no longer than 24h followed by a single follow up contact 7 days later.

1.3 Number of subjects

Approximately 132 patients are planned to be included in the study. Based on ZS-004 and patients treated with medications only in ZS-007, the SD for S-K change from baseline at 4 hours is assumed to be 0.7 mmol/L. With 66 patients per group a two-sided 95% confidence interval for the mean difference in S-K change will extend 0.239 mmol/L from the observed difference in means.

2. ANALYSIS SETS

2.1 Definition of analysis sets

The full analysis set, including all randomised subjects, will be used for the primary objective, secondary objectives and exploratory objectives. Patients will be analysed according to their randomised study medication.

The safety analysis set includes all subjects who were randomly assigned to study treatment and ingested at least 1 dose of IP. The safety objective will be analysed using the safety analysis set, according to patients' randomised study medication, except that erroneously treated patients (e.g., those randomised to SZC but actually given placebo or vice versa) will be accounted for in their actual treatment group, while patients who in error have received both SZC and placebo will be accounted for in their randomised treatment group.

2.2 Violations and deviations

The IPDs are described in Appendix A1. Whether they will be programmatically identified is also specified. There will be no IPDs leading to exclusion in primary analysis, which will be implemented upon full analysis set per ITT principle, regardless of protocol deviations.

3. PRIMARY AND SECONDARY VARIABLES

To derive analysis variables, several terms need to be clarified.

Baseline is defined as the measurement at 0h. Time point 0h is defined as the start of the administration of SZC/placebo.

The central laboratory S-K will be used. If central laboratory data is missing, i-STAT will be used instead, adding the average difference between the central lab S-K and i-STAT at the relevant time point. The difference between central lab S-K and i-STAT will be estimated from the mean difference in those subjects with both values available at the relevant time point. For subjects with both S-K and i-STAT missing, regardless of whether the subjects discontinued the study, data will be imputed using last observation carried forward up to 4h inclusive, unless otherwise established. If both S-K and i-STAT is missing at baseline, the measurement at screening will be used as baseline.

The additional therapies administered for lowering potassium are defined as 2nd dose of insulin, Beta-agonists, Diuretics, Dialysis, Sodium bicarbonate and Potassium binders when administered with the expressed intent to lower S-K.

3.1 Primary variable

The primary efficacy variable is mean absolute change in S-K from baseline until 4h.

3.2 Secondary variables

- Proportion of patients whose S-K <6.0mmol/L at 1h or 2h, S-K <5.0mmol/L at 4h, and no additional therapy administered for hyperkalaemia from 0h to 4h inclusive. Patients who have any missing potassium value from 1h to 4h inclusive will be treated as non-responders.

- Mean absolute change in S-K from baseline to 1h and 2h, respectively.

- The fraction of patients achieving normokalaemia (S-K 3.5-5.0mmol/L) at 1, 2 and 4h, respectively.

- The fraction of patients achieving S-K <5.5mmol/l at 1, 2, and 4h, respectively.

- The fraction of patients achieving S-K<6.0mmol/l at 1, 2, and 4h, respectively.

- The fraction of patients administered additional potassium lowering therapy due to hyperkalaemia from 0 to 4h inclusive.

3.3 Exploratory variables

All the exploratory variables will be reported in CSR.

- Mean absolute change in S-K from baseline to 6, 8, 10, 12 and 24h

- The fraction of patients achieving normokalaemia (S-K 3.5-5.0mmol/L) at 6, 8, 10, 12 and 24h

- The fraction of patients achieving S-K <5.0mmol/L, S-K <5.5mmol/l and S-K <6.0mmol/l respectively at 6, 8, 10, 12 and 24h

- The fraction of patients administered additional potassium lowering therapy due to hyperkalaemia from 4 to 24h

- Time from randomization until leaving the treating department. Time will be presented in hours with one decimal place, converted from minutes.

- Disposition after leaving the treating department. Disposition in this variable means where patients will go right after leaving the initial treatment department within visit 1 period. Disposition options include going home, going to dialysis and other treating departments. Only the first destination will be analysed if there is more than one move after leaving the initial treatment department.

- Time from randomization until discharge from hospitalization. Time will be presented in hours with one decimal place, converted from minutes.

3.4 Safety variables

3.4.1 AEs

AEs, including SAEs, will be collected from time of signature of informed consent form throughout the treatment period and including the follow-up period (visit 2 or last contact). However, AE/SAEs occurring between 0h to 24h and AE/SAEs occurring after 24h (time calculated from the start of the administration of insulin) will be analysed separately.

3.4.2 Vital signs

Temperature, pulse rate, respiratory rate and systolic blood pressure and diastolic blood pressure will be collected at screening, 4, 10 and 24h time points. The safety variable of each of these VS is the change from baseline to each available time point. Baseline is defined as the measurement at screening.

3.4.3 Physical examinations

Physical examinations will be performed at screening and 24h. The change in a physical examination from screening will be examined through any new or aggravated clinically relevant abnormal medical finding, which will be reported as an AE unless unequivocally related to the disease under study. Therefore, there will be no separate safety variables and analyses for PEs.

3.4.4 ECGs

ECGs will be collected at screening, 4h and 24h time points, using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. The safety variable of each of these ECG measurements is the change from baseline to each available time point. Baseline is defined as the measurement at screening.

3.4.5 Clinical laboratory parameters

The laboratory parameters to be included in the safety analyses are defined in Table 7 in CSP. Central laboratory value will be used for assessments of clinical chemistry and haematology. These data (except potassium) will be collected at screening and 24h only. The safety variable of each of these laboratory parameters is the change from screening.

However, potassium and glucose measurements will be collected at all scheduled time points from screening until 24h, and only i-STAT data will be collected for glucose. The change in potassium and glucose from baseline to each time point, hypokalaemia based on S-K <3.5mmol/L and hypoglycaemia based on blood glucose <70mg/dL will be assessed.

4. ANALYSIS METHODS

4.1 General principles

The denominator used in percentage should be the total number of subjects in treatment group, unless otherwise specified in programming specification.

4.2 Analysis methods

4.2.1 Efficacy analysis

All efficacy analyses will be performed on full analysis set.

The primary objective is to assess the effect of SZC vs placebo when added to insulin and glucose on the reduction of potassium at 4 hours after start of dosing SZC/placebo. To examine the primary objective, a linear regression model, including treatment group, baseline S-K, time from the start of dosing insulin to the start of dosing SZC/placebo and the dose (units/kg) of the first course of insulin as covariates, will be employed. The difference in least square means between treatment groups with associated 95% CIs will be presented in addition to the mean absolute changes and standard deviations.

The secondary variables of mean absolute change from baseline in S-K to different time points will be analysed, similarly to the analysis for the primary variable. 95% CIs of the least square mean difference will be presented in addition to mean and SD of the absolute change. Secondary variables of fraction of patients will be analysed for the full analysis set using logistic regression including the same covariates as the primary analysis. Odds ratio and its 95% CIs will be presented in addition to frequency and percentages. Secondary variables are declared supportive, thus, there is no need for multiplicity adjustment.

Sensitivity analysis will be performed for the primary variable, where only those subjects with non-missing central lab potassium data at both baseline and 4h will be included, therefore, there will be no missing data imputation in the sensitivity analysis. An analysis will also be performed using i-STAT data rather than central lab data, where only subjects with non-missing i-STAT data at baseline and 4h will be included in the analysis.

4.2.2 Safety analysis

All safety analyses will be performed on safety analysis set, i.e. including all patients who have received at least one dose of study drug.

AEs will be coded using the MedDRA dictionary. AEs occurring between 0h to 24 h and AEs occurring after 24 h will be analysed separately. Number of subjects with events and percentages will be tabulated by preferred term and system organ class. AEs, SAEs, AEs leading to discontinuation of IP and AEs with outcome of death will be summarised for each treatment group as applicable. AEs will also be summarised by intensity and separately, by causality (as determined by the investigator). SAEs and AEs leading to discontinuation of IP will also be summarised by causality. Number of AEs and SAEs will also be summarized by preferred term and system organ class, respectively.

Laboratory data will be summarised by presenting shift tables using normal ranges (baseline to most extreme post-baseline value) and by presenting summary statistics of observed and change from baseline values (means, medians, quartiles, ranges). The incidence of clinically notable lab abnormalities will be summarised. The frequency and percentages of hypokalaemia and hypoglycaemia will be tabulated.

VS data will be summarised by presenting summary statistics of observed and change from baseline values. The incidence of clinically notable VS abnormalities will be summarised.

ECG data will be summarised by presenting summary statistics of observed and change from baseline values. The incidence of clinically notable ECG abnormalities will be summarised.

4.2.3 Exploratory analysis

Exploratory objectives will be presented using summary statistics. Mean, SD, median, min and max will be provided for the variable of absolute change in S-K.

Frequency and percentages will be provided for proportions, and additionally, 95% Clopper–Pearson CI of the proportion in each treatment group will be presented separately. P-values are not applicable in these exploratory analyses.

Disposition after leaving the initial treating department will be summarized by frequency and percentages. The summary of time from randomization will be based on statistics mean, SD, min and max.

5. INTERIM ANALYSES

N/A.

6. CHANGES OF ANALYSIS FROM PROTOCOL

N/A.

7. REFERENCES

N/A.

8. APPENDIX

Appendix A1 Important Protocol Deviation

Code	Description	IPD	Programmable IPD
1.1	Informed consent not obtained prior to any mandatory study specific procedures, sampling, and analyses	Yes	Yes
1.2	<18 years of age at the time of signing the informed consent form	Yes	Yes
1.3	Whole blood potassium < 5.8 mmol/L	Yes	Yes
1.4	Inability to have repeated blood draws or effective venous catheterization	Yes	Yes
2.1	Possible pseudohyperkalaemia as assessed by the investigator, e.g. secondary to hemolyzed blood specimen	Yes	Yes
2.2	Hyperkalaemia caused by any condition for which a therapy directed against the underlying cause of hyperkalaemia would be a better treatment option than treatment with insulin and glucose. This includes hyperkalaemia reasonably likely to be caused by physical injury, intoxication, pre-renal kidney failure, substance abuse, diabetic ketoacidosis, and rhabdomyolysis	Yes	Yes
2.3	Life-threatening cardiac arrhythmias requiring immediate treatment before an informed consent can be collected	Yes	Yes
2.4	Any condition representing a contra-indication to treatment with the rapid acting insulin to be used, e.g. allergy to any of the constituents of the insulin product to be used, or hypoglycaemia at study entry	Yes	Yes

2.5	Presence of any other acute or chronic medical condition which, in the opinion of the investigator, places the patient at undue risk due to the severity of illness or potentially jeopardizes patients'ability to follow study procedures due to required interventions, investigations or procedure in the acute setting. Patients having any acute or chronic medical condition other than hyperkalaemia that would alone require immediate treatment in the hospital setting at Visit 1 are not eligible for the study.	Yes	Yes
2.6	Dialysis session expected within 4h after randomization	Yes	Yes
2.7	Treated with sodium polystyrene sulfonate (SPS, Kayexalate, Resonium), calcium polystyrene sulfonate (CPS, Resonium calcium) or patiromer (Veltassa) within the past 24h	Yes	Yes
2.8	Treated with any therapy intended to lower S-K between arriving at the hospital and randomization during Visit 1 with exception of patients meeting the following criteria: • Treated with no more than one course of insulin since arriving at the hospital • S-K measured by i-STAT device or local laboratory prior to administration of insulin. S-K must have met Inclusion criterion 4. • Reasonably likely to randomize, have screening and 0h assessments done, and dose the patient with IP within 30 minutes of the start of administration of insulin.	Yes	Yes
2.9	Known hypersensitivity or previous anaphylaxis to ZS or to components thereof	Yes	Yes
2.10	Known pregnancy or actively attempting to become pregnant	Yes	Yes
2.11	Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)	Yes	Yes
2.12	Judgment by the investigator that the subject should not participate in the study as the subject is unlikely to comply with study procedures, restrictions or	Yes	Yes

	requirements		
2.13	Previous randomization in the present study	Yes	Yes
3.1	Patient withdrawal of consent not handled correctly	Yes	Yes
3.2	Adverse Event precluding further dosing in the opinion of the investigator or sponsor	Yes	Yes
3.3	Severe non-compliance to the study protocol	Yes	Yes
3.4	Patient became pregnant (screening pregnancy test positive), but not discontinued from study drug	Yes	Yes
3.5	Whole blood potassium <3.5mmol/L as measured with i-STAT before the administration of ZS at 10h	Yes	Yes
3.6	Dialysis administered	Yes	Yes
4.2	Use of expired study drug or drug affected by temperature excursion	Yes	No
4.3	Received wrong type of study drug (i.e. not the one patient was randomized to)	Yes	Yes
4.4	Received incorrect dose or wrong frequency of investigational product	Yes	Yes
5.1	Additional potassium lowering drugs (eg insulin, beta agonists, potassium binders) administered with the intent to lower potassium before 4h (except in cases where it was allowed by protocol (one dose of insulin) or necessary for the safety of the patient).	Yes	No
5.2	Potassium substitution (e.g. KCl). All treatments for hypokalemia not withheld from enrolment to Visit 1 discharge	Yes	Yes
5.3	Gastric pH-dependent bioavailability drugs were administered/taken within +/- 2 hours of IP /ZS	Yes	Yes
6.1	Visit or procedures not done within the timeframe defined by the CSP	No	N/A
6.2	Visit procedure not done according to description in the CSP	No	N/A

6.3	Defined order of the visit's procedures required by the CSP not followed	No	N/A
6.4	Study drug storage temperature and/or documentation of monitoring is inadequate	No	N/A
6.5	Storage area security / accessibility inadequate	No	N/A
6.6	Study drug disposition not documented	No	N/A
6.7	Significant compliance issues	Yes	No
6.8	iStat Cartridges not stored at the correct temperature, temperature excursion occurred.	No	N/A
8.1	Delay of SAE reporting (initial or follow-up)	Yes	Yes
9.1	Delay of pregnancy reporting	Yes	No
9.2	Delay of IP overdose reporting (initial or follow-up)	Yes	No
9.3	Other safety issues not specified in the deviations described above	Yes	No
7.1	Examinations/assessments for the study were not done according to GCP.	Yes	No
7.2	Other GCP deviations e.g. failure to report changes in the consent form to an IEC. Patient consented with obsolete version of ICF. Patient not re-consented with updated ICF version at next patient's visit. Not signed any OC form. Failure to notify GP of subject participation (if applicable)	Yes	No