16.1 STUDY INFORMATION

16.1.1 Protocol, Protocol Amendments

16.1.1.1 Protocol

Document included:

- Clinical Study Protocol, Version 1.0, dated 28 Sep 2020

16.1.1.2 Protocol Amendments

Not Applicable

Clinical Study Protocol

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

Parexel Study No.:	CCI [redacted]
Sponsor Study Code:	D9480C00012
EudraCT No.:	2020-000515-68
Study Type	Drug-drug interaction (DDI) study
Test Product:	Sodium zirconium cyclosilicate/SZC
Interaction Products:	Tacrolimus and cyclosporin
Therapeutic Indication:	Hyperkalaemia
Pharmacological Class:	Non-polymer, inorganic cation-exchanger
Development Phase:	Phase I
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden
Study Centre:	Parexel International GmbH PPD [redacted] 14050 Berlin Germany
Date of Protocol:	Final 1.0, 28 September 2020

This clinical study will be conducted according to the protocol and in compliance with Good Clinical Practice, with the Declaration of Helsinki and with other applicable regulatory requirements.

PROTOCOL SYNOPSIS

Title of the 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

Principal Investigator
Dr. Thomas Koernicke

Study Centre
This study will be conducted at a single study centre:
Parexel International GmbH
PPD
14050 Berlin
Germany

Study Rationale
Sodium zirconium cyclosilicate (SZC), is an oral, non-polymer inorganic cation-exchanger that has been approved as a novel therapy for the treatment of hyperkalaemia. It selectively captures potassium ions in exchange for sodium and hydrogen ions in the gastrointestinal lumen, thereby reducing serum potassium concentration and removing potassium from the body through increased faecal excretion. Sodium zirconium cyclosilicate exerts its effect locally and is not absorbed systemically. Due to its insoluble, inorganic, and crystalline properties, SZC is not absorbed or metabolised by the body and therefore no metabolic or transporter-based drug-drug interactions (DDIs) are anticipated in association with SZC treatment. However, SZC can bind to hydrogen ions which may result in increased pH in acidic environments such as the stomach. In general, an increase in gastric pH can alter the solubility of drugs with pH-dependent solubility and may result in an altered absorption profile of the drugs. Results from a Phase 1 study performed in healthy subjects to examine the potential for DDIs between SZC and a set of 9 compounds showed that co-administration of SZC affected the pharmacokinetics (PK), primarily the Cmax values, of 5 compounds tested (Study ZS-009).

This study will investigate if the PK of tacrolimus and cyclosporin may be altered by the increased gastric pH resulting from SZC co-administration.

Number of Subjects Planned
A total of 60 subjects will be randomised (30 per cohort) to ensure at least 56 evaluable subjects (28 subjects per cohort) at the end of the last treatment period.

Study Period
Estimated date of first subject enrolled: December 2020 (signing of informed consent).
Estimated date of last subject completed: March 2021.

Study Objectives

Primary Objective:

- To assess the effect of co-administered SZC on the PK of tacrolimus and cyclosporin in healthy subjects as described by Cmax and AUCinf.

Secondary Objectives:

- To assess the effect of co-administered SZC on the PK of tacrolimus and cyclosporin in healthy subjects, as described by AUClast, $t½\lambda_z$, and tmax.
- To examine the safety and tolerability of co-administration of SZC and tacrolimus/cyclosporin as compared to tacrolimus/cyclosporin alone in healthy volunteers.

Study Design

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

The study will comprise:

- A screening period of maximum 28 days;
- Two treatment periods:
  - Treatment Period 1 starts 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 will be discharged from the Clinical Unit after the last PK sample was collected for this treatment period (Day 4).
  - Treatment Period 2 starts with admission to 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 will be 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 IMP administration.

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

- Treatment A: Tacrolimus [redacted].
- Treatment B: Tacrolimus [redacted] + SZC [redacted].
- Treatment C: Cyclosporin [redacted].
- Treatment D: Cyclosporin [redacted] + SZC [redacted].

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

in Treatment Period 1 of Cohort 2 will receive Treatment D in Treatment Period 2 and vice versa.

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

Expected Duration of the Study
The expected total study duration, including the screening period, for each subject will be at least 58 days (8 weeks).

Targeted Study Population
This study will be conducted in healthy male and female subjects of non-childbearing potential, 18 to 50 years of age.

Investigational Medicinal Products

Investigational Medicinal Product Name	**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 sachet	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
Special handling requirements:	Not applicable	Not applicable	Not applicable

Outcome Endpoints

Pharmacokinetic Endpoints:
Where possible, PK parameters will be assessed for tacrolimus and cyclosporin on whole blood samples.

- Primary PK parameters: Cmax, AUCinf
  - AUCinf and Cmax measured for each subject and each visit on which PK data are collected.
- Secondary PK parameters: AUClast, $t½\lambda_z$, tmax

– AUClast, t½λ_z, and tmax measured for each subject and each visit on which PK data are collected.

Additional PK parameters may be determined where appropriate.

Safety and Tolerability Endpoints:
Safety and tolerability variables will include

- Adverse events, vital signs (systolic and diastolic BP, pulse, and tympanic temperature), 12-lead ECGs, laboratory assessments (haematology, clinical chemistry, and urinalysis).

Statistical Methods

Presentation and Analysis of Pharmacokinetic Data:
All PK concentration, parameter summaries and statistical analyses will be presented for the PK analysis set, unless otherwise specified. The PK concentration and parameter listings will be presented for the safety analysis set and will include all reportable individual PK results. Individual PK concentration and parameter data for any subjects not included in the PK statistical analyses will be included in the listings and flagged with an appropriate footnote.

A listing of PK blood sample collection times, as well as derived sampling time deviations and concentrations at each protocol scheduled time point will be provided. Whole blood concentrations will be summarised by treatment and nominal time points descriptively. The PK parameters will be summarised by treatment using appropriate descriptive statistics.

Individual concentrations with time deviations of ≥ ±10% from the protocol scheduled time, will be used in the PK analysis but will be flagged for exclusion from the summary tables and corresponding figures.

Protocol scheduled times will be used to present the PK concentration summary tables and corresponding gmean concentration-time figures.

Presentation and Analysis of Safety and Eligibility Data:
All safety data (scheduled and unscheduled) will be presented in the data listings. Continuous variables will be summarised using descriptive statistics (n, mean, SD, minimum, median, maximum). Categorical variables will be summarised in frequency tables (frequency and proportion). The analysis of the safety variables will be based on the safety analysis set.

Adverse events will be summarised by system organ class (SOC) and preferred term (PT) using MedDRA vocabulary. Furthermore, listings of SAEs and AEs that led to withdrawal will be made and the number of subjects who had any AE, SAEs, AEs that led to withdrawal, and AEs with severe intensity will be summarised. Serious adverse events that occur before dosing will be reported separately.

Tabulations and listings of data for vital signs, clinical laboratory tests and ECGs will be presented. Any new or aggravated clinically relevant abnormal medical physical examination

finding compared to the baseline assessment will be reported as an AE. Data will be 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 will be reported in Système International units in the CSR.

Out-of-range values for safety laboratory will be 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).

Sample Size Determination

CCI [redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Please note that definitions of abbreviations for pharmacokinetic variables are also presented in Section 10.2.1 of this protocol.

Abbreviation or special term	Explanation
AE(s)	Adverse event(s) (see definition in Section 6.3.1.1)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AV	Atrioventricular
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
BLQ	Below the limit of quantification
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CI	Confidence interval
ClinBase™	Parexel's electronic source data capturing and information management system
COVID-19	Coronavirus disease 2019
CRF	Case report form
CRO	Contract research organisation
CRP	C-reactive protein
CSP	Clinical study protocol
CSR	Clinical study report
CV	Coefficient of variation
DCF	Data clarification form
DDI	Drug-drug interaction
DILI	Drug induced liver injury
DMP	Data management plan
DNA	Deoxyribonucleic acid
DVS	Data validation specification
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone

Abbreviation or special term	Explanation
GCP	Good Clinical Practice
gCV	Geometric mean of CV
gmean	geometric mean
GMP	Good Manufacturing Practice
h	hour(s)
Hb	Haemoglobin
HBsAg	Hepatitis B surface antigen
HCT	Haematocrit
HIV	Human immunodeficiency virus
HL	Hy's Law
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMPs	Investigational medicinal products
IRB	Institutional Review Board
LLOQ	Lower limit of quantification
LSM	Least-squares mean
MedDRA	Medical Dictionary for Regulatory Activities
OAE	Other significant adverse events
OTC	Over-the-counter
PD	Pharmacodynamics
PDF	Portable Document Format
PHL	Potential Hy's Law
PK	Pharmacokinetics
PT	Preferred term
qd	Once daily
QRS	ECG interval measured from the onset of the QRS complex to the J point
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
R&D	Research and Development
RR	The time between corresponding points on 2 consecutive R waves on ECG

Abbreviation or special term	Explanation
SAE	Serious adverse event (see definition in Section 6.3.1.2).
RT-PCR	Reverse transcriptase polymerase chain reaction
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SmPC	Summary of Product Characteristics
SoA	Schedule of assessments
SOC	System Organ Class
SOP	Standard operating procedure
SUSAR	Serious unsuspected serious adverse reaction
SZC	Sodium zirconium cyclosilicate
TBL	Total bilirubin
UK	United Kingdom
ULN	Upper limit of normal
US/USA	United States of America
WAD	Windows Allowance Document
WBC	White blood cell
WHO	World Health Organization

INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden
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Principal Investigator:	Dr. Thomas Koernicke Parexel Early Phase Clinical Unit Berlin PPD 14050 Berlin Germany Tel: PPD
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Analytical Laboratory: (pharmacokinetic sample analysis)	Bioanalytical Chemistry Covance Laboratories, Inc. PPD PPD Wisconsin 53704 USA Contact: PPD Bioanalytical Partnership Program Manager Covance Laboratories Inc. Tel: PPD Fax: PPD e-mail: PPD

Adverse Event Reporting:	AstraZeneca Patient Safety Data Entry Site Tata Consultancy Services Fax: PPD E-mail: PPD

A list and contact details of Investigators and other key study team members are provided in the Project Plan in the electronic Investigator's Site File. A list of all participating Investigators will be provided in the CSR.

1. INTRODUCTION

1.1. Background

Despite the association of hyperkalaemia with morbidity and mortality; and its high prevalence in common diseases, such as diabetes, chronic kidney disease, heart failure, and in patients on renin angiotensin aldosterone system (RAAS) inhibitor therapy, the treatment options available are limited and associated with significant safety and tolerability issues.

Sodium zirconium cyclosilicate (SZC) is an oral, non-polymer, inorganic cation-exchanger that has been approved as a novel therapy for the treatment of hyperkalaemia. It selectively captures potassium ions in exchange for sodium and hydrogen ions in the gastrointestinal tract, thereby reducing serum potassium concentration and removing potassium from the body through increased faecal excretion. Sodium zirconium cyclosilicate exerts its effect locally and it is not absorbed systemically. Clinical use is therefore not associated with systemic toxicity. The formulation developed for therapeutic use is an insoluble, odourless, tasteless, white, powder for oral suspension.

The efficacy of SZC in correcting hyperkalaemia and maintaining normokalaemia long term, irrespective of underlying morbidity, and its favourable safety profile have been well documented in the clinical programme. Sodium zirconium cyclosilicate has a rapid onset of effect and it maintains normokalaemia for up to 12 months. Unlike other oral drugs for hyperkalaemia (eg, resins and Patiromer), SZC is highly selective for potassium ions and its use is not associated with any clinically significant changes in the concentrations of other electrolytes such as calcium or magnesium.

All in all, SZC fulfils an unmet medical need; and provides an efficacious and safe therapeutic option for patients with hyperkalaemia.

1.1.1. Background to COVID-19

There is currently an outbreak of respiratory disease (COVID-19) caused by the novel SARS CoV-2 that was first detected in Wuhan City, Hubei Province, China in 2019. This new virus has rapidly spread across the globe causing the WHO to declare a pandemic situation on 11 March 2020. The countermeasures initiated by national and local governments worldwide and the recommendations issued by the health authorities have impacted current and new clinical studies. As the threat of pandemic burden, including new outbreaks locally or globally, will impact the further conduct of clinical studies, appropriate risk assessments and mitigation measures will need to be taken into consideration in all clinical studies to protect subjects, site staff and society as a whole.

Both the EMA (EMA 28 April 2020) and the FDA (FDA 16 April 2020), as well as national health authorities in Europe, have issued new guidelines that aim to provide recommendations

for actions for conduct of clinical studies of medical products during the COVID-19 pandemic. Since the pandemic situation is evolving, guidelines, recommendations, national laws and local restrictions may change at a high pace. Given the circumstances of a potentially relapsing pandemic or epidemic situations with regard to the spread of COVID-19, special attention will be paid to protect subjects participating in the study and site staff involved in the investigations against infection with SARS-CoV-2 as requested by the newly issued EMA guideline.

1.2. Rationale for Conducting this Study

Sodium zirconium cyclosilicate being an inorganic and crystalline compound, is not absorbed or metabolised by the body and therefore no metabolic or transporter-based drug-drug interactions are anticipated in association with SZC treatment. However, SZC can bind hydrogen ions which may result in increased pH in acidic environments such as the stomach. In general, an increase in gastric pH can alter the solubility of drugs with pH-dependent solubility and may result in an altered absorption profile of the drugs. Results from a Phase 1 study performed in healthy subjects to examine the potential for drug-drug interactions between SZC and a set of 9 compounds showed that co-administration of SZC affected the PK, primarily the Cmax values, of 5 compounds tested (Study ZS-009).

In general, other oral medications should be administered at least 2 hours before or 2 hours after SZC. Sodium zirconium cyclosilicate is not expected to impact systemic exposure of drugs that do not exhibit pH-dependent solubility and so spacing is not needed if it has been determined that the concomitant medication does not exhibit pH-dependent solubility.

Tacrolimus and cyclosporin are considered narrow therapeutic drugs and important to protect from graft rejection. Both tacrolimus and cyclosporin may cause hyperkalaemia and thus spacing is considered a complication in this patient population when there is a requirement to co-administer tacrolimus/cyclosporin with SZC for treatment of hyperkalaemia.

This study will investigate if the PK of tacrolimus and cyclosporin may be altered by the increased gastric pH resulting from SZC co-administration.

2. STUDY OBJECTIVES

2.1. Primary Objective

Table 1 Primary Objective and Outcome Measures

Primary Objectives	Outcome Measures
To assess the effect of co-administered SZC on the 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.

Abbreviations: AUCinf = area under concentration-time curve from time zero to infinity; Cmax = maximum observed concentration; PK = pharmacokinetics; SZC = sodium zirconium cyclosilicate.

2.2. Secondary Objective

Table 2 Secondary Objective and Outcome Measures

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, $t½\lambda_z$, and tmax.	AUClast, $t½\lambda_z$, 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.	AEs, vital signs (systolic and diastolic BP, pulse, and tympanic temperature), 12-lead ECGs, laboratory assessments (haematology, clinical chemistry and urinalysis).

Abbreviations: AEs = adverse events; AUClast = area under the concentration-time curve from time zero to time of last quantifiable concentration; BP = blood pressure; ECGs = electrocardiograms; PK = pharmacokinetics; SZC = sodium zirconium cyclosilicate; $t½\lambda z$ = half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve; tmax = time to reach maximum observed concentration.

For details, please refer to Section 10.2.1 on PK variables and Section 6.3 on safety variables.

3. STUDY DESIGN

3.1. Overall Study Design and Flow Chart

This study will be 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 will comprise:

- A screening period of maximum 28 days;
- Two treatment periods:
  - Treatment Period 1 starts 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 will be discharged from the Clinical Unit after the last PK sample was collected for this treatment period (Day 4).
  - Treatment Period 2 starts with admission to 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 will be 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 IMP administration.

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

- Treatment A: Tacrolimus [redacted].
- Treatment B: Tacrolimus [redacted] + SZC [redacted].
- Treatment C: Cyclosporin [redacted].
- Treatment D: Cyclosporin [redacted] + SZC [redacted].

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

Each subject will receive a single dose of oral capsules of tacrolimus [redacted]/cyclosporin [redacted] on 2 occasions, once alone and once in combination with oral suspension of SZC [redacted]. All drug administrations will occur after a 12 hour overnight fast.

Details on IMPs administration is provided in Section 5.4.3.

The Study Flow-Chart is presented in Figure 3-1 and the Overall Graphical Representation of the study scheme is illustrated in Figure 3-2.

The Schedule of Assessments displaying assessments/tasks and time points is presented in Table 3.

The study design is deemed appropriate for conduct in healthy volunteers during the COVID-19 pandemic (Section 3.3.3).

Figure 3-1 Study Flow Chart

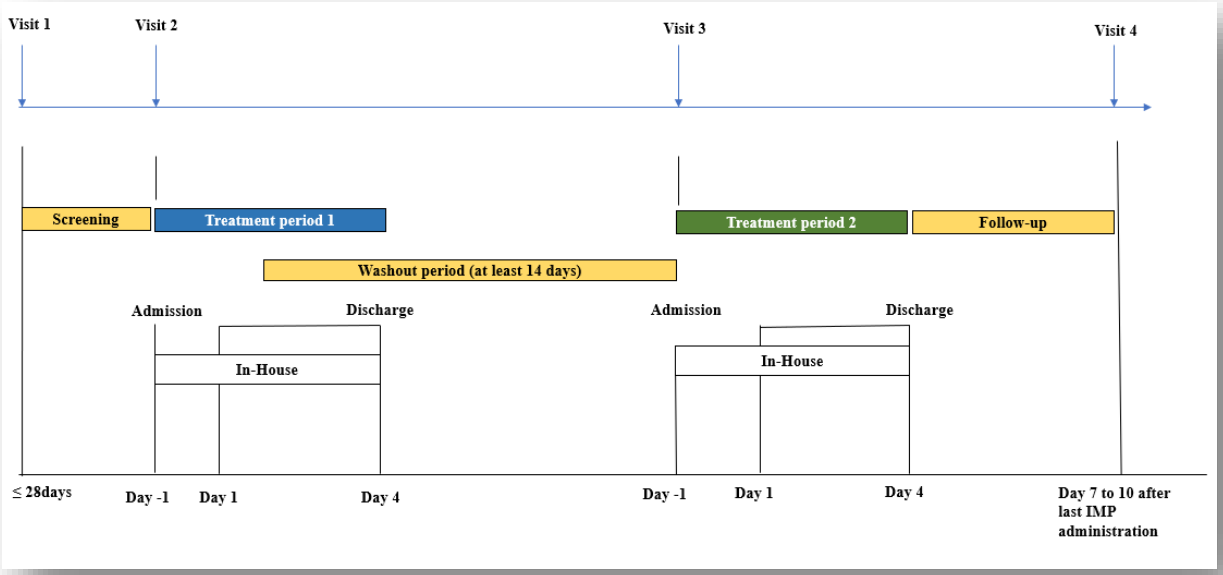
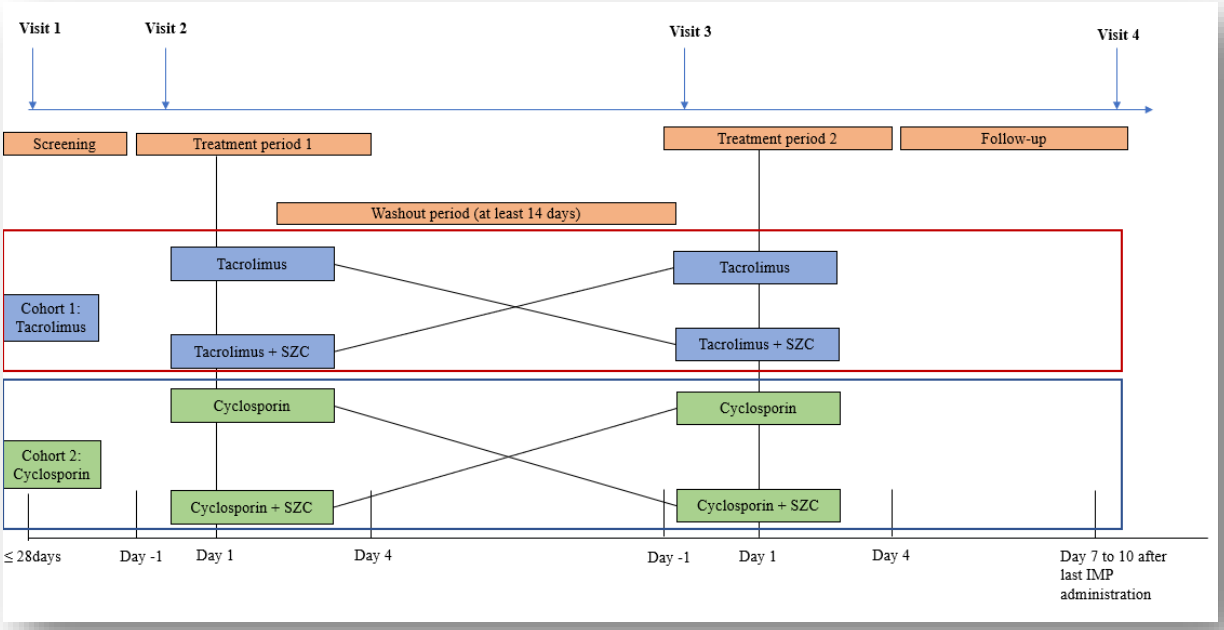


Figure 3-2 Overall Graphical Representation of the Study



Abbreviations: IMPs = investigational medicinal products; SZC = sodium zirconium cyclosilicate.
Single doses of all IMPs on indicated days: SZC: CCI, tacrolimus: CCI, cyclosporin: CCI.

Table 3 Schedule of Assessments

Visit Number	**Visit 1**	**Visit 2**		**Visit 3**		**Visit 4**
Study Period	**Screening**	**Treatment Period 1** [a]		**Treatment Period 2**		**Follow-up/Early Termination Visit**
Study Days	**-28 to -2**	**-1**	**1 to 4**	**-1**	**1 to 4**	**At 7-10 days after last IMP administration**
Inclusion/exclusion criteria	X	X				
Informed consent	X					
Randomisation		X				
Demographic data	X					
Weight and height	X					X (only weight)
Medical and surgical history	X					
Prior and concomitant medications	X	X	X	X	X	X
Urinary drug/alcohol, cotinine screen	X	X		X		
Viral serology	X					
FSH testing [b]	X					
Residence at Clinical Unit [c]		X	X	X	X	
Non-residential visit	X					X
Investigational Medicinal Product Administration						
Tacrolimus/cyclosporin [d]			X (Day 1, 0 h)		X (Day 1, 0 h)	
SZC			X (Day 1, 0 h) [e]		X (Day 1, 0 h) [f]	
Pharmacokinetics						
Blood sample for PK analysis of tacrolimus/cyclosporin [g]			X		X	X
Safety and Tolerability						
Physical examination	X	X (brief)		X (brief)		X
12-Lead ECG	X	X	X [h]	X	X [h]	X
Vital signs	X	X	X [i]	X	X [i]	X

Visit Number	Visit 1	Visit 2		Visit 3		Visit 4
Study Period	**Screening**	**Treatment Period 1 [a]**		**Treatment Period 2**		**Follow-up/Early Termination Visit**
Study Days	**-28 to -2**	**-1**	**1 to 4**	**-1**	**1 to 4**	**At 7-10 days after last IMP administration**
Clinical laboratory assessments	X	X	X[j]	X	X[j]	X
Serum potassium			X[k]		X[k]	
Urinalysis	X	X	X[j]	X	X[j]	X
Adverse events questioning and monitoring	Only SAEs	Only SAEs	X	X	X	X
COVID-19 Assessments						
Tympanic temperature	X	X	X[l]	X	X[l]	X
Pre-visit phone call [m]	X	X		X		X
SARS-CoV-2 RT-PCR [n]		X		X		
SARS-CoV-2 antibody testing	X					

[a] Dosing on Day 1 of Treatment Period 1 is followed by a washout period of at least 14 days.
[b] Female subjects only.
[c] Residential periods start on Day -1 and end at 72 hours after dosing on Day 1 of each treatment period. Subjects should come to the Clinical Unit in the morning of Day -1 of each treatment period to have fasting safety laboratory samples collected and having results available in the afternoon to decide on the subject's eligibility/continuation.
[d] Single doses of tacrolimus CCI or cyclosporin CCI will be administered per assigned cohort and treatment sequence on Day 1 of each treatment period, after an overnight fast of 12 hours.
[e] For subjects assigned to BA or DC treatment sequence.
[f] For subjects assigned to AB or CD treatment sequence.
[g] Blood samples for tacrolimus/cyclosporin PK analysis to be collected at pre-dose, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours post-dose.
[h] 12-Lead ECGs to be taken at pre-dose, 4, 24, 48, and 72 hours post-dose.
[i] Vitals signs (BP, pulse; supine) to be performed at pre-dose, 4, 24, 48, and 72 hours post-dose.
[j] Clinical laboratory assessments and urinalysis to be performed 48 hours post-dose.
[k] Blood samples for serum potassium levels to be taken at pre-dose and at 4, and 72 hours post-dose.
[l] Tympanic temperature will be performed daily; pre-dose on Day 1.
[m] Phone calls will be made 1 day prior to each respective visit to record signs and symptoms of COVID-19 or any contact with persons having confirmed SARS-CoV-2 infection. In case of signs or symptoms or contact, the visit will be cancelled and reason for cancellation will be appropriately documented.
[n] The result of the SARS-CoV-2 RT-PCR testing must be available prior to dosing on Day 1 of each treatment period.

Abbreviations: BP = blood pressure; COVID-19 = coronavirus disease 2019; ECG = electrocardiogram; FSH = follicle stimulating hormone; PK = pharmacokinetics; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse events; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SZC = sodium zirconium cyclosilicate.

3.1.1. Order of Assessments

It is important that PK sampling occurs as close as possible to scheduled time. In order to achieve this, other assessments scheduled at the same time may be initiated prior to the time point. The sequence at a particular time point is:

1 Electrocardiograms
2 Vital signs (systolic and diastolic BP, pulse, and tympanic temperature)
3 Pharmacokinetic blood sampling (will be drawn at the specified time points)
4 Safety blood sampling for clinical laboratory examinations

Details of acceptable tolerance windows for safety PK assessments will be included in a WAD which will be agreed upon and signed off before the start of the study.

3.1.2. End of Study

The end of study is defined as the last subject's last visit/contact to the Clinical Unit.

3.1.3. Expected Duration of the Study

The expected total study duration, including the screening period, for each subject will be at least 58 days (8 weeks).

Table 4 Expected Duration of Each Study Part

Screening	Between 1 to 27 days before dosing (Day -28 to Day -2).
Treatment Period 1	Five days during which subjects will be resident at the Clinical Unit from the day before dosing (Day -1) with discharge on Day 4 after the last PK sample.
Washout Period	At least 14 days between the 2 treatment periods, starting the day after the IMP administration in Treatment Period 1.
Treatment Period 2	Five days during which subjects will be resident at the Clinical Unit from the day before next IMP dosing with discharge on Day 4 after the last PK sample.
Follow-up Visit	7 to 10 days after the last IMP administration.
Total Duration	Approximately 58 days (8 weeks).

Abbreviations: IMP = investigational medicinal product; PK = pharmacokinetics.

3.2. Rationales for Study Design and Dose Selection

3.2.1. Rationale for Study Design

The present study will be an open-label, randomised sequence, 2-period, 2-cohort, 2 treatments in each cohort, cross-over study in healthy subjects to investigate if the PK of tacrolimus and cyclosporin may be altered by SZC co-administration.

The US FDA recommendations of clinical drug interaction studies advocates the use of cross-over design over parallel designs for potential DDI studies to reduce the inter-subject variability.

The choice of healthy volunteers as the subject population for this drug interaction study is also justified by recommendations provided by regulatory authorities, with the possibility of findings in this study to be used to predict the findings in intended patient population.

All the PK endpoints selected for this study are also in line with the PK assessments that can be used for interpretation of drug interactions as recommended by the regulatory authorities.

3.2.2. Dose Rationale

The doses of the IMPs used in drug interaction studies should maximise the possibility of identifying a drug-drug interaction, and the use of maximum dose and the shortest dosing interval of the IMPs under the intended conditions of use or as labelled is strongly advocated.

Long-term maintenance treatment with SZC of up to 12 months was evaluated in hyperkalaemic patients in 2 open-label studies (ZS-004E and ZS-005) utilising a dose titration scheme with a starting dose of [CCI] qd or [CCI] qd, titrated to a maximum of [CCI] qd or a minimum of [CCI] once every other day. The dose of [CCI] was shown to be safe and tolerable in both the studies (IB, SZC 2019). Based on this data, the dose of [CCI] SZC to be evaluated in the current study population of healthy volunteers is considered to be safe.

The doses selected for tacrolimus ([CCI]) and cyclosporin ([CCI]) are the typical starting doses in organ transplanted patients and therefore is deemed to be safe in the current study population of healthy volunteers (Prograf SmPC, Cyclosporin SmPC).

3.3. Risk-benefit Assessment

3.3.1. Risks

3.3.1.1. Risks Associated with SZC

The safety of SZC has been evaluated in clinical trials for the reduction of hyperkalaemia involving over 2600 patients. The most commonly reported ADRs were oedema-related events, which were reported by 5.7% of SZC subjects; 2.7%, 5.2%, 14.3%, and 1.7% of subjects randomised to SZC [CC], [CCI], [CCI], and placebo, respectively. Of the oedema-related events, 53% were managed with initiating diuretic treatment or adjusting the diuretic dose, while the remainder did not require treatment. Hypokalaemia (defined as serum potassium levels <3.5 mmol/L), a result of the pharmacological action of the drug, was observed in 4.1% of subjects treated with SZC. These events were resolved with dose adjustment or discontinuation of SZC treatment.

To date, 3 clinical trials were conducted with SZC in healthy volunteers at doses of CCI and CCI (CCI), and no events of hypokalaemia in were reported in any of these 3 studies.

More detailed information about the known risks and reasonably expected adverse events of SZC may be found in the IB (IB, SZC 2019).

3.3.1.2. Risks Associated with Tacrolimus

The most commonly reported AEs associated with the use of tacrolimus include increased risk of viral, bacterial, fungal, and protozoal infections, Epstein Barr Virus-associated lymphoproliferative disorders and skin malignancies, blood and lymphatic system disorders like anaemia, leukopenia, thrombocytopenia, leucocytosis, red blood cell analyses abnormal, allergic and anaphylactoid reactions, metabolism and nutrition disorders like hyperglycaemic conditions, diabetes mellitus, and hyperkalaemia, psychiatric disorders like insomnia, nervous system disorders like tremor and headache, eye disorders like vision blurred and photophobia, ear disorders like tinnitus, cardiac disorders like ischaemic coronary artery disorders and tachycardia, vascular disorders like hypertension, respiratory disorders like dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis, cough, nasal congestion and inflammations, gastrointestinal disorders like diarrhoea and nausea, hepatobiliary disorders like cholestasis and jaundice, hepatocellular damage and hepatitis, and cholangitis, skin disorders like pruritus, rash, alopecia, acne, and sweating increased, musculoskeletal disorders like arthralgia, muscle spasms, pain in extremity, and back pain, kidney problems like renal impairment, and others like asthenic conditions, febrile disorders, oedema, pain and discomfort, body temperature perception disturbed, hepatic enzymes and function abnormalities, blood alkaline phosphatase increased, and weight increased.

More detailed information about the known risks and reasonably expected adverse events of tacrolimus may be found in SmPC (Prograf SmPC).

3.3.1.3. Risks Associated with Cyclosporin

The principal AEs observed in clinical trials and associated with the administration of cyclosporin include renal dysfunction, tremor, hirsutism, hypertension, diarrhoea, anorexia, nausea and vomiting. Leukopenia, hyperlipidaemia, headache, diarrhoea, gingival hyperplasia, peptic ulcer, abdominal discomfort, abnormal hepatic function, myalgia and muscle cramps, pyrexia, and fatigue are also among the commonly reported AEs associated with the use of cyclosporin in clinical trials.

More detailed information about the known risks and reasonably expected adverse events of cyclosporin may be found in SmPC (Cyclosporin SmPC).

3.3.2. Benefits

This study will not provide any direct medical benefits to healthy subjects who participate in this clinical study. Subjects will be monitored under supervision in a Clinical Unit, where management of any AEs can take place. The chosen doses for all the 3 IMPs have been well tolerated in other populations that have been studied.

The identified risks with all the 3 IMPs are manageable with proper monitoring, precautionary measures and mitigation. Overall, the benefit/risk assessment supports the administration of these IMPs to patients with respective indications, and thus the administration of single doses to healthy volunteers in the current study.

3.3.3. Risk Assessment for COVID-19 Pandemic

The study drug, SZC is an oral, non-polymer inorganic cation-exchanger that has been approved as a novel therapy for the treatment of hyperkalaemia. It selectively captures potassium ions in exchange for sodium and hydrogen ions in the gastrointestinal lumen, thereby reducing serum potassium concentration and removing potassium from the body through increased faecal excretion. As SZC exerts its effect locally and is not absorbed systemically or metabolised by the body, no metabolic or transporter-based drug-drug interactions are anticipated in association with SZC treatment (IB, SZC 2019).

Cyclosporin is a potent immunosuppressive agent and is used to prevent graft rejection following solid organ transplantation. Although the mode of action is not fully understood, all available evidence suggests that cyclosporin acts specifically and reversibly on lymphocytes. Cyclosporin has been reported to inhibit the replication of diverse coronaviruses in vitro but this effect is not confirmed for the SARS-CoV-2. Cyclosporin may be beneficial in severe stages of COVID-19 based on inhibition on pro-inflammatory interleukin-2 (IL-2) (Cyclosporin SmPC).

Tacrolimus is an immunosuppressive drug used mainly after allogeneic organ transplant to lower the risk of organ rejection. Tacrolimus side effects would not pose risks in healthy volunteers who does not have pre-existing risk factors (Prograf SmPC).

It appears to be unlikely, that SZC, tacrolimus, or cyclosporin will worsen COVID-19 in case the subject acquires SARS-CoV-2. Only healthy subjects who are currently not infected with SARS CoV-2 under the specific precaution will be enrolled. Thus, the study is deemed feasible in the appropriate study population and no impact of the COVID-19 pandemic is expected in this healthy volunteer study.

For subjects in this study, the risk to be exposed to SARS-CoV-2 or to suffer from COVID-19 will be similar to the general population. However, the risk of exposure to infected people cannot be completely excluded as the subjects may need to expose themselves to public areas

(eg, commute to the site) and have additional human contact (eg, with site staff and other participants of the clinical study).

Measures to mitigate the additional risks caused by COVID-19 include:

- This study is going to restart enrolling only when the Sponsor and Parexel in collaboration deem it is safe to start the study. In addition, the study will not start until the local confinement measures or other safety restrictions linked to the COVID-19 pandemic are lifted by the local authorities.
- Current national laws and local recommendations for prevention of pandemic will be strictly adhered to.
- Subjects will be closely monitored for any signs and symptoms of COVID-19, including fever, dry cough, dyspnoea, sore throat, fatigue, and loss of taste or smell throughout the study. Once clinical signs of infection are reported by subjects, the Investigator needs to determine whether samples can be collected, and safety data can be recorded on site. If not, AEs and concomitant medications will be obtained via phone calls. Daily body temperature measurements during in-house confinement and outpatient visits will be implemented.
- The IMP will not be administered to subjects upon identification of any signs of COVID-19 infection.
- Confirmation of COVID-19 infection will be made by mandatory testing at screening (serology) and at admission (RT-PCR) to mitigate risk for infection at the site and for the participants.
- The probability of virus transmission will be controlled as much as possible by:
  - Advice for subject to adhere to local requirements for reduction of the public exposure while ambulatory.
  - All subjects are contacted by phone 1 day prior to every visit for assessing COVID-19 symptoms and signs and are asked not to attend the site in case of suspected reports. In addition, subjects are asked for any contact with a person who has tested positive for SARS-CoV-2. If applicable, subjects will be referred to the local health care system for further follow-up and treatment.
  - Physical distancing and person-to-person contact restrictions will be applied during site visits and in-house confinement.
  - Where physical distancing is not possible, personal protective equipment will be used by subject (face mask, gloves) and staff (for example but not limited to face masks, gloves, protectors, medical suits) if deemed appropriate by the Investigator and site staff and guided by local requirements.
  - Logistical improvements of the site and structural measures of the study site building will be implemented to further improve physical distancing.

4. STUDY POPULATION

4.1. Selection of Study Population

The Investigator should keep a subject screening log of all potential subjects who consented and were subjected to screening procedures.

Subjects who fail to meet the inclusion criteria or meet any exclusion criterion should not, under any circumstances, be randomised in the study. There can be no exceptions to this rule.

This study will be conducted in male and female subjects. The study may not necessarily be balanced regarding gender. The study was not formally powered to detect differences between genders for the primary endpoint. It is not planned to perform sub-analyses on gender.

4.1.1. Inclusion Criteria

For inclusion in the study, subjects should fulfil the following criteria:

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 must be of non-childbearing potential, confirmed at screening and fulfil the criteria detailed in Section 4.2.1.1 by fulfilling 1 of the following criteria.
   (i) Postmenopausal defined as amenorrhea for at least 12 months or more following cessation of all exogenous hormonal treatments and FSH levels in the postmenopausal range.
   (ii) Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.

4 Male subject must adhere to the contraception methods details in Section 4.2.1.2.

5 Have a BMI between 18.5 and 30 kg/m^2 inclusive and weigh at least 50 kg and no more than 100 kg inclusive.

6 Subject is able to understand and communicate in German.

7 Willing and able to comply with all required study procedures.

4.1.2. Exclusion Criteria

Subjects will not enter the study if any of the following exclusion criteria are fulfilled. For values deviating from the reference or specified range, 1 retest is allowed.

1 History of any clinically significant disease or disorder which, in the opinion of the Investigator, may either put the volunteer at risk because of participation in the study, or influence the results or the volunteer's ability to participate in the study.

2 History or presence of gastrointestinal, hepatic or renal disease, or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs.

3 Any clinically significant illness, medical/surgical procedure, or trauma within 4 weeks prior to screening.

4 Any clinically significant abnormalities in clinical chemistry, haematology, or urinalysis results, at screening visit and/or admission to the Clinical Unit as judged by the Investigator.

5 Abnormal vital signs, after 5 minutes rest in supine position, at screening visit and/or admission to the Clinical Unit, defined as any of the following:

- Systolic BP > 140 mmHg.
- Diastolic BP > 90 mmHg.
- Pulse < 50 or > 90 bpm.

6 Any clinically important abnormalities in rhythm, conduction or morphology of the 12-lead safety ECG, at screening visit and/or admission to the Clinical Unit, defined as any of the following:

- Prolonged QTcF > 450 ms or family history of long QT syndrome.
- PR (PQ) interval shortening < 120 ms (PR > 110 ms but < 120 ms is acceptable if there is no evidence of ventricular pre-excitation).
- PR (PQ) interval prolongation (> 220 ms) intermittent second (Wenckebach block while asleep is not exclusive) or third-degree AV block, or AV dissociation.
- Persistent or intermittent complete bundle branch block (BBB), incomplete bundle branch block (IBBB), or intraventricular conduction delay (IVCD) with QRS > 110 ms. Subjects with QRS > 110 ms but < 115 ms are acceptable if there is no evidence of ventricular hypertrophy or pre-excitation.

7 Any positive result on screening visit for serum hepatitis B surface antigen or anti-hepatitis B core antigen antibody, hepatitis C antibody, and HIV testing.

8 Positive screen for drugs of abuse, alcohol, or cotinine at screening visit or on each admission to the Clinical Unit.

9 Known or suspected history of alcohol or drug abuse or excessive intake of alcohol as judged by the Investigator. Excessive intake of alcohol defined as the regular consumption of more than 24 g of alcohol per day for men or 12 g of alcohol per day for women.

10 Current smokers or those who have smoked or used nicotine products (including e-cigarettes) within the 3 months prior to screening visit.

11 Has received another new chemical entity (defined as a compound which has not been approved for marketing) within 3 months of the first administration of IMP in this study. The period of exclusion begins 3 months after the final dose or 1 month after the last visit whichever is the longest.
Note: subjects consented and screened, but not randomised in this study or a previous phase I study, are not excluded.

12 Plasma donation within 1 month of screening visit or any blood donation/loss more than 500 mL during the 3 months prior to screening visit.

13 History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the Investigator or history of hypersensitivity to drugs with a similar chemical structure or class to SZC, tacrolimus, or cyclosporin.

14 Use of drugs with enzyme-inducing properties such as St John's Wort within 3 weeks prior to screening.

Use of any prescribed or non-prescribed medication including antacids, analgesics (other than paracetamol/acetaminophen), herbal remedies, megadose vitamins (intake of 20 to 600 times the recommended daily dose) and minerals during the 2 weeks prior to the first administration of IMP or longer if the medication has a long half-life.

15 Excessive intake of caffeine-containing drinks or food (eg, coffee, tea, chocolate) as judged by the Investigator. Excessive intake of caffeine defined as the regular consumption of more than 600 mg of caffeine per day (eg, > 5 cups of coffee) or would likely be unable to refrain from the use of caffeine-containing beverages during confinement at the investigational site.

16 Involvement of any AstraZeneca, Parexel, or study site employee or their close relatives.

17 Subjects who have previously received SZC.

18 Judgment by the Investigator that the subject should not participate in the study if they have any ongoing or recent (ie, during the screening period) minor medical complaints that may interfere with the interpretation of study data or are considered unlikely to comply with study procedures, restrictions, and requirements.

19 Subjects with any special dietary restrictions such as subjects who are lactose intolerant or are vegetarians/vegans.

20 Subjects who cannot communicate reliably with the Investigator.

21 Vulnerable subjects, eg, those who are kept in detention, protected adults under guardianship, trusteeship, or committed to an institution by governmental or juridical order.

22 Subject has a positive RT-PCR test for SARS-CoV-2 on admission.

23 Subject has clinical signs and symptoms consistent with SARS-CoV-2 infection, eg, fever, dry cough, dyspnoea, sore throat, fatigue, loss of taste or smell or a positive SARS-CoV-2 test result within the last 4 weeks prior to screening or on admission.

24 Subject who had a severe course of COVID-19 (extracorporeal membrane oxygenation, mechanically ventilated).

25 Recent (within previous 14 days) exposure to someone who has COVID-19 symptoms or positive test result.

26 Recent (within previous 14 days) visit to a healthcare facility where COVID-19 patients are being treated.

27 Subjects who are regularly exposed to COVID-19 as part of their daily life (eg, health care professionals working in COVID-19 wards or at emergency departments).

4.2. Restrictions During the Study

The following restrictions apply for the specified times during the study period:

1 On Day 1 of each treatment period, subjects will be fasted for 12 hours prior to dosing until 4 hours after dosing. No fluids will be allowed apart from water which can be given until 1 hour prior to dosing and then from 2 hours after dosing (excluding water used in conjunction with IMP administration; see Section 5.4.3).

2 Subjects should not lie fully supine (unless specified for certain assessments) for 4 hours after dosing.

3 Subjects should not engage in any strenuous activity from 72 hours prior to check-in until after their final follow-up visit.

4 Prior to each treatment period, subjects should abstain from alcohol for 72 hours prior to check-in until after their last PK sampling visit. Subjects should also abstain from alcohol for 72 hours before their final follow-up visit.

5 Prior to each treatment period, subjects should abstain from caffeine-containing foods and beverages for 24 hours prior to check-in until discharge from the Clinical Unit.

6 Subjects should abstain from grapefruit or grapefruit juice, Seville oranges, quinine (eg, tonic water) from 7 days prior to check-in on Day -1 until after their follow-up visit.

7 During in-house stay, subjects will receive a standard diet, which excludes all alcohol and grapefruit-containing products. No additional food or beverages must be consumed while in the Clinical Unit.

8 During the subjects' outpatient periods, subjects should abstain from consuming high energy drinks (eg, Red Bull®), and food containing poppy seeds and any OTC medication or herbal preparations until after their final follow-up visit has been completed. Subjects should also limit their caffeine intake to equivalent of 3 servings of coffee per day (1 serving = 330 mL cola, 180 mL coffee, or 240 mL tea). Subjects should consume no more than 2 units of alcohol per day and completely abstain from alcohol from 72 hours prior to their next check-in.

9 Subjects will be required to abstain from blood or plasma donation until 3 months after the final medical examination at the follow-up visit.

10 Subjects should avoid any vaccination from screening until 14 days after the final dose of IMP.

11 Subjects should avoid excess unprotected sun exposure and should not receive concomitant ultraviolet B irradiation or psoralen and ultraviolet A photochemotherapy from screening until the final medical examination at the follow-up visit.

12 For medication restrictions, please refer to Section 5.6.

13 Subjects will be advised to adhere to local requirements for reduction of the public SARS-CoV-2 exposure while ambulatory. All subjects will be contacted by phone to assess COVID-19 symptoms and signs 1 day prior to each respective visit and will be asked not to attend the site in case of suspected infection. In addition, subjects will be asked for details of any contact with a person who has confirmed infection. If applicable, subjects will be referred to the local health care system. Physical distancing and person-to-person contact restrictions will be applied and explained to subjects while staying at the study site. Where physical distancing is not possible, subjects will be asked to use face masks and/or gloves if deemed appropriate by the Investigator and site staff and guided by local requirements.

4.2.1. Reproductive Restrictions

4.2.1.1. Women of Non-childbearing Potential

Women of non-childbearing potential are defined as female subjects who are permanently surgically sterilised or postmenopausal.

Permanent sterilisation includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy at least 6 weeks before screening but excludes bilateral tubal ligation. Bilateral oophorectomy alone is acceptable only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.

Females are considered postmenopausal if they have had amenorrhea for at least 12 months or more following cessation of all exogenous hormonal treatments and without an alternative medical cause and the FSH level is in the postmenopausal range.

4.2.1.2. Male Subjects

Restrictions for Male Subjects

There is limited or no information about effects that SZC, cyclosporin, or tacrolimus could have on the development of the foetus in humans. Therefore, it is important that woman of childbearing potential, who are the partners of male subjects, do not become pregnant during the study and for a total period of 3 months after the male subject has attended the study follow-up visit.

Male subjects who have been sterilised are required to use one barrier method of contraception (condom) from the time of IMP administration until after the follow-up visit. The subject must have received medical assessment of the surgical success.

As a precaution, all non-sterilised male subjects should avoid fathering a child by either true abstinence[1] or use a condom and their female partner/spouse has to be either of non-childbearing potential or has to use a highly effective contraception form of birth control, starting from the time of IMP administration until 3 months after the study follow-up visit. The female partner/spouse should be stable on their chosen method of birth control for at least 3 months after the first IMP dosing.

Highly effective contraception form of birth control, ie, a form of birth control with a failure rate of less than 1% per year when used consistently and correctly, are:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine system
- Bilateral tubal occlusion of female partner

Sperm Donation

Male subjects should not donate sperm for the duration of the study and for at least 3 months after the study follow-up visit.

Pregnancy

Subjects will be instructed that if their partner becomes pregnant during the study, this should be reported to the Investigator. The Investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject's partner is subsequently found to be pregnant after the volunteer is included in the

[1] Sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. It is only acceptable if preferred and usual lifestyle of the subject.

study, then consent will be sought from the partner and if granted, any pregnancy will be followed and the status of mother and/or child will be reported to the Sponsor after delivery.

A pregnancy notification form and follow-up will be completed.

4.3. Replacement of Subjects

As there is a goal of meeting a particular sample size in this study, the subjects who are withdrawn from the study due to AEs or changes in safety parameters will not be replaced unless required to meet the specific sample size for statistical purposes and if the Sponsor's responsible physician and the Investigator agree it is safe to do so. Subjects who withdraw or are withdrawn from the study for other reasons may be replaced following discussion with the Sponsor.

5. STUDY CONDUCT

5.1. Subject Enrolment and Randomisation

The Investigator will ensure:

- Signed informed consent is obtained from each potential subject before any study specific procedures are performed.
- Each potential subject is assigned a unique enrolment number at screening upon signing the informed consent.
- The eligibility of each subject is in accordance with the inclusion and exclusion criteria.
- Each eligible subject is assigned a unique randomisation code.

Randomisation can be done on the evening prior to the day of first IMP dosing.

Randomisation codes will be assigned strictly sequentially as subjects become eligible for enrolment (codes to be used without leading zero[s]).

When using unique enrolment number, the specific format must be followed (ie, reduced enrolment number “01001” in ClinBase™ and on labels, full enrolment number “E0001001” for outputs).

If a subject withdraws his/her participation in the study, then his/her randomisation code cannot be reused. If a replacement is mandated, replacement subjects will receive a new randomisation number and will be allocated to the same treatment sequence as the replaced subject.

5.1.1. Procedures for Randomisation

Upon completion of the randomisation requirements specifications form, the randomisation will be produced by Parexel according to the AstraZeneca randomisation system (AZRand).

Subjects will be enrolled into Cohort 1 and Cohort 2 sequentially.

Subjects in Cohort 1 and Cohort 2 will be randomised in a 1:1 ratio to receive one of the 2 treatment sequences and then cross-over to the other: Tacrolimus alone (treatment A) followed by the combination treatment of tacrolimus and SZC (treatment B) or vice versa in Cohort 1 and cyclosporin alone (treatment C) followed by the combination treatment of cyclosporin and SZC (treatment D) or vice versa in Cohort 2.

The randomisation will be completed for each cohort using consecutive randomisation codes.

The number of subject identifiers generated for the study will account for the number of enrolment subjects per the sample size calculation (N = 60 total, as N = 30 for each of the

2 cohorts and N = 15 for each of the 4 treatment sequence) as well as providing sufficient randomisation numbers for replacements. For this study, a total of 120 subject identifiers will be randomly assigned to the treatment sequence(s): AB|BA and CD|DC.

5.2. Procedures for Handling Incorrectly Enrolled Subjects

Subjects who fail to meet the inclusion criteria or meet any exclusion criterion should not, under any circumstances, be randomised into the study. There can be no exceptions to this rule. Where a subject, who does not meet the selection criteria, is randomised in error and this is identified before dosing, the subject should be withdrawn from the study. If a subject is withdrawn prior to dosing they will be replaced. If a subject, who does not meet the selection criteria and has been dosed before the error is identified, the subject should be withdrawn and advised to continue safety assessments to ensure their safety. The Investigator will inform the AstraZeneca Lead Physician of the error and a joint decision made as to whether the subject should be replaced.

5.3. Blinding

This is an open-label study and blinding is not applicable.

5.4. Treatments

5.4.1. Identity of the Investigational Medicinal Product

Details on the identity of the IMP are presented in Table 5.

Table 5 Identity of the Investigational Medicinal Product

Investigational Medicinal Product Name	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 Sachet	CCI	CCI
Dose:	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
Special handling requirements:	Not applicable	Not applicable	Not applicable

Details of the batch numbers will be included in the trial master file and the final CSR.

5.4.2. Supply of Investigational Medicinal Product

The IMP, SZC will be supplied by AstraZeneca in sachets packed in cartons.

The IMPs, tacrolimus and cyclosporin will be sourced by Parexel.

A technical agreement between the Investigator and AstraZeneca will be in place to cover all pharmacy related activities, detailing roles and responsibilities prior to receipt of the IMPs at the Clinical Unit.

A release document signed by a legally authorised Qualified Person will be placed in the appropriate section of the Trial Master File to document labelling and dispensing of the IMPs to the subject.

5.4.3. Dose and Treatment Regimens

Each subject will receive single oral doses of SZC and/or tacrolimus/cyclosporin under fasted conditions. The doses will be administered after an overnight fast of at least 12 hours.

Sodium zirconium cyclosilicate will be administered orally as suspension, containing CCI of IMP dissolved in 45 mL of water. Tacrolimus and cyclosporin will be administered as oral capsules for swallowing with 200 mL of non-carbonated water at room temperature.

On days of IMP co-administration, SZC will be administered immediately followed by tacrolimus/cyclosporin.

Subjects will be allowed to drink water to prevent dehydration until 1 hour before dosing. Water will be allowed ad libitum from 2 hours after dosing and a standard meal will be given 4 hours after dosing.

After dosing, subjects will remain semi-supine on their bed or sitting (except when necessary for study procedures) until 4 hours after dosing.

Other restrictions, including posture control are described in Section 4.2. Data of subjects may be excluded from the PK analysis set as described in Section 11.1.2.

5.4.4. Labelling

Labels will be prepared in accordance with GMP and local regulatory guidelines.

The labels will fulfil GMP Annex 13 requirements for labelling.

5.4.5. Storage and Handling Procedures

All IMPs will be stored in a secure facility, details of storage conditions will be provided on the label of the IMPs.

The AstraZeneca staff will be permitted upon request to audit the supplies, storage, dispensing procedures, and records.

5.5. Concomitant and Post-study Treatment(s)

Apart from paracetamol/acetaminophen, no concomitant medication or therapy will be allowed.

The subjects should be instructed that no other medication is allowed, including herbal remedies, vitamin supplements and OTC products, without the consent of the Investigator.

Medication, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the Investigator during the in-house period. Such instances will be registered as important protocol deviations unless the medication is paracetamol/acetaminophen.

When any medication is required, it should be prescribed by the Investigator. Following consultation with AstraZeneca Lead Physician, the Investigator should determine whether or not the subject should continue in the study. Administration of concomitant medications may be documented as a protocol deviation after consultation of the Investigator with AstraZeneca Lead Physician.

5.6. Treatment Compliance

Dosing will take place at the Parexel Early Phase Clinical Unit.

The administration of all IMPs will be recorded in ClinBase™.

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

5.6.1. Drug Accountability, Dispensing and Destruction

The IMPs provided for this clinical study will be used only as directed in this CSP.

In accordance with GCP, the investigational site will account for all supplies of SZC, tacrolimus and cyclosporin. Details of receipt, storage, assembly/dispensing and return will be recorded.

All unused supplies of all IMPs will either be destroyed by Parexel or returned at the end of the study in accordance with instruction by the Sponsor.

5.7. Discontinuation of Investigational Product and Withdrawal from Study

Individual subjects may be discontinued from IMPs in the following situations:

- Severe non-compliance to study protocol.

Individual subjects will be discontinued from IMPs in the following situations:

- Healthy subject decision. The healthy subject is at any time free to discontinue treatment, without prejudice to further treatment.
- Adverse events which in the opinion of the Investigator warrant discontinuation of the subject from treatment for his/her well-being, including (but not limited to):
  - A serious adverse reaction (ie, a SAE considered at least possibly related to IMP administration).
  - A severe non-serious adverse reaction (ie, a severe non-serious AE considered at least possibly related to IMP administration).
- Any significant and clinically relevant changes in the safety parameters (eg, ECG, BP, pulse, laboratory assessments, and AE) making the continuation of IMP administration unjustified, including:
  - Any case of Potential Hy's Law (PHL) or Hy's Law (HL) according to threshold values listed in Appendix C.
  - QTc prolongation defined as QTcF > 500 ms, or a prolongation from baseline of > 60 ms, confirmed on a repeat 12-lead ECG.
  - Hypertension defined as an increase in resting supine systolic BP > 40 mmHg to above 180 mmHg and persisting for at least 10 minutes.
  - Tachycardia defined as resting supine heart rate > 125 bpm persisting for at least 10 minutes.
  - Symptomatic bradycardia defined as resting supine heart rate < 45 bpm or asymptomatic bradycardia defined as resting heart rate < 40 bpm while awake persisting for at least 10 minutes.
  - Severe hypokalaemia defined as serum potassium < 3.0 mmol/L (confirmed by repeat measurement).
- Any suspected or confirmed COVID-19 case in the judgment of the Investigator or Sponsor to protect the safety of the subject, other study participants or study site staff.

The appropriate AE form in the CRF must be completed.

5.7.1. Procedures for Withdrawal of a Subject from the Study

If a subject withdraws or is withdrawn from the study, the subject will be encouraged to continue with safety assessments in the respective treatment period and return to the Clinical Unit for an Early Termination Visit to ensure the subject's safety.

5.7.2. Procedures for Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods) until the end of study. These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study. Site personnel, or an independent third party, will attempt to collect the vital status of the subject within legal and ethical boundaries for all subjects randomised, including those who did not get IMP.

5.8. Premature Termination of the Study

The study will be terminated prematurely if:

- The Investigator and the Sponsor assess that the number and/or severity of AEs justify discontinuation of the study in accordance with stopping rules listed in the Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07 Rev.1), ie,:
  - A 'serious' adverse reaction (ie, an SAE considered at least possibly related to the IMP administration) in 1 subject.
  - 'Severe' non-serious adverse reactions (ie, severe non-serious AEs considered at least possibly related to the IMP administration) in 2 subjects, independent of within or not within the same SOC.
- The Sponsor considers the applied doses of the IMPs to be no longer relevant.
- The Sponsor decides to discontinue the study.

- New data become available and raise concern about the safety of IMPs so that continuation would pose potential risks to the subjects.
- New data become available regarding COVID-19, which raise concern for the safe study conduct so that continuation would pose potential risks to the subjects or the study site staff.

Premature termination of the study must be mutually agreed upon by the Investigator and the Sponsor and must be documented. However, study results will be reported according to the requirements outlined in this CSP as far as applicable.

6. COLLECTION OF STUDY VARIABLES

6.1. Recording of Data

Standard measures to assess PK, safety and tolerability apply during the study. For the single doses of IMPs planned to be given during this study, no safety issues are expected.

For timing of assessments refer to Table 3.

6.2. Enrolment and Screening Procedures

Viral serology for assessment for hepatitis and HIV, and tests for use/abuse of drugs of abuse, alcohol, and smoking (cotinine) will be carried out, and subjects who have positive results for any of these will be excluded from the study. In addition, SARS-CoV-2 serology at screening and SARS-CoV-2 RT-PCR on admission will be assessed for eligibility. Follicle stimulating hormone (females only) and use of concomitant medication will also be assessed and reported.

Phone calls will be made 1 day prior to each respective visit to record signs and symptoms of COVID-19 or any contact with persons having confirmed SARS-CoV-2 infection. In case of signs or symptoms or contact, the visit will be cancelled and reason for cancellation will be appropriately documented.

6.3. Safety and Eligibility Measurements

Safety and tolerability variables will include:

- Adverse events
- Clinical laboratory assessments (haematology, clinical chemistry, and urinalysis).
- Physical examination
- 12-Lead ECGs
- Vital signs (systolic and diastolic BP, pulse, and tympanic temperature)

6.3.1. Adverse Events

6.3.1.1. Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including washout period, even if no IMP has been administered.

6.3.1.2. Definitions of Serious Adverse Event

An SAE is an AE occurring during any study phase (ie, screening, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above

For further guidance on the definition of an SAE, see Appendix A of this CSP.

Adverse events for malignant tumours reported during a study should generally be assessed as SAEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a non-serious AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

6.3.1.3. Other Significant Adverse Events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs or where relevant AEs leading to discontinuation of IMP and withdrawal from the study. Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Safety Physician, be considered OAEs and reported as such in the CSR. A similar review of other data from laboratory tests, vital signs, ECGs and other safety assessments will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

6.3.1.4. Recording of Adverse Events

Time Period for Collection of Adverse Events

Non-serious AEs will be collected from administration of IMP in Treatment Period 1 throughout the treatment period and including the Follow-up Visit.

Serious AEs will be recorded from the time of informed consent.

Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the subject's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in ClinBase™.

AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collected for each AE:

- AE diagnosis/description.
- The date and time (if known) when the AE started and stopped.
- Maximum intensity.
- Whether the AE is serious or not.
- Investigator causality rating against the IMPs (yes or no).
- Action taken with regard to IMP.
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE.
- Date Investigator became aware of SAE.
- AE is serious due to.
- Date of hospitalisation.
- Date of discharge.
- Probable cause of death.
- Date of death.

- Autopsy performed.
- Causality assessment in relation to study procedure(s).
- Causality assessment to other medication.

The following intensity ratings will be used:

1 Mild (awareness of sign or symptom, but easily tolerated).

2 Moderate (discomfort sufficient to cause interference with normal activities).

3 Severe (incapacitating, with inability to perform normal activities).

It is important to distinguish between serious and severe AEs:

- Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.3.1.2.
- An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

Causality Collection

The Investigator will assess causal relationship between IMPs and each AE, and answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the IMP?"

For SAEs, causal relationship will also be assessed for other medication, any additional drug and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as "yes".

A guide to the interpretation of the causality question is found in Appendix A of this CSP.

Adverse Events Based on Sign and Symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: "Have you had any health problems since you were last asked?" or revealed by observation will be collected and recorded in ClinBase™.

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms.

However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse Events Based on Examinations and Tests

The results from protocol-mandated laboratory tests, vital signs, ECGs and other safety assessments will be summarised in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, ECGs and other safety assessments should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IMPs.

If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information.

Wherever possible the reporting Investigator should use the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value).

In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-protocol-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Hy's Law

Cases where the subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 x ULN together with total bilirubin ≥ 2 x ULN may need to be reported as SAEs. Please refer to Appendix C for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

COVID-19

Adverse event questioning will include specific questions regarding signs and symptoms of COVID-19, including fever, dry cough, dyspnoea, sore throat, fatigue, and loss of taste or smell as well as potential recent (within previous 14 days) exposure to someone who has COVID-19 symptoms or positive test result.

Suspected and confirmed SARS-CoV-2 infection and COVID-19 will be recorded as AEs.

6.3.1.5. Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the IMPs, or to the study procedure(s). All SAEs will be recorded in ClinBase™.

If any SAE occurs in the course of the study, then Investigators or other site personnel will inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events and **within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately.

Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The reference document for definition of expectedness/listedness is the IB for SZC, and respective SmPCs for tacrolimus and cyclosporin.

6.3.1.6. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of the IMP under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of the IMP under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

For all studies except those utilising medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB or and will notify the IRB/IEC, if appropriate according to local requirements.

6.3.2. Clinical Laboratory Assessments

6.3.2.1. Haematology

White blood cell (WBC) count	Neutrophils absolute count
Red blood cell (RBC) count	Lymphocytes absolute count
Haemoglobin (Hb)	Monocytes absolute count
Haematocrit (HCT)	Eosinophils absolute count
Mean corpuscular volume (MCV)	Basophils absolute count
Mean corpuscular haemoglobin (MCH)	Platelets
Mean corpuscular haemoglobin concentration (MCHC)	Reticulocytes absolute count

6.3.2.2. Serum Clinical Chemistry

Sodium	Alkaline phosphatase (ALP)
Potassium	Alanine aminotransferase (ALT)
Urea	Aspartate aminotransferase (AST)
Creatinine	Gamma glutamyl transpeptidase (GGT)
Albumin	Total Bilirubin
Calcium	Unconjugated bilirubin
Phosphate	
Glucose(fasting)	
C-reactive protein (CRP)	
T_4 [a]	Follicle stimulating hormone (FSH) [a, b]
TSH [a]	

[a] Screening only.
[b] Female subjects only.

6.3.2.3. Urinalysis

Glucose	
Protein	
Blood	
Upon a positive urine test from leucocytes, blood, nitrite or protein, the Investigator may require further urine analysis, such as flow cytometry. Results of additional urine analyses will be included in the database. If the flow cytometry examination shows a different result than the urine sticks, the urine will be investigated by fully automated digital imaging where leukocytes, erythrocytes, casts in urine will be analysed.	

6.3.2.4. Viral Serology and SARS-CoV-2 Virology

Hepatitis B surface antigen (HBsAg)	Hepatitis B core antibody
Hepatitis C antibody	SARS-CoV-2 antibody testing
Human immunodeficiency virus (HIV) I and II testing	
SARS-CoV-2 by RT-PCR (specimen may be collected by oropharyngeal and/or nasopharyngeal swabs)	

Additional investigations may be performed as judged by the Investigator, in collaboration with the Sponsor.

6.3.2.5. Drugs of Abuse, Alcohol and Cotinine

Amphetamine / Ecstasy	Benzodiazepines
Ethanol	Methadone Metabolites
Cannabinoids	Barbiturates
Cocaine	Phencyclidine
Opiates	Urine Creatinine
Cotinine	
Tricyclic antidepressants (TCA)	

6.3.3. Physical Examination

Full

The complete physical examinations will include an assessment of the general appearance, respiratory, cardiovascular, abdomen, skin, head, and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculoskeletal and neurological systems.

Brief (Abbreviated)

The brief physical examinations will include an assessment of the general appearance, skin, abdomen, cardiovascular system and respiratory.

6.3.4. Resting 12-lead Electrocardiogram

At the time points specified in the SoA (Table 3), a 10-second 12-lead safety ECG, including QTcF, PR, QRS QT interval, and HR will be obtained after 10 minutes supine rest, using the site's own ECG machines.

The Investigator will judge the overall interpretation as normal or abnormal and this evaluation will be reported in ClinBase™. If abnormal, it will be further documented as to whether or not the abnormality is clinically significant by the Investigator. For all abnormalities (regardless of clinical significance) the specific type and nature of the abnormality will be documented in ClinBase™. Clinically significant findings should also be documented on the AE page of the CRF if applicable.

The Investigator may add extra 12-lead resting ECG safety assessments if there are any abnormal findings or if the Investigator considers it is required for any other safety reason. These assessments should be entered as an unscheduled assessment.

All subjects who have QTc prolongation defined as QTcF > 500 ms, or a prolongation from baseline of > 60 ms on repeat 12-lead ECG, should immediately have serum potassium assessed, if not already done within 1 hour of performing the ECG.

All ECG readings will be digitally stored as source documents.

6.3.5. Vital Signs

The following variables will be collected after the subject has rested in the supine position for at least 5 minutes:

- Systolic BP (mmHg)
- Diastolic BP (mmHg)
- Pulse (bpm)
- Tympanic temperature (°C)

The measurement of vital signs will be carried out according to the relevant Parexel SOPs.

6.4. Pharmacokinetics

6.4.1. Collection of Pharmacokinetic Samples

Whole blood samples for the determination of concentrations of tacrolimus/cyclosporin will be collected for each treatment period as specified in the SoA (Table 3).

Samples will be collected, handled, labelled, stored and shipped as detailed in the Laboratory Manual.

6.4.2. Pharmacokinetic Drug Assays

The PK samples will be analysed by Covance on behalf of AstraZeneca, using validated assays.

Full details of the analytical method and analyses performed will be described in a separate bioanalytical report.

7. BIOLOGICAL SAMPLES PROCEDURES

All biological samples will be performed by trained staff and in accordance with the Clinical Unit's SOPs.

7.1. Total Blood Volume

The approximate total amount of blood to be collected from each subject in this study, excluding repeat samples, is summarised in Table 6.

Table 6 Total Blood Volume

	Volume per Sample	Number of Samples	Total
Haematology	2.7 mL	6	16.2 mL
Clinical chemistry [a]	7.5 mL	6	45 mL
Serum potassium	2.6 mL	6	15.6 mL
PK assessments for tacrolimus/cyclosporin	1 mL	45	45 mL
SARS-CoV-2 antibody testing (ELISA)	2.6 mL	1	2.6 mL
Total			124.4 mL

[a] Viral serology testing and follicle stimulating hormone testing (for female subjects) will be performed using the clinical chemistry sample collected at the screening visit.

Abbreviations: ELISA = enzyme-linked immunosorbent assay; PK = pharmacokinetics; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Repeat blood samples may be collected for safety reasons. The maximum volume to be drawn from each subject must not exceed 500 mL.

7.2. Handling, Storage and Destruction of Biological Samples

Samples will be disposed of, on instruction from AstraZeneca, after the CSR has been finalised, unless samples are retained for additional or future analyses.

7.2.1. Pharmacokinetic Samples

Pharmacokinetic samples will be disposed of after the bioanalytical report finalisation or 6 months after issuance of the draft bioanalytical report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis or additional assay development work, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

7.3. Labelling and Shipment of Biohazard Samples

Samples will be labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix B of this CSP 'IATA 6. 2 Guidance Document'.

Any samples identified as Infectious Category A materials will not be shipped and no further samples will be taken from the subject unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

7.4. Chain of Custody of Biological Samples

A full chain of custody will be maintained for all samples throughout their lifecycle.

The Investigator will ensure full traceability of collected biological samples from the subjects while in storage at the centre until shipment and will keep documentation of receipt of arrival.

The sample receiver will keep full traceability of samples while in storage and during use, until used, disposed of, or until further shipment or disposal (where appropriate) and will keep documentation of receipt of arrival.

7.5. Withdrawal of Informed Consent for Donated Biological Samples

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed if not already analysed and the action documented.

As collection of donated biological samples is an integral part of the study, the subject is withdrawn from further study participation.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented, and the signed document returned to the Clinical Unit.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH-GCP and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2. Subject Data Protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

All clinical study findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

The anonymity of participating subjects must be maintained. Subjects will be specified in outputs and other documents containing subject data by their subject number, not by name. Documents that identify the subject (eg, signed ICF) will be maintained in confidence by the Investigator.

Study data will be stored in accordance with local and global data protection laws.

8.3. Ethics and Regulatory Review

The study will be submitted to the national regulatory agency, BfArM, for review and approval, by Parexel in accordance with local regulatory procedures.

The study will be submitted to IEC for ethical review and approval by the Investigator in accordance with local procedures.

Parexel will provide the IEC and Investigator with safety updates/reports according to local requirements, including SUSARs, where relevant.

AstraZeneca will provide the regulatory authority with safety updates/reports according to local requirements, including SUSARs, where relevant.

Compensation will be reasonable and related to the nature and degree of inconvenience and discomfort as a result of participation in the study. Information on how subjects will be compensated is contained in the ICF.

8.4. Insurance

The Sponsor has covered this clinical study by means of an insurance of the clinical study according to national requirements. The name and address of the relevant insurance company,

the certificate of insurance, the policy number and the sum insured are provided in the Investigator's Site File.

8.5. Informed Consent

The subjects shall be informed of the nature, significance, implications and risks of this clinical study, and informed consent will be freely given and evidenced in writing, dated and signed, or otherwise marked, by the subject as evidence to indicate his/her free informed consent, prior to the start of the study.

The nature of the informed consent will comply with the Declaration of Helsinki, the current requirements of GCP (EMA/CHMP/ICH/135/1995) and local regulation which ever offers the greater subject protection.

8.6. Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol.

If a protocol amendment requires a change to the ICF, the IEC should approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by the IEC.

9. DATA QUALITY ASSURANCE AND DATA MANAGEMENT

9.1. Quality Control and Source Data Verification

Source data verification will be conducted with due regard to subject confidentiality.

The Clinical Unit will allow the study monitor and Sponsor representative direct access to all study documents, medical files and source documents to enable verification of the study data, while maintaining the anonymity of the subject and confidentiality of the data.

Internal quality control will be performed at all stages of the study by the Clinical Unit.

9.2. Audit/Inspections

The Clinical Unit facilities and all study data/documentation may be audited/inspected by independent auditor/inspector/any representatives of regulatory authorities. The Investigator must allow the applicable persons access to all relevant facilities and data/documents. The Investigator must be available to discuss any findings/issues.

If an audit was performed, the audit certificate will be included in the CSR.

9.3. Study Monitoring

The conduct of the study will be monitored by an independent Parexel monitor to ensure compliance with applicable regulatory requirements and GCP. The summary of the documentation of the monitoring visits will form part of the study documentation and will be archived as such.

Monitoring visits at site will be limited to a minimum required as deemed appropriate during COVID-19 pandemic.

9.4. Data Collection

The ClinBase™ system is an electronic source data capturing and information management system. The system combines all aspects of source data capturing with process control and clinical study management. All clinical and laboratory data, except those which are paper-based or provided by external vendor, will be collected in ClinBase™. Only paper-based data will be subject to data entry. For electronic source data, no data entry will be performed.

The responsible study monitor will check data at the monitoring visits to the Clinical Unit. The Investigator will ensure that the data collected are accurate, complete and legible. Data will be monitored within ClinBase™ by the study monitor before being exported. Any changes made during monitoring will be documented with a full audit trail within ClinBase™.

9.4.1. Case Report Forms and Source Documents

All data obtained using paper collection methods during the clinical study will be recorded in ClinBase™. All source documents from which ClinBase™ entries are derived should be placed in the subject's personal records.

The original ClinBase™ entries for each subject will be checked against source documents by the study monitor. Instances of missing or uninterpretable data will be discussed with the Investigator for resolution.

9.4.2. Access to Source Documents

During the course of the clinical study, a study monitor will make Clinical Unit visits to review protocol compliance, compare ClinBase™ entries and individual subject's personal records, assess IMP accountability and ensure that the clinical study is being conducted according to pertinent regulatory requirements. ClinBase™ entries will be verified against source documents. The review of medical records will be handled confidentially to ensure subject anonymity.

Checking of the ClinBase™ entries for completeness and clarity and verifying with source documents will be required to monitor the clinical study for compliance with GCP and other regulations. Moreover, regulatory authorities of certain countries, IRBs/IECs may wish to carry out source data inspections on-site, and the Sponsor's clinical quality assurance group may wish to carry out audits. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and subject confidentiality. The Investigator assures the Sponsor of the necessary support at all times.

9.5. Data Management

Parexel will utilise standardized and validated procedures and systems to collect, process and file the clinical data of this study. Any system used will be compliant with FDA 21 Code of Federal Regulations Part 11 requirements.

A DMP will be prepared to describe the processes and data flow within the clinical study. Timelines, versions for the computer systems and the coding will be defined in the DMP, and if applicable, sponsor specific requests will also be documented within. The DMP will be finalised before first dose where possible, but before database lock.

A DVS will be created to outline the validation checks to be performed during the study. The DVS must be finalised before data validation.

After the data has been monitored by the responsible study monitor all data received will be reviewed, logged and filed.

The raw data intended for further processing will be checked by standard routines or according to the DVS and queries will be generated and sent to the Investigator for review and resolution. Corrections resulting from these queries will be confirmed on the data clarification forms. This process will be repeated until no further discrepancies are found. The data will then be declared as clean. Applicable documentation will be stored in the study files.

Only trained study staff will have access to the clinical database and every change in data will have a full audit trail.

10. EVALUATION AND CALCULATION OF VARIABLES

10.1. Safety Variables

10.1.1. Adverse Events

All AEs will be coded using the latest version of the MedDRA vocabulary and will be listed for each subject.

Adverse events will be assigned to a treatment based on the start date/time of the AE in relation to dosing in that period; for tabulation purposes the AE will then be assigned to the treatment received in the respective treatment period as follows:

- Treatment Period 1: AEs with start date/time at the time of or after dosing in Treatment Period 1 until the time of dosing in Treatment Period 2.
- Treatment Period 2: AEs with start date/time at the time of or after dosing in Treatment Period 2 until the Follow-up Visit.

For assigning AEs to a specific treatment/dose, the following guidelines should be followed:

- Adverse events with start date/time at the time of or after dosing (for each specific treatment) until the next treatment/dose or until Follow-Up Visit will be assigned to the specific treatment/dose (including washout period).
- Adverse events with unknown start times, but with start date known, will be imputed with a time of 00:00, unless the start date corresponds to any given dosing date. In this case the start time will be imputed with the time of dosing. If this results in a start date/time after end date/time of the AE, then the time will also be imputed with 00:00.
- Adverse events with completely unknown start dates will be imputed with the date and time of dosing, unless the end date is known and prior to dosing; in that case the start date will be imputed as the date of Screening and a time of 00:00.
- Adverse events with partially known start dates/times will be treated as follows:
  - If only the day is missing, then the day will be imputed with the first day of the month, unless the month and year in which the AE started is a month and year in which IMP was administered, then the day will be imputed with the first day on which IMP was administered in that month. If this results in a start date after the end date, then the day will be imputed with the first day of the month.
  - If only the month is missing and the year is a year in which IMP was administered, then the month will be imputed with the first month in which IMP was administered. If this results in a start date after the end date of the AE, then the month will be imputed with JAN. If the known year part is not a year in which IMP was administered, then the month will also be imputed with JAN.
  - If both the day and month is missing and the year is a year in which IMP was administered, then the day and month will be imputed with the day and month of

dosing. If this results in a start date after end date, then the day and month will be imputed with 01JAN. If the year is not a year in which IMP was administered, then the day and month will also be imputed with 01JAN.

– If only the year is missing, then the year will be imputed with the year of dosing.

Adverse events with onset (start date/time) after dosing in Treatment Period 1 will be summarised by treatment and overall for all subjects, including tabulations by causality and severity (mild, moderate and severe). All tabulations will be presented by SOC and PT. Furthermore, separate listings of SAEs, AEs that led to discontinuation and AEs that led to death will be presented.

The following information will be included in the listings: verbatim term, SOC, PT and lowest level term, start date/time, end date/time, time from last dose, causality, action taken, whether the AE was classified as serious and the outcome.

All tabulations will include the number and percentage of subjects. In addition, a separate tabulation will be presented showing the number of events by treatment and PT.

Finally, an overview of all AEs will be presented, separately for the number and percentage of subjects. This will include categories for any AE, AEs leading to discontinuation, AEs with outcome of death and SAEs.

10.1.2. Laboratory Assessments

Haematology and clinical chemistry values will be listed by subject and time point including changes from baseline and repeat/unscheduled measurements. Summary tabulations including absolute value and changes from baseline will be presented by treatment and time point for the safety analysis set. The baseline for the measurements will be the last measurement prior to dosing in the respective treatment periods. When a value is not available prior to treatment, the screening value will be taken as baseline. Changes from baseline will be calculated and presented for all post-baseline time points including the Follow-up Visit. Shift tables will also be presented for certain parameters.

A summary of the key subject information on the laboratory changes outside the predefined criteria will also be presented.

Any laboratory parameters with results from the laboratory given as "< xx" or ">xx" in the database will be imputed with the absolute value of the number without the sign (eg, < 2.2 will be imputed as 2.2) for the descriptive statistics and changes from baseline.

The listings will include the following information: test name, date of measurement, reference range, result and flags for any measurements that are outside the reference range (eg,

AstraZeneca, program, or laboratory ranges). Clinical laboratory data will be reported in System International units in the CSR.

Additional listings will be presented for the following:

- Urinalysis (macroscopic and microscopic, if applicable).
- FSH.

The results of viral serology (including SARS-CoV-2 serology), SARS-CoV-2 RT PCR, and the drugs of abuse and alcohol screen will not be listed in the CSR.
Lastly, a summary describing subjects with potential Hy's Law results will be presented by subject and time point. Parameters might include ALT, AST, total bilirubin and ALP.

10.1.3. Physical Examination

The baseline/screening results of the physical examination will be documented in medical history for each subject.

Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment will be reported as an AE.

10.1.4. Resting 12-lead Electrocardiogram

Results of the safety ECGs (normal/abnormal assessments and specific findings) will be listed for each subject.

Electrocardiogram parameter results will also be listed by treatment for each subject and time point of PR, RR, QRS, QT interval and the derived values of QTcF and HR. All parameters will have changes from baseline derived and presented.

The following ECG parameters will be derived:

- QTcF will be calculated as $QTcF = QT*RR^{-1/3}$ where the QT interval is in milliseconds and the RR interval is in seconds
- HR will be calculated, based on the RR interval as HR = 60/RR interval, where the RR interval is in seconds

Descriptive statistics will be presented by treatment and time-point for the original and changes from baseline values of PR, RR, QRS, QT; derived values and changes from baseline for QTcF and HR will also be included. The baseline for the ECG measurements will be the pre-dose assessment on Day 1.

Outliers with respect to QTcF will also be tabulated for the following categories:

- Absolute value > 450 ms and ≤ 480 ms.
- Absolute value > 480 ms and ≤ 500 ms.
- Absolute value > 500 ms.
- Increase from baseline > 30 ms and ≤ 60 ms.
- Increase from baseline > 60 ms.

All calculations of ECG parameters and reporting described in this section will be performed by Parexel.

10.1.5. Vital Signs

The results of the vital signs measurements will be listed by subject and time point including the date/time of the assessment, changes from baseline and repeat/unscheduled measurements. The baseline for vital signs measurements will be last measurement prior to dosing in the respective treatment periods. Descriptive statistics will be presented by treatment and time point for both observed values and changes from baseline.

10.2. Pharmacokinetics

10.2.1. Whole Blood Pharmacokinetic Parameters

The following PK parameters will be determined where possible from the whole blood concentrations of tacrolimus/cyclosporin.

Primary PK parameters

AUCinf	Area under concentration-time curve from time zero to infinity
AUClast	Area under the concentration-time curve from time zero to time of last quantifiable concentration
Cmax	Maximum observed concentration

Secondary PK parameters

tmax	Time to reach maximum observed concentration following drug administration
t½λz	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve
CL/F	Apparent total body clearance of drug after extravascular administration
Vz/F	Apparent volume of distribution during the terminal phase after extravascular administration

The following diagnostic parameters will also be determined:

λz	Terminal elimination rate constant
λz lower	Lower (earlier) t used for λz determination
λz upper	Upper (later) t used for λz determination
λz, N	Number of data points used for λz determination
λz span ratio	Time period over which λz was determined as ratio of t½λz
Rsq adj	Statistical measure of fit for the regression used for λz determination adjusted for the number of used data points (n obs)
AUCextr	Extrapolated area under the curve from tlast to infinity, expressed as percentage of AUCinf

Additional PK parameters may be determined where appropriate.

10.2.2. Calculation or Derivation of Pharmacokinetic Parameters

The PK analyses of the whole blood concentration data for tacrolimus/cyclosporin will be performed by Covance, on behalf of AstraZeneca, according to the AstraZeneca standards (LDMS_001_00201968 dated 13 July 2020).

PK parameters will be derived using non-compartmental methods with Phoenix® WinNonlin® Version 8.1, or higher.

Pharmacokinetic analysis will, where possible, be carried out using actual times recorded in the raw data. If actual times are missing, nominal times will be used.

Concentration data will be used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with the amount and concentration units, will be presented as they are received from the analytical laboratory unless otherwise specified on the PK order form.

The Cmax and tmax will be derived directly from the plasma concentration-time profiles. For multiples peaks the highest post-dose concentration will be reported as Cmax. In the case that the multiple peaks are of equal magnitude, the earliest tmax will be reported.

Plasma concentrations which are BLQ prior to the administration of the first dose and up to the quantifiable concentration will be set to a value of zero with the following exceptions:

- After the first quantifiable concentration, any BLQ concentrations will be set to missing for all concentration profiles.
- Where 2 or more consecutive concentrations are BLQ at the end of a profile, the profile will be deemed to have terminated and therefore any further quantifiable concentrations

will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

- Any embedded BLQ value (between 2 quantifiable concentrations) will be set to missing for the purposes of PK analysis.
- If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.

Terminal elimination half-life, calculated as (ln2)/λz, will be estimated by log-linear least-squares regression of the terminal part of the concentration-time curve. For the determination of λz, the start of the terminal elimination phase for each subject will be defined by visual inspection and will be the first point observed after Cmax at which there is no systematic deviation from the log-linear decline in plasma concentrations. A minimum of 3 data points will be used in calculating λz, and the duration of time over which λz is recommended to be at least 3 times the subsequently estimated terminal half-life. Where an elimination half-life is estimated over less than 3 times the subsequently estimated terminal half-life, the robustness of the data will be discussed in the study report. The adjusted correlation coefficient (Rsq_adj) should be ≥ 0. 80. Where Rsq_adj < 0. 8 t½λz and related parameters will be listed, flagged and excluded from descriptive and inferential statistics.

AUCinf is estimated by AUClast + Clast/λz where Clast is the observed last quantifiable drug concentration.

AUCs (including AUCinf and AUClast) will be calculated using the linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing (linear up log down).

The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive plasma concentrations above the LLOQ, with at least 1 of these concentrations following Cmax.

If AUCinf cannot be determined for all subjects or all dose levels, an alternative AUC measure, such as AUC to a fixed time point, may be used in the evaluation of DDI.

If the concentration at the time of dosing is missing, then this will be set to 0.

Pharmacokinetic parameters associated with positive pre-dose value(s) of greater than 5% Cmax may be excluded from the summary statistics of PK tables and statistical analysis at the discretion of the pharmacokineticist.

11. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

11.1. Description of the Analysis Sets

11.1.1. Safety Analysis Set

The safety analysis set will include all subjects who received at least 1 dose of tacrolimus (Cohort 1) or cyclosporin (Cohort 2) and for whom any safety post-dose data are available.

Unless otherwise stated, the randomised set will be used for the presentation of all demographic and disposition data, and the safety analysis set will be used for all safety analyses. Exposure to IMP will also be presented using the safety analysis set.

11.1.2. Pharmacokinetic Analysis Set

The PK analysis set will consist of all subjects in the safety analysis set and who received at least one quantifiable whole blood concentration post-dose tacrolimus (Cohort 1) or for cyclosporin (Cohort 2) with no important protocol deviations or AEs thought to impact the analysis of the PK data. A subject may be excluded if vomiting occurs at or before 2x the median tmax for the dose group and treatment. Data from subjects for whom the pre-dose concentration is > 5% of Cmax may be excluded for that treatment period.

The exclusion of any subjects or time points from the calculation of the PK parameters will be documented by the PK Scientist including the reason(s) for exclusion.

The available concentration data and PK parameter data for any subjects excluded from the PK analysis set will be listed only. Concentration data for subjects excluded from the PK analysis set will be presented in the individual figures of concentration versus time plots.

11.1.3. Randomised Set

The randomised set will consist of all subjects randomised into the study.

11.2. Methods of Statistical Analyses

11.2.1. General Principles

The statistical methodology below describes the statistical analysis as it is foreseen when the study is being planned.

If circumstances should arise during the study rendering the analysis inappropriate, or if in the meantime improved methods of analysis should come to light, different analyses may be performed. A separate SAP will not be written for the study. Any deviations from the statistical methodology defined in this protocol, reasons for such deviations and all alternative/additional statistical analyses that may be performed will be described in the CSR.

Such changes to analyses may be written into an abbreviated SAP, if appropriate. The verification and review of all statistical modelling assumptions will be documented appropriately.

All analyses discussed below will be replicated for both of the cohorts.

Data listings will be based upon the safety analysis set. All original and derived PK parameters will be summarised using the PK set. Demographic and disposition data will be summarised, using the safety set. Safety data will be summarised using the safety set.

All summaries done "by treatment" will be performed by actual treatment, rather than treatment to which a subject was randomised.

For each cohort, demographic and baseline data will be summarised for all subjects in the randomised, by sequence and overall. Pharmacokinetic data will be summarised by treatment, or treatment and time point, as appropriate. Adverse events will be presented by treatment and overall. Safety data collected at multiple occasions within the same period will be presented by treatment, time point and overall.

Frequency counts (number of subjects [n] and percentages) will be made for categorical variables. Descriptive statistics (n, mean, SD, median, minimum and maximum) will be calculated for continuous variables. Descriptive statistics will only be presented if $n \geq 3$. If no subjects have data at a given time point, then only $n = 0$ will be presented. If $n < 3$, only the n, minimum and maximum will be presented. The other descriptive statistics will be left blank.

The following rules will apply to any repeated safety assessments occurring within each treatment period:

- If the repeated measurement of a specific parameter occurs prior to IMP administration (Day 1), then the last obtained value prior to dosing will be used (as baseline) in the descriptive statistics and in the calculation of changes from baseline;
- If the repeated measurement of a specific parameter occurs after IMP administration (Day 1), then the first (non-missing) value after dosing will be used in descriptive statistics and in the calculation of changes from baseline.

The planned sequence for measurement of multiple assessments at the same time point is described in Section 3.1.1.

For safety assessments performed at screening and the follow-up, the following rules will apply for any repeated assessments:

- If the repeated assessment occurs at screening the last available value will be used in the summary statistics;

- If the repeated assessment occurs at the Follow-up Visit the first non-missing assessment will be used in the summary statistics.

All statistical analyses and production of tables, figures and listings will be performed using SAS® version 9.4 or later.

11.2.2. Missing Data

Missing dates and times in the AE data will be handled as described in Section 10.1.1. Concentrations that are non-quantifiable in the PK data will be handled as described in Section 10.2.2.

There will be no imputations of other missing data. All subjects will be included in the safety analyses as far as the data permit.

11.2.3. Subject Disposition

A randomisation listing will be presented and include the following: each subject's randomisation number, the subject's full enrolment number, the treatment to which the subject has been randomised and the country where the study centre is located.

Subjects and/or data excluded from the PK analysis set will be listed including the reason for exclusion. Subject disposition will be listed and summarised, and the summary will include the following information: number of subjects randomised and dosed, number and percentage of subjects dosed in the study, number and subjects completing study and number and percentage of subjects who were withdrawn (including reasons for withdrawal). Disposition data will be presented based on all subjects randomised.

Subject discontinuations will be listed including the date of study exit, sequence, period, treatment received, date/time discontinuation, and treatment/study discontinuation (including reason for discontinuation) information.

11.2.3.1. Demographic and Baseline Data

Demographic variables (age, gender, race, ethnicity, height, weight and BMI) will be listed by subject. Demographic characteristics (age, gender, race and ethnicity) and subject characteristics (height, weight and BMI) will be summarised separately for all randomised subjects. The denominator for percentages will be the number of randomised subjects.

Medical history data will be listed by subject including visit, description of the disease/procedure, MedDRA SOC, MedDRA PT, start date and stop date (or ongoing if applicable).

11.2.4. Prior and Concomitant Medication and Drug Administration

11.2.4.1. Prior and Concomitant Medication

Prior medications are those that started and stopped prior to the first dose of IMP; all medications taken after first dosing are considered as concomitant (including medications that started prior to dosing and continued after). Prior medication started within 3 months prior to the first dose of IMP will be recorded also in the concomitant medication module of ClinBase™. Prior medications that were started before 3 months of first dose of IMP will not be recorded.

Prior and concomitant medication will be listed by subject and will include the following information: reported name, PT, the route of administration, dose, frequency, start date/time, duration, stop date/time and indication. Prior and concomitant medication will be coded according to the Sponsor's drug dictionary.

The duration will be calculated as:

- Duration = end date/time – start date/time (+1 day, if time is not available)

The duration may be presented in hours or days in the listing depending on the applicability to the emerging data. For medications with partial or completely missing start date/times and/or end date/times, the duration will not be calculated.

Medications with missing or partial start date/time and/or end date/time such that it is not possible to classify as prior or concomitant will be considered as concomitant in the listings.

11.2.4.2. Drug Administration

Drug administration dates and times will be listed for each subject.

11.2.5. Safety and Tolerability

All safety data (scheduled and unscheduled) will be presented in the data listings. Continuous variables will be summarised using descriptive statistics (n, mean, SD, minimum, median, maximum). Categorical variables will be summarised in frequency tables (frequency and proportion). The analysis of the safety variables will be based on the safety analysis set.

Safety measurement with start date/time at the time of or after dosing (for each specific treatment) until the next treatment/dose or until Follow-Up Visit will be assigned to the specific treatment/dose (including washout period).

Adverse events will be summarised by SOC and PT using MedDRA vocabulary. Furthermore, listings of SAEs and AEs that led to withdrawal will be made and the number of subjects who had any AE, SAEs, AEs that led to withdrawal, and AEs that led to death will be summarised. Serious adverse events that occur before dosing will be reported separately.

Tabulations and listings of data for vital signs, clinical laboratory tests and ECGs will be presented. Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment will be reported as an AE. Data will be 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, by treatment. Clinical laboratory data will be reported in Système International units in the CSR.

Out-of-range values for safety laboratory will be 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).

11.2.6. Pharmacokinetics

All PK concentration, parameter summaries and statistical analyses will be presented for the PK analysis set, unless otherwise specified. The PK concentration and parameter listings will be presented for the safety analysis set and will include all reportable individual PK results. Any PK concentration and parameter data not included in the PK statistical analyses will be included in the listings and flagged with an appropriate footnote.

A listing of PK blood sample collection times, as well as derived sampling time deviations and concentrations at each protocol scheduled time point will be provided. Whole blood concentrations will be summarised by treatment and nominal time points descriptively. The PK parameters will be summarised by treatment using appropriate descriptive statistics.

The listings, summaries and figures will be presented in accordance with the most recent version of the AstraZeneca Corporate CSRHLD Standards and the Final version of the TFL shells for this study. This include the applicable descriptive statistics, handling of individual concentrations below the LLOQ for listings, descriptive statistics and figures, and precision and rounding rules for concentrations and PK parameter data.

Individual concentrations with time deviations of $\geq \pm 10\%$ from the protocol scheduled time, will be used in the PK analysis but will be flagged for exclusion from the summary tables and corresponding figures.

Protocol scheduled times will be used to present the PK concentration summary tables and corresponding gmean concentration-time figures.

11.2.6.1. Graphical Presentation of Pharmacokinetic Data

Individual, combined individual, and gmean plots will be presented. All gmean plots or combined individual plots showing all subjects by treatment will be based on the PK analysis set. Separate plots for each Cohort will be provided. Individual plots by subject will be based on the safety analysis set.

For consistency, the plasma concentration values used in the gmean data graphs will be those given in the descriptive statistics summary table for each time point.

Individual plasma concentrations versus actual elapsed time after dose will be plotted on both the linear and semi-logarithmic scale with both treatments overlaid on the same plot and separate plots for each subject, and separate plots for each cohort.

Combined individual plasma concentration versus actual times will be plotted on both the linear and semi-logarithmic scale. Plots will be grouped by treatment and separate plots for each cohort.

The gmean plasma concentration (-/+gSD) versus nominal sampling time will be plotted on both the linear and semi-logarithmic scale with treatments overlaid on the same figure, and separate plots for each cohort.

11.2.6.2. Statistical Analysis of Pharmacokinetic Data

The below analyses will be performed for each of the 2 cohorts.

The difference in mean PK parameters (Cmax, AUCinf) for the 2 cohorts will be 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 means (LSM) for each treatment, the difference thereof, and the corresponding 2-sided 90% confidence intervals (CIs) for the log-transformed values will be presented. The corresponding geometric LSM for each treatment, the ratio thereof, and the 2-sided 90% CI will be estimated and presented as well.

The limits for the 90% CIs for the geometric mean ratio will be compared to the pre-specified interval (0.8000% to 1.2500%) for conclusion of no DDI (ie, if the CI lies entirely within the predetermined 0.8 and to 1.25 range, it will be concluded that SZC has no meaningful effect on the PK for tacrolimus/cyclosporin).

Statistical analysis will be done by using PK analysis set.

This mixed effects statistical model will be repeated for the secondary PK variables of AUClast, $t½\lambda_z$, and tmax, for both cohorts.

11.3. Protocol Deviations

Protocol deviations are considered any deviation from the CSP relating to a subject, and include the following:

- Inclusion/exclusion criteria deviations

- Dosing deviations (eg, incorrect treatment received, subject was not fasted as per the protocol requirements prior to and after dosing)
- Time window deviations for safety and/or PK assessments
- Subjects receiving prohibited concomitant medications
- Other procedural and study conduct deviations recorded by the Clinical Unit on a protocol deviation log

The criteria for the assessment and reporting of protocol deviations will be stipulated in a separate study specific protocol deviation specification document. This will include a WAD which stipulates tolerance windows for safety and PK assessments. Measurements performed within these tolerance windows will not be considered as protocol deviations and will not be reported.

All protocol deviations will be discussed at the data review meeting prior to database hard lock in order to define the analysis sets for the study.

Important protocol deviations will be listed by subject. Protocol deviations (missing assessments/visits) related to COVID-19 will be listed separately.

Protocol deviations will be handled in accordance with Parexel SOPs.

For handling of protocol amendments, see Section 8.6.

11.4. Determination of Sample Size

CCI [redacted]

12. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

12.1. Medical Emergencies and AstraZeneca Contacts

In case of medical emergency, the primary contact is the Principal Investigator, who may contact the Sponsor's Lead Physician. If the Principal Investigator cannot be reached, the site's staff will contact the Deputy Principal Investigator or designee or may contact Sponsor's Lead Physician.

Name	Role in the Study	Contact Details
Thomas Koernicke	Principal Investigator	Parexel Early Phase Clinical Unit Berlin PPD 14050 Berlin Germany Tel: PPD
Fredrik Thorén	Sponsor's Lead Physician	AstraZeneca Pharmaceuticals PPD Sweden Tel: PPD Mobile: PPD

12.2. Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except:

- If the pregnancy is discovered before the study patient has received any IMP.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Please refer to Section 4.2.1.2 for further details.

12.2.1. Paternal Exposure

Male subjects should refrain from fathering a child during the study and for 3 months following the last dose.

In case of pregnancy of the partner of a male patient, the partner's pregnancy should be reported on the pregnancy form (consent from the partner must be obtained before the pregnancy form is completed) following the same timeframe and routing as described for any subject's pregnancy. Pregnancy of the patient's partner is not considered to be an AE. These pregnancies will also be followed up, and the outcome of the pregnancy (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should, if possible, be obtained and documented.

Please refer to Section 4.2.1.2 for further details.

13. LEGAL AND ADMINISTRATIVE ASPECTS

13.1. Archiving of Study Documents

All source documents generated in connection with the study will be retained in the limited access file storage area, respecting the privacy and confidentiality of all records that could identify the subjects. Direct access is allowed only for authorized people for monitoring and auditing purposes. Source documents will be handled, stored and archived according to in-house procedures.

The Investigator's Site File will be archived by the contract research organisation for at least 15 years after completion of the study.

13.2. Publication of Study Results

All of the study information and data collected during the study are confidential and the property of AstraZeneca. After completion of the study, AstraZeneca may prepare a joint publication with the Investigator. The Investigator must undertake not to submit any data from this CSP for publication without prior consent of AstraZeneca at a mutually agreed time.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

13.3. Clinical Study Report

An integrated CSR will be prepared in accordance with the standards of the ICH guideline for structure and content of clinical study reports (ICH E3). Copies of the CSR will be provided to the IRB/IEC and the national regulatory authority in accordance with regulatory requirements and Parexel SOPs. In the event of premature termination of the study or other conditions specified in ICH E3, an abbreviated CSR may be prepared.

14. REFERENCE LIST

Cyclosporin SmPC
Summary of product characteristics, Sandimmun (Cyclosporin)

EMA 28 April 2020
European Medicines Agency. Guidance on the Management of clinical trials during the COVID-19 (Coronavirus) pandemic, Version 3, dated 28 April 2020. Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf

FDA 16 April 2020
Food and Drug Administration; FDA Guidance on conduct of clinical trials of medical products during COVID-19 public health emergency, dated March 2020, updated on 16 April 2020. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency

IB, SZC 2019
Investigator's Brochure, LOKELMA™ (also known as sodium zirconium cyclosilicate), Edition Number 9.0, 21 September 2019.

Prograf SmPC
Summary of product characteristics, Prograf® (Tacrolimus).

15. APPENDICES

Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event

Life-threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Intervention

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the subject or may require medical intervention to prevent 1 or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment.
- Hepatotoxicity caused by paracetamol/acetaminophen overdose requiring treatment with N-acetyl cysteine.
- Intensive treatment in an emergency room or at home for allergic bronchospasm.
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion) or convulsions that do not result in hospitalisation.
- Development of drug dependency or drug abuse.

A Guide to Interpreting the Causality Question

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the IMP.

- Time course / Exposure to suspect drug:

Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile:

Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR, could the AE be anticipated from its pharmacological properties?

- Dechallenge experience:

Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause:

The AE cannot be reasonably explained by other aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience:

Did the AE reoccur if the suspected drug was reintroduced after having been stopped?

Note: AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests:

A specific laboratory investigation (if performed) has confirmed the relationship?

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship. The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix B International Airline Transportation Association 6. 2 Guidance Document

Labelling and Shipment of Biohazard Samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories (http://www. iata. org/whatwedo/cargo/dangerous_goods/infectious_substances. htm). For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are for example, Ebola and Lassa Fever viruses. Category A pathogens:

Are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are for example, hepatitis A, B, C, D and E viruses, and human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- Are to be packed in accordance with UN3373 and IATA Instruction 650.

Exempt refers to all other materials with minimal risk of containing pathogens.

- Clinical trial samples will fall into Category B or Exempt under IATA regulations.
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging. (http://www. iata. org/whatwedo/cargo/dangerous_goods/infectious_substances. htm)
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content.**
- International Airline Transportation Association compliant courier and packaging materials should be used for packing and transportation. Packing should be done by an IATA certified person, as applicable.
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix C Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

C 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report PHL cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory and/or elevated TBL from a local laboratory.

The Investigator will also AE data (eg, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IMP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

C 2 Definitions

Potential Hy's Law

Aspartate aminotransferase or ALT ≥ 3 x ULN **together with** TBL ≥ 2 x ULN at any point during the study following the start of IMPs irrespective of an increase in ALP.

Hy's Law

Aspartate aminotransferase or ALT ≥ 3 x ULN **together with** TBL ≥ 2 x ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i. e. , on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

C 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- AST ≥ 3 x ULN.
- ALT ≥ 3 x ULN.
- TBL ≥ 2 x ULN.

If local laboratories are being used:

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative.
- Determine whether the subject meets PHL criteria (see Section 2 within this appendix for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory CRF module(s).

C 4 Follow-Up

C 4.1 Potential Hy's Law Criteria not met

If the subject does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the subject has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

C 4.2 Potential Hy's Law Criteria met

If the subject does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of PHL; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.

- For subjects that met PHL criteria prior to starting IMP, the Investigator is not required to submit a PHL SAE unless there is a significant change[2] in the subject's condition.
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up (including any further laboratory testing) and the continuous review of data.
  - Subsequent to this contact the Investigator will:
    - Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
    - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the HL laboratory kit should be used (if applicable).
    - Complete the 3 liver CRF modules as information becomes available.

C 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from the date the PHL criteria were met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

Where there is an agreed alternative explanation for the AST or ALT and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets any criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF module(s).

[2] A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE CRF entries accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the AST or ALT and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes:
  - The 'Medically Important' seriousness criterion should be used if no other seriousness criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If there is an unavoidable delay of over 15 calendar days in obtaining the information necessary to assess whether the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provide any further update to the previously submitted SAE of PHL (report term now 'Hy's Law case'), ensuring causality assessment is 'related to IMP' and seriousness criterion is 'medically important', according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

C 6 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory when using a central laboratory. For studies using a local laboratory, the list may be modified based on clinical judgment. Any test results need to be recorded.

Hy's Law laboratory kit for central laboratories (18 December 2018)

Additional standard biochemistry and coagulation tests	GGT (Gamma glutamyl transferase) LDH (Lactate dehydrogenase) Prothrombin time INR (International normalised ratio)	
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HBsAg HBV DNA	IgG anti-HCV HCV RNA* IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV	
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin)	
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)	
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin Transferrin saturation	

* HCV RNA is only tested when anti-HCV is positive or inconclusive.

REFERENCES

Aithal GP, Watkins PB, Andrade RJ, et al. Case definition and phenotype standardization in drug-induced liver injury. Clinical Pharmacology & Therapeutics 2011;89(6):806–15.

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'.

Clinical Study Protocol – Germany Addendum

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

Parexel Study No.:	PPD
Sponsor Study Code:	D9480C00012
EudraCT No.:	2020-000515-68
Study Type	Drug-drug interaction (DDI) study
Test Product:	Sodium zirconium cyclosilicate/SZC
Interaction Products:	Tacrolimus and cyclosporin
Therapeutic Indication:	Hyperkalaemia
Pharmacological Class:	Non-polymer, inorganic cation-exchanger
Development Phase:	Phase I
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden
Study Centre:	Parexel International GmbH PPD 14050 Berlin Germany
Date of Protocol:	Final 1.0, 28 September 2020

This clinical study will be conducted according to the protocol and in compliance with Good Clinical Practice, with the Declaration of Helsinki and with other applicable regulatory requirements.

ASTRAZENECA SIGNATURES

Declaration of Sponsor or Responsible Medical Expert (Physician)

Protocol Title: 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

Protocol Version: Final 1.0, 28 September 2020

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal products, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice applicable to this clinical study.

Sponsor Signatory/Responsible Medical Expert

PPD

Signature

PPD

Date of signature

PPD

Declaration of Sponsor or Responsible Medical Expert (Biostatistician)

Protocol Title: 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

Protocol Version: Final 1.0, 28 September 2020

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal products, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice applicable to this clinical study.

Sponsor Signatory/Responsible Medical Expert

PPD

Signature

PPD

Date of signature

PPD

Declaration of Sponsor or Responsible Medical Expert (Clinical Development Lead)

Protocol Title: 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

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Sponsor Signatory/Responsible Medical Expert

PPD

Signature

PPD

Date of signature

PPD

Declaration of the Principal Investigator

Protocol Title: 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

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Principal/Coordinating Investigator

PPD

Signature

PPD

Date of signature

Thomas Koernicke

Declaration of the Deputy Principal Investigator

Protocol Title: 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

Protocol Version: Final 1.0, 28 September 2020

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Deputy Principal Investigator

PPD

Signature

PPD

Date of signature

PPD