1 SYNOPSIS

Title of Study:	A Two-Cohort, Randomised Sequence, Cross-over, Open-label Study to Assess the Effect of a Single Dose of Sodium Zirconium Cyclosilicate (SZC) on the Pharmacokinetics of Tacrolimus and Cyclosporin in Healthy Subjects	
Study Numbers:	Parexel Study No.: CCI Sponsor Study No.: D9480C00012	
Investigational Medicinal Products:	Test Product: Sodium zirconium cyclosilicate/SZC Interaction Product: Tacrolimus and cyclosporin	
Indication Studied:	Hyperkalaemia	
Development Phase:	Phase 1	
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden	
Principal Investigator:	Thomas Koernicke	
Study Centre:	Parexel Early Phase Clinical Unit - Berlin	
Study Duration:	First subject first visit: 30 March 2021	Last subject last visit: 16 September 2021

Study Objective and Endpoints:

Primary Objective and Endpoints:

Primary Objectives	Outcome Measures
To assess the effect of co-administered SZC on the pharmacokinetics (PK) of tacrolimus and cyclosporin in healthy subjects as described by Cmax and AUCinf.	AUCinf and Cmax measured for each subject and each visit on which PK data are collected.

Secondary Objectives and Endpoints:

Secondary Objectives	Outcome Measures
To assess the effect of co-administered SZC on the PK of tacrolimus and cyclosporin in healthy subjects, as described by AUClast, t½λz, and tmax.	AUClast, t½λ_z, and tmax measured for each subject and each visit on which PK data are collected.
To examine the safety and tolerability of co-administration of SZC and tacrolimus/cyclosporin as compared to tacrolimus/cyclosporin alone.	Adverse events (AEs), vital signs (systolic and diastolic blood pressure, pulse, and tympanic temperature), 12-lead electrocardiograms (ECGs), laboratory assessments (haematology, clinical chemistry, and urinalysis).

Study Design:

This study was an open-label, randomised sequence, 2-period, 2-cohort, 2-treatment in each cohort, cross-over study in healthy subjects (males and females of non-childbearing potential), performed at a single study centre.

The study comprised:

- A screening period of maximum 28 days;
- Two treatment periods:
  - Treatment Period 1 started with admission to the Clinical Unit on Day -1, followed by dosing on Day 1 with the assigned treatment (A, B, C, or D) as per assigned cohort and treatment sequence, followed by a washout period of at least 14 days. Subjects were discharged from the Clinical Unit after the last pharmacokinetics (PK) sample was collected for this treatment period (Day 4).
  - Treatment Period 2 started with admission to the Clinical Unit on Day -1, followed by dosing on Day 1 with cross-over treatment as per assigned cohort, followed by a follow-up period of 7 to 10 days. Subjects were discharged from the Clinical Unit after the last PK sample was collected for this treatment period (Day 4).
- A follow-up visit/early termination visit at 7 to 10 days after the last investigational medicinal product (IMP) administration.

Subjects were assigned to either Cohort 1 (tacrolimus) or to Cohort 2 (cyclosporin). Each cohort had 2 treatment periods. Subjects in each cohort were randomly assigned to one of 2 treatment sequences (AB|BA or CD|DC) where,

- Treatment A: Tacrolimus CCI .
- Treatment B: Tacrolimus CCI + SZC CCI
- Treatment C: Cyclosporin CCI .
- Treatment D: Cyclosporin CCI + SZC CCI

Subjects who received Treatment A in Treatment Period 1 of Cohort 1 received Treatment B in Treatment Period 2 and vice versa. Subjects who received Treatment C in Treatment Period 1 of Cohort 2 received Treatment D in Treatment Period 2 and vice versa.

Each subject received a single dose of oral capsules of tacrolimus CCI or cyclosporin CCI on 2 occasions, once alone and once in combination with oral suspension of SZC CCI All drug administrations occurred after a 12 hour overnight fast.

Study Subjects:

Planned for Inclusion:

Sixty subjects (30 subjects in Cohort 1 and 30 subjects in Cohort 2) were planned for inclusion.

Randomised:

Sixty-two subjects (31 subjects in Cohort 1 and 31 subjects in Cohort 2) were randomised into the study.

Completed Study:

In Cohort 1 30 (96.8%) subjects completed the study.

In Cohort 2, 29 (93.5%) subjects completed the study.

Main Inclusion Criteria:

Subjects who met the following criteria were considered eligible to participate in the study:

1 Provision of signed and dated, written informed consent prior to any study specific procedures.

2 Healthy male and female subjects aged 18 to 50 years (both inclusive) with suitable veins for cannulation or repeated venipuncture.

3 Females were of non-childbearing potential, confirmed at screening and fulfilled the criteria detailed in Section 4.2.1.1 of the clinical study protocol (CSP) (Appendix 16.1.1).

4 Male subject must have adhered to the contraception methods details in Section 4.2.1.2 of the CSP (Appendix 16.1.1).

Had a body mass index between 18.5 and 30 kg/m^2 inclusive and weighed at least 50 kg and no more than 100 kg inclusive.

Investigational Medicinal Products:

Investigational Medicinal Product:	**Sodium Zirconium Cyclosilicate**	**Tacrolimus**	**Cyclosporin**
Trade Name:	Lokelma™	Prograf	Sandimmun Neoral/Optoral
Manufacturer:	AstraZeneca	Astellas Pharma	Novartis
Formulation:	Powder for oral suspension	Hard capsules	Soft capsules
Strength/concentration:	CCI	CCI	CCI
Dose:	CCI	CCI	CCI
Route of administration:	Oral	Oral	Oral
Specific device for drug administration, if applicable:	Not applicable	Not applicable	Not applicable
Regimen:	Single dose of CCI consisting of 3 sachets suspended in 45 mL of water	Single dose of CCI	Single dose of CCI
Batch/Manufacturing Lot Number:	CCI	CCI	CCI
Expiry Date:	CCI	CCI	CCI

Duration of Treatment:

Subjects in Cohort 1 received a single dose of tacrolimus CCI and a single dose of tacrolimus CCI + SZC CCI.

Subjects in Cohort 2 received a single dose of cyclosporin CCI and a single dose of cyclosporin CCI + SZC CCI

Treatment Compliance:

The administration of all IMPs was recorded in ClinBase™.

Compliance was assured by direct supervision. After IMP administration, a check of the subject's mouth and hands was performed.

Statistical Methods:

Determination of Sample Size:

CCI

Presentation and Analysis of Pharmacokinetic Data:

All PK concentration, parameter summaries and statistical analyses are presented for the PK analysis set, unless otherwise specified. The PK concentration and parameter listings are presented for the safety analysis set and included all reportable individual PK results. Individual PK concentration and parameter data for any subjects not included in the PK statistical analyses are included in the listings and flagged.

The difference in mean PK parameters (Cmax, AUCinf) for the 2 cohorts were analysed using a mixed effects model following a natural logarithmic transformation of the individual PK parameters, with period, treatment, and sequence as fixed effects, and subject nested within sequence as random effects. Least-squares (LS) means for each treatment, the difference thereof, and the corresponding 2-sided 90% confidence intervals (CIs) for the log-transformed values are presented. The corresponding geometric LS mean for each treatment, the ratio thereof, and the 2-sided 90% CI were estimated and presented.

The limits for the 90% CIs for the gmean ratio were compared to the pre-specified interval (0.8000% to 1.2500%) for conclusion of no drug-drug interaction (ie, if the CI lies entirely within the predetermined 0.8 and to 1.25 range, it would have concluded that SZC had no meaningful effect on the PK for tacrolimus/cyclosporin).

Statistical analyses were done using PK analysis set.

The mixed effects statistical model was repeated for the secondary PK variables of AUClast, t½λz, and tmax, for both cohorts.

Presentation and Analysis of Safety Data:

All safety data (scheduled and unscheduled) were presented in the data listings. Continuous variables were summarised using descriptive statistics (n, mean, standard deviation, minimum, median, maximum, 1st quartile, 3rd quartile). Categorical variables were summarised in frequency tables (frequency and proportion). The analysis of the safety variables was based on the safety analysis set.

Adverse events were summarised by system organ class and preferred term (PT) using Medical Dictionary for Regulatory Activities vocabulary. Furthermore, listings of serious adverse event (SAEs) and AEs that led to withdrawal would have been made and the number of subjects who had any AE, SAEs, AEs that led to withdrawal, and AEs with severe intensity would have been summarised. Serious AEs that occurred before dosing would have been reported separately.

Tabulations and listings of data for vital signs, clinical laboratory tests and ECGs were presented. Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment would have been reported as an AE. Data were summarised for the observed values at each scheduled assessment, together with the corresponding changes (and/or percentage change) from the baseline when baseline value exists. Clinical laboratory data were reported in Système International units in the clinical study report.

Out-of-range values for safety laboratory were flagged in individual listings as well as summarised descriptively using agreed standard reference ranges and/or extended reference ranges (eg, AZ program, or laboratory ranges).

Protocol Deviations:

One important deviation was recorded for 1 subject in Cohort 2 (cyclosporin):

- Subject PPD tested drug-positive for Tetrahydrocannabinol in urine pre-dose in Treatment Period 2. The subject was withdrawn from the study.

Pharmacokinetic Results:

Cohort 1 (Tacrolimus)

- The inter-subject variability in Cmax was moderate and similar between treatment arms, with geometric CV% values of 37.61% and 35.88% for treatment with tacrolimus alone or with SZC, respectively. The inter-subject variability in AUClast and AUCinf was high and similar between both treatment arms. The geometric CV% values for AUClast were 50.79% and 51.13% for treatment with tacrolimus alone or with SZC, respectively, and the geometric CV% values for AUCinf were 50.20% and 48.95% for treatment with tacrolimus alone or with SZC, respectively.
- The geometric LS mean Cmax was 28.90% lower when tacrolimus was co-administered with SZC with the upper 90% CI below 80%: ratio 71.1% (90% CI 65.44% to 77.24%).
- The geometric LS mean AUCinf was 37.09% lower when tacrolimus was co-administered with SZC with the upper 90% CI below 80%: ratio 62.91% (90% CI 55.64% to 71.13%). The geometric LS mean AUClast was 34.43% lower when tacrolimus was co-administered with SZC with the upper 90% CI below 80%: ratio 65.57% (90% CI 58.69% to 73.24%). The reductions in both of these measures of systemic exposure were similar. The 90% CIs for both of these parameters were fully below the range of 80% to 125%, and it thus could not be concluded that there is no meaningful effect of SZC on the PK of tacrolimus.
- The t½λz was similar between treatments with gmean values of 33.59 hours and 33.31 hours, for treatment with tacrolimus alone or with SZC, respectively. The profiles were well-defined with Rsq adjusted > 0.8 for all subjects, although the mean span ratio was less than 3 times the t½λz, with values of 2.662 (tacrolimus alone) and 2.373 (tacrolimus + SZC) with an overall range of 1.02 to 4.92. %AUCextr was generally < 20%. Apparent CL/F and Vz/F were higher when tacrolimus was co-administered with SZC compared with tacrolimus administered alone, suggesting a reduction in bioavailability (F).
- Differences in exposure, while maintaining a similar t½λz between groups, combined with higher CL/F and Vz/F indicate that the extent of absorption of tacrolimus was reduced when co-administered with CCI SZC.
- Geometric LS mean tmax was earlier by 16.14% when tacrolimus was co-administered with SZC with the upper 90% CI fully below 100% and the lower 90% CI below 80%: ratio 83.86% (90% CI 73.38% to 95.84%). However, the overall range of tmax values was similar between groups and suggests that the impact of SZC on the rate of absorption of tacrolimus was less marked than its impact on the extent of absorption.

Cohort 2 (Cyclosporin)

- Inter-subject variability in Cmax was generally low to moderate and similar between treatment arms, with geometric CV% values of 19.54% and 26.46% for treatment with cyclosporin alone or with SZC, respectively. Inter-subject variability in AUClast and AUCinf was generally low to moderate and similar between both treatment arms. The geometric CV% values for AUClast were 26.46% and 24.39% for treatment with cyclosporin alone or with SZC, respectively, and the geometric CV% values for AUCinf were 25.90% and 23.91% for treatment with cyclosporin alone or with SZC, respectively.
- Statistical analysis of the primary PK parameters, Cmax and AUCinf, and the secondary PK parameters AUClast, t½λz and tmax demonstrated that the geometric LS means were similar between treatments with ratios ranging between 97.04% and 102.9%. The 90% CIs included 100% in all cases and were fully contained within the range of 80% to 125% from which it may be concluded that there is no meaningful effect of SZC on the PK of cyclosporin.
- The t½λz was similar between treatments with gmean values of 9.223 hours and 8.647 hours for treatment with cyclosporin alone or with SZC, respectively. The profiles were well-defined with Rsq adjusted > 0.8 for all subjects, although the mean span ratio was less than 3 times the t½λz, with mean values of 1.893 (cyclosporin alone) and 1.903 (cyclosporin + SZC) and an overall range of 1.11 to 3.11. %AUCextr was < 10% for all subjects.

Safety Results:

Cohort 1 (Tacrolimus)

- A total of 12 AEs were reported for 7 (22.6%) subjects during Treatment A (tacrolimus [redacted]) compared to 15 AEs reported for 13 (43.3%) subjects during Treatment B (tacrolimus [redacted] + SZC [redacted]). The AEs were generally mild in intensity for both treatment groups with no systematic pattern in AE PTs. No SAEs were reported. No clinically relevant trends were observed for laboratory, vital signs or ECGs for Treatment A or Treatment B.

Cohort 2 (Cyclosporin)

- A total of 8 AEs were reported for 8 (25.8%) subjects during Treatment C (cyclosporin [redacted]) compared to 9 AEs reported for 7 (24.1%) subjects during Treatment D (cyclosporin [redacted] + SZC [redacted] The AEs were generally mild in intensity for both treatment groups with no systematic pattern in AE PTs. No SAEs were reported. No clinically relevant trends were observed for laboratory, vital signs or ECGs for Treatment C or Treatment D.

Conclusion:

Pharmacokinetic Conclusion

- Tacrolimus exposure (AUC) was reduced by approximately one third when it was co-administered with SZC. The 90% CIs for the exposure parameters were fully below the range of 80% to 125%, and it thus could not be concluded that there is no meaningful effect of SZC on the PK of tacrolimus. As t½λz was unchanged when tacrolimus was co-administered with SZC, it appears that the reduction in tacrolimus exposure is attributable to a reduction in its absorption rather than a change in clearance.
- The co-administration of SZC had no meaningful effect on the PK profile of cyclosporin. Ratios of Cmax, AUCinf and AUClast were all close to 100% with 90% CI which spanned 100% and were fully contained within the 80% to 125% range.

Safety Conclusion

- The administration of tacrolimus alone and in combination with SZC was generally well tolerated in study subjects. The safety and tolerability of tacrolimus when administered alone and in combination with SZC were similar.
- The administration of cyclosporin alone and in combination with SZC, was generally well tolerated in study subjects. The safety and tolerability of cyclosporin when administered alone and in combination with SZC were similar.

Version and Date of Report: Final, 09 Feb 2022

This study was conducted in compliance with International Council for Harmonisation Good Clinical Practice guidelines.