STATISTICAL ANALYSIS PLAN

A randomised, single blind, placebo controlled, phase 1 trial to evaluate the safety, tolerability, pharmacokinetic and pharmacodynamic activity of Ruxolitinib when co-administered with artemether-lumefantrine in healthy participants

Protocol No.: MMV_Ruxolitinib_19_01

Product Codes: Ruxolitinib Phosphate (Jakavi®), Artemether-lumefantrine (Riamet®)

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SAP APPROVAL

By my signature, I confirm that this SAP has been reviewed and has been approved for use on the MMV_Ruxolitinib_19_01 study:

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ABBREVIATIONS

ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
AL	Artemether-Lumefantrine
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
β-HCG	β-Human Chorionic Gonadotropin
BDI	Beck Depression Inventory
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CK	Creatine Kinase
CRA	Clinical Research Associate
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic Blood Pressure
DHA	Dihydroartemisinin
DTS	Data Transfer Specification
ECG	Electrocardiography
eCRF	Electronic Case Report Form
EDC	Electronic Data capture
eGFR	Estimated Glomerular Filtration Rate
FAS	Full Analysis Set
FSH	Follicular Stimulating Hormone
GGT	Gamma Glutamyl Transpeptidase
HBsAg	Hepatitis B Surface Antigen
HDL	High Density Lipoprotein
HEENT	Head, Eyes, Ears, Nose, Throat
HIV	Human Immunodefiniciency Virus
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
MCV	Mean Cell Volume
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamics
PK	Pharmacokinetics
PN	Preferred Name
PT	Preferred Term
QTcB	Corrected QT interval with Bazett's Formula
QTcF	Corrected QT interval with Fridericia's Formula
RCC	Red Cell Count
RDW	Red Cell Distribution Width
RUX	Ruxolitinib
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
SBQ	Swiss BioQuant Central
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
SOP	Standard Operating Procedure
SRC	Safety Review Committee
SSR	Southern Star Research
TEAE	Treatment Emergent Adverse Event
WCC	White Cell Count
WHODRL	World Health Organization-Drug Reference List

1 INTRODUCTION

This Statistical Analysis Plan (SAP) provides the outline for the statistical analysis deliverables required for the MMV_Ruxolitinib_19_01 study.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. In addition, post hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post hoc, or unplanned, exploratory analyses performed will be clearly identified as such in the final CSR.

Any significant changes from planned analyses will also be described in the final CSR.

A separate pharmacokinetic (PK) analysis plan will be prepared to detail the PK related analyses.

2 PROJECT OVERVIEW

2.1 Study Design

This Phase1 study intends to evaluate whether the JAK1 inhibitor ruxolitinib (RUX) could be safely co-administered with the registered antimalarial (artemether-lumefantrine/AL), for potential use in the future as an “immune booster” in patients treated for an acute episode of . Along with standard Phase1 objectives (safety, tolerability and PK), the study also aims to evaluate whether the pharmacodynamic activity of RUX (pSTAT3 inhibition) could be impacted in the presence of AL.

This study is a randomised, single-blind, placebo-controlled, single centre phase 1 trial designed to assess the safety, tolerability, PK and pharmacodynamics (PD) of combined oral doses of:

- artemether-lumefantrine (AL; 20 mg/120 mg) and Ruxolitinib (Rux; 20 mg), or
- artemether-lumefantrine (AL; 20 mg/120 mg) and placebo.

The study will be composed of 2 groups (Group 1a and Group 1b) to be enrolled sequentially. Group 1a will participate first as the sentinel safety group.

The study is designed specifically to monitor safety and tolerability of the combination of AL+Rux, and to obtain PK and preliminary PD data. Eight participants will be randomised to receive AL+Rux or AL+placebo in a 3:1 ratio overall (1:1 in Group 1a, and 5:1 in Group 1b). This is typical of first-in-human studies, and this approach is used in this study as the combination of AL+Rux has not been studied previously.

The study schema is presented in Figure 1.

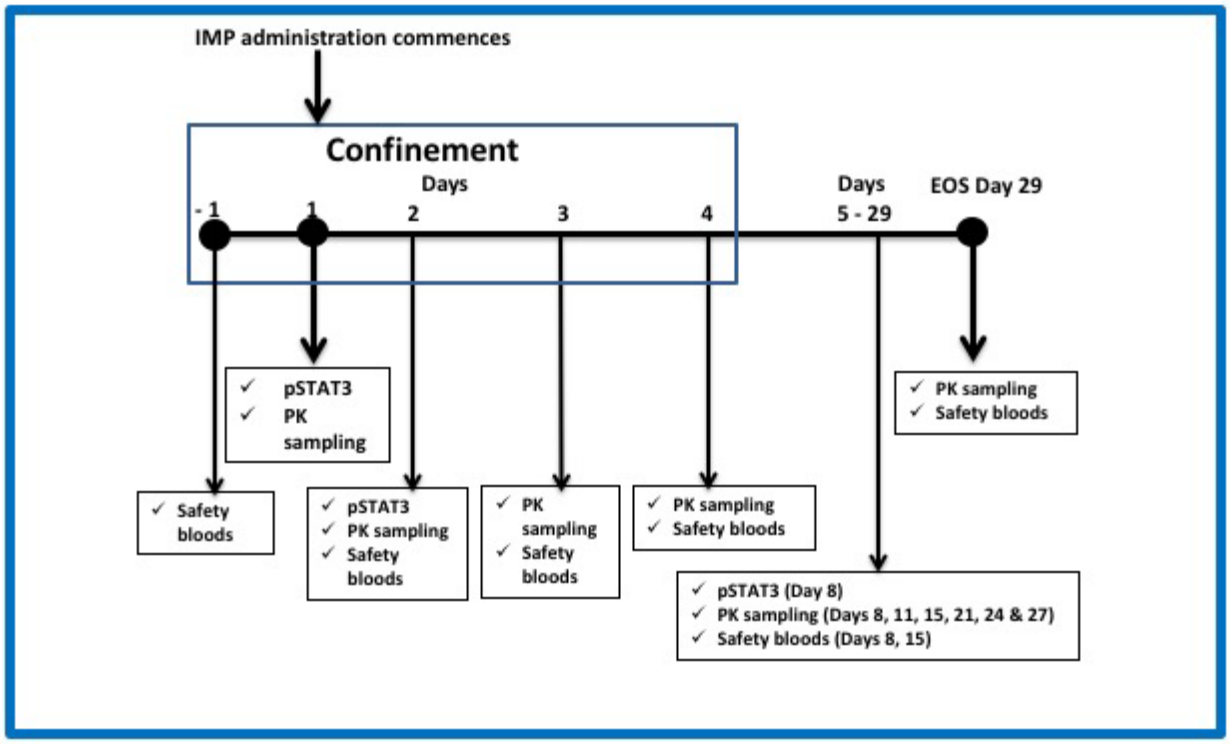

Figure 1: Study Schema

2.2 Sample Size

Eight healthy males or females, aged between 18 and 55 years old, who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled in two sequential groups of 2 participants (Group 1a) and 6 participants (Group 1b).

The 2 participants in Group 1a will serve as sentinels for Group 1b.

As the combination of Rux+AL has not been tested previously, a first-in-human approach of a sample size of 8 participants has been selected.

2.3 Treatment Assignment and Randomization

Randomisation procedures are described in the Randomisation Plan and Randomisation Procedure.

A randomisation number will be allocated to each participant as per the randomisation schedule before the administration of IMPs (AL+Rux or AL+placebo).

Overall, randomisation will be in a ration of 3:1 (active:placebo):

- Participants in Group 1a will be randomised to a treatment allocation (AL+Rux or AL+placebo) in a ratio of 1:1. The randomisation will be single blinded (treatment known to Investigator but not participant).
- Participants in Group 1b will be randomised to a treatment allocation (AL+Rux or AL+placebo) in a ratio of 5:1. The randomisation will be single blinded (treatment known to Investigator but not participant).

2.3.1 Replacement of Withdrawn/Discontinued Participants

- Participants who sign the informed consent form and are randomised but do not receive IMP may be replaced. Replacement volunteers are permitted as back-up.
- Participants who sign the informed consent form, and are randomised and receive at least one dose of IMP, and subsequently withdraw, or are withdrawn or discontinued from the trial, may only be replaced after mutual agreement between the Sponsor and the Principal Investigator or delegate. The decision regarding the replacement of participants will be documented.

2.4 Study Objectives and Endpoints

Primary Objective	Primary Endpoints
1. To assess the safety and tolerability of 3-day b.i.d dosing of AL+Rux and AL+placebo.	1. Incidence, severity, and relationship of observed and self-reported adverse events (AEs) up to 28 days after AL+Rux and AL+placebo administration in all participants by treatment regimen. 2. Clinical laboratory evaluations including haematology, biochemistry, and urinalysis. 3. Vital signs (blood pressure and heart rate) 4. 12-lead standard ECG: QT, QTcB and QTcF; HR, PR, QRS.
Secondary Objectives	**Secondary Endpoints**
1. To assess the effect of AL+Rux and AL+placebo on pSTAT3 inhibition.	1. pSTAT3 inhibition ex-vivo on whole blood cells by: • pSTAT3 levels pre- and post- AL+Rux administration intra participant and, • pSTAT3 levels per treatment regimen post AL+Rux and post AL+placebo administration
2. To characterise the PK profile of artemether and its major metabolite dihydroartemisinin [DHA], lumefantrine, and Rux (part 1 and 2).	2. PK parameters of artemether, DHA, lumefantrine, and Rux using non-compartmental methods: AUC_{last}, $AUC_{0-\infty}$, AUC_{0-8}, AUC_{60-72}, C_{max} (first and last dose), t_{max} (first and last dose), elimination half-life ($t_{½}$), t_{lag}, C_{168h} (for lumefantrine only), CL/F, Vz/F and λz in all participants.
3. To assess additional safety variables (tympanic body temperature and respiration rate)	3. Safety variables tympanic body temperature (°Celcius) and respiratory rate.

3 STATISTICAL CONSIDERATIONS

Data analysis will be performed according to Southern Star Research's Standard Operating Procedures (SOPs).

The general analytical approach for all safety endpoints will be descriptive in nature. Unless otherwise stated, the following statistical approaches will be taken:

Continuous variables:	Descriptive statistics will include the number of non-missing values, mean, standard deviation (SD), median, minimum, and maximum. The minimum and maximum values will be presented to the same number of decimal places as recorded in the raw data; mean, median and SD will be presented to one more decimal place than the raw data.
Categorical variables:	Descriptive statistics will include frequency counts and percentages per category. Percentages will be rounded to one decimal place, with the denominator being the number of participants in the relevant population with non-missing data.
Imputation:	No missing data will be imputed.
Confidence intervals (CIs):	If required, CIs will be two sided and will use 95% confidence levels. Any analyses requiring significance testing will use a two-sided test at the 5% significance level.
Unscheduled assessments:	Unscheduled visits will be excluded from visit-based summary tables.
Early termination visits:	Assessments conducted at Early Termination will be excluded from visit-based summary tables.

3.1 Data Capture

3.1.1 Database

The primary method of data collection is via the study database, developed within the chosen Electronic Data Capture (EDC) platform, IBM Clinical Development. The database has been designed based on the final protocol, the system/core configuration, electronic Case Report Form (eCRF) specifications and/or mock eCRF and consistency check specifications.

Data will be entered directly into the EDC system. Site-collected data will be entered directly from source notes at the site and will be verified by Clinical Research Associates (CRAs) to ensure data integrity.

Refer to the Data Management Plan for further details.

3.1.2 Third Party Data

3.1.2.1 Safety Laboratory (SydPath)

Central safety laboratory data will be received from SydPath as specified in the SydPath Data Transfer Specification (DTS). An initial transfer will be delivered prior to database lock and reconciled against CRF data. Following successful reconciliation and resolution of any data issues, the data will be incorporated into the End of Study analysis.

No unit conversion of laboratory data will be performed.

3.1.2.2 PK Laboratory (SBQ)

PK samples will be analysed by Swiss BioQuant Central (SBQ). Final PK assay data will be transferred to SSR, as specified in the SBQ DTS, for incorporation into the PC SDTM.

3.1.2.3 PK Analysis and Modelling

PK assay results will be transferred from SBQ to Paul van Giersbergen for PK analysis and modelling. PK parameter data will be transferred to SSR, as specified in a DTS, for incorporation into the PP SDTM. A PK consultant (Paul van Giersbergen) will perform the pk analysis according to the attached plan (Appendix 1).

3.1.2.4 Pharmacodynamics - pSTAT (TetraQ)

pSTAT laboratory results will be received from TetraQ as specified in the TetraQ DTS. An initial transfer will be delivered prior to database lock and reconciled against CRF data. Following successful reconciliation and resolution of any data issues, a Tetra Q consultant (Stephanie Reuter Lange) will perform the pharmacodynamic analysis according to the attached plan (Appendix 2).

3.2 Statistical Programming

3.2.1 Programming Specifications

A programming specifications document will be prepared to detail the SAS programming of CDISC (SDTM and ADaM) datasets and listings, tables and figures.

3.2.2 Baseline

Baseline will be defined as the last available assessment prior to the first IMP administration.

3.2.3 Change from Baseline

Change from Baseline will be calculated as:

$$change\ from\ baseline = (postbaseline\ value) - baseline\ value$$

3.2.4 Study Day

Study Day will be derived as the number of days relative to date of first administration of AL, where the day of first administration = 1.

3.2.5 Listings, Tables and Figures

Listings, tables and figures will be delivered as individual .rtf files in accordance with the mock listings, tables and figures, with separate sets of outputs for each study part.

3.2.6 Treatment Groups

Participants will be analysed in the following treatment groups:

- AL+Rux (n=6; 1 participant from Group 1a + 5 participants from Group 1b)
- AL+placebo (n=2; 1 participant from Group 1a and 1 participant from Group 1b)

Unless otherwise stated, summary tables will be presented by treatment group and overall.

4 ANALYSIS SETS

In the first instance, four (4) analysis sets will be used for the analyses: Full Analysis Set (FAS), Safety Set, PK Set and Pharmacodynamics (PD) Set.

The number of participants in each analysis set will be summarised, with a corresponding listing.

4.1 Analysis Set Descriptions

4.1.1 Full Analysis Set

The FAS will consist of all enrolled participants. The FAS will be used to assess all participant disposition, baseline, demographic, treatment exposure and protocol deviation data.

4.1.2 Safety Set

The Safety Set will include all enrolled participants who received at least one dose (full or partial) of AL. The Safety Set will be used to assess all safety data.

4.1.3 PK Set

The PK Set will include all enrolled participants who received at least one dose AL, Rux, and/or placebo and have sufficient samples for analysis. The PK Set will be used to assess all PK data.

Protocol deviations will be reviewed and exclusion of subjects from the PK analysis set will be decided during final data review prior to database lock.

4.1.4 Pharmacodynamics (PD) Set

The PD Set will include all enrolled participants who received at least one dose (full or partial) of AL and Ruxolitinib or AL and Placebo, a valid baseline pSTAT3 result and at least one valid post-baseline pSTAT3 result. The pSTAT3 Set will be used to assess all PD data.

Protocol deviations will be reviewed and exclusion of subjects from the PD analysis set will be decided during final data review prior to database lock.

5 PARTICIPANT DISPOSITION

5.1 Disposition

Analysis Set: FAS

A listing of participant disposition will present:

- Date of informed consent
- Date of randomisation
- Date of first dose of AL administration
- Did the participant complete the study?
- Date of completion / early withdrawal
- Primary reason for early withdrawal (including instances where early termination was related to COVID-19)

Detailed early withdrawal information will also be listed in a separate listing.

If there are any deaths reported, a separate death listing will be prepared.

The number and percentage of participants entering and discontinuing the study will be summarised along with the reason for discontinuation. The participant disposition summary table will include:

- Number of participants randomised
- Number of participants who received at least one dose of study medication
- Number of participants who completed the full study
- Number of participants withdrawn from the study early
- Reason for early withdrawal

5.2 Clinical Trial Unit Admission, Confinement and Discharge

All admission, confinement and discharge data will be listed.

6 PROTOCOL DEVIATIONS

Analysis Set: FAS

All protocol deviations will be listed. A protocol deviation summary table will present the total number of protocol deviations as well as the number of participants who reported at least one protocol deviation, broken down by deviation category(minor/major)

6.1.1 Definition of variables

- Date deviation detected
- Date of deviation
- Deviation category (to be categorised by the Sponsor prior to Database Lock)
    - Minor
    - Major
- Deviation type
    - Informed consent
    - Eligibility
    - Visit not done
    - Visit performed out of window
    - Study procedure not done
    - Study procedure done out of window
    - Safety reporting
    - Investigational Product
    - Privacy and Data Protection
    - Concomitant Medication
    - Other
- Deviation description

7 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Analysis Set: FAS

7.1 Demographics

Demographic data will be listed for all enrolled participants and summarised by treatment arm and overall. Data includes:

- Date of birth
- Age
- Sex
- Race
- Women of Child-bearing potential

7.2 Medical history

All medical history data will be listed, grouped by participant.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedRA) and summarised by system organ class (SOC) and preferred term (PT).

7.3 Prior Medications

Prior medications will be coded using the World Health Organization-Drug Reference List (WHODRL), the version of which will be included in the footnote of the listing.

Prior medications will be listed for all enrolled participants. Prior medications are defined as any medication that is started before administration of IMP, regardless of when it ended. If a medication has a missing or partial missing start/end date or time and it cannot be determined whether it was taken before IMP or concomitantly, it will be considered as prior and concomitant.

7.4 Body Measurements

Height and weight data at Screening will be listed for all participants.

7.5 Eligibility

Eligibility will be listed for all enrolled participants.

7.6 Drug Screen

Drug screen data will be listed for all participants.

8 TREATMENT EXPOSURE

Analysis Set: Safety Set

8.1.1 Parameters

- Date/time of administration
- Number of tablets administered

8.1.2 Biostatistical methods

Participant exposure to all protocol-specified treatments will be listed and summarised. Exposure will be summarised as:

- AL
  - Total dose (mg)
  - Total number of tablets
  - Compliance*
- Ruxolitinib
  - Total dose (mg)
  - Total number of tablets
  - Compliance*

* Compliance, derived as:

$$Compliance\ (\%) = \frac{Total\ number\ of\ tablets\ administered}{Expected\ number\ of\ tablets\ administered} x100$$

9 PHARMACOKINETICS

The secondary endpoint PK parameters will be estimated using non compartmental methods from plasma concentration-time data. Refer to the PK Plan, Appendix 1, as prepared by SBQ.

A formal analysis report will be prepared at the completion of the work and included in the CSR appendices.

10 PHARMACODYNAMICS

The secondary endpoint pSTAT3 inhibition ex-vivo on whole blood cells will be assessed using a validated ELISA. Refer to thePD analysis plan, Appendix 2, as prepared by TetraQ.

A formal analysis report will be prepared at the completion of the work and included in the CSR appendices.

11 SAFETY

11.1 Safety Endpoints

Safety and tolerability will be assessed by clinical review of the following parameters:

- AEs (including SAEs and AESIs)
- Vital signs and other body measurements including respiratory rate and body temperature
- 12-lead ECG
- Haematology, chemistry, coagulation and urinalysis
- Physical examination

All descriptive statistics for safety parameters will be evaluated using the Safety Set.

11.2 Adverse Events

11.2.1 Definitions

- Treatment Emergent Adverse Event (TEAE)
  - A TEAE is defined as an AE that commences on, or after, the first administration of IMP. AEs without an onset date or time will be defined as treatment emergent except if an incomplete date (e.g., month and year) clearly indicates that the event started prior to first administration of IMP, or if the AE stop date indicates that the event started and/or stopped prior to the first administration of IMP.
- Adverse Events of Special Interest (AESI)
  - An adverse event of special interest (AESI) (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or programme, for which ongoing monitoring and rapid communication by the PI to the Sponsor is appropriate.

11.2.2 Parameters

- Event Term
- Dates and times of onset and resolution
- Severity (CTCAE Grades 1 to 5)
- Outcome (Recovered/resolved, Recovering/resolving, Not recovered/not resolved, Recovered with sequelae/resolved with sequelae, Fatal, Unknown)
- Relationship of AE to Ruxolitinib (Not Related, Related)
- Relationship of AE to Artemether-lumefantrine (Not Related, Related)
- Relationship of AE to Placebo (Not Related, Related)
- Relationship of AE to Non-IMP Treatments / Study Procedures (Not Related, Related)
- Action taken with Ruxolitinib, Artemether-lumefantrine and Placebo (Dose not changed, Drug interrupted, Drug withdrawn, Not applicable, Unknown)
- Other actions taken (including withdrawal from the study)
- Seriousness (and SAE category)
- AESI status (Yes/No)
- Relatedness to COVID-19

Derived parameters:

- Duration in hours
- Time of onset relative to first AL administration

11.2.3 Biostatistical methods

Adverse events will be coded using MedDRA, and the MedDRA version will be included in the footnote of all AE listings and tables.

11.2.3.1 Listings

All AE data will be listed for each participant, including severity, relationship to IMPs, relationship to non-IMP protocol-specific treatments, outcome and actions taken. In addition, listings of AEs leading to discontinuation of the study, SAEs and deaths, will be provided as applicable.

11.2.3.2 Tables

AE summary tabulations will be restricted to TEAEs only.

All reported TEAEs, including SAEs and AESIs, will be mapped to standard MedDRA coding terms and grouped by SOC and PT.

An **overview summary table** of AEs will be provided by treatment arm including:

- Number of events reported
  - Total TEAEs
  - Severe TEAEs
  - Artemether-lumefantrine Related TEAEs
  - Ruxolitinib Related TEAEs
  - Placebo Related TEAEs
  - Serious TEAEs
- Number of participants reporting at least one of the following:
  - TEAE
  - Severe TEAE
  - Artemether-lumefantrine Related TEAEs
  - Ruxolitinib Related TEAEs
  - Placebo Related TEAEs
  - Serious TEAE
- Number of participants withdrawn from the study due to a TEAE
- Number of deaths

The number of events, as well as the number and percentage of participants experiencing a TEAE, will be summarised for each SOC and PT by treatment arm and overall for the following categories of events:

- All TEAEs
- TEAEs by severity
- TEAEs by relationship (separate tables for each relationship type assessed)
- Serious TEAEs
- TEAEs leading to study withdrawal
- TEAEs of Special Interest (AESIs)

For the summaries of TEAEs, participants who experience the same AE (in terms of the MedDRA preferred term) more than once will only be counted once.

11.3 Concomitant Medications

Concomitant medications will be coded using the WHODRL, the version of which will be included in the footnote of all relevant listings and tables

Concomitant medications are defined as medications continued or newly received at or after administration of AL, through to the End of Study visit. If a medication has a missing or partial missing start/end date or time and it cannot be determined whether it was taken before initial treatment or concomitantly, it will be considered as prior and concomitant.

Concomitant medications will be summarised by Anatomical Therapeutic Chemical (ATC) (class level 3) and Preferred Name (PN). The summary tables will show the number and percentage of participants taking each medication by ATC and PN.

Participants who take the same medication (in terms of the ATC and PN) more than once will only be counted once for that medication.

11.4 Laboratory

11.4.1 Parameters

11.4.1.1 Hematology

- Basophils (absolute)
- Eosinophils (absolute)
- Hematocrit
- Hemoglobin
- Lymphocytes (absolute)
- Mean Cell Volume (MCV)
- Monocytes (absolute)
- Neutrophils (absolute)
- Platelet count
- Red cell count (RCC)
- Red cell distribution width (RDW)
- Reticulocyte count
- White cell count (WCC)

- Blood group and Rh(D) (Screening only)

1.1.1.1 *Chemistry*

- Alanine Aminotransferase (ALT)
- Albumin
- Alkaline phosphatase (ALP)
- Aspartate Aminotransferase (AST)
- Bicarbonate
- Bilirubin (direct)
- Bilirubin (total)
- Calcium
- Chloride
- Correct calcium
- Creatinine
- Creatine Kinase (CK)
- Estimated Glomerular Filtration Rate (eGFR, CKD-EPI equation)
- Gamma Glutamyl Transpeptidase (GGT)
- Glucose (Fasted)
- Lactate dehydrogenase (LDH)
- Magnesium
- Phosphate
- Potassium
- Protein Total
- Sodium
- Urea
- Uric acid

Lipids at Screening only

- Cholesterol Total
- High Density Lipoprotein (HDL)
- Low Density Lipoprotein (LDL)
- Triglyceride

Pregnancy Test and FSH

- β-Human Chorionic Gonadotropin (β-HCG) (women of child bearing potential only)
- Follicular Stimulating Hormone (FSH) (post-menopausal women only)

1.1.1.1 *Urinalysis*

Dipstick Testing
- Bilirubin
- Blood (erythrocytes)
- Glucose
- Ketone bodies
- Leucocytes
- Nitrites
- Proteins
- pH
- Specific gravity

Quantiative Assessments
- Creatinine
- Glucose
- Protein
- Protein:Creatinine Ratio

Additional Assessments where urine dipstick result more than traces
- Bacteria
- Red blood cells
- White blood cells

11.4.1.2 Coagulation

- INR
- Prothrombin Time
- Activated partial thromboplastin time (APTT)

11.4.1.3 Serology

- Hepatitis B Surface Antigen (HBsAg)
- Anti-HBc: IgG plus IgM if IgG is positive
- Hepatitis C Antibody (anti-HCV)
- Human Immunodefiniciency Virus (HIV) 1/2 (anti-HIV1 and anti-HIV2 Ab)

11.4.1.4 Tuberculosis Testing

- Latent *M. tuberculosis* infection testing using Quantiferon-TB gold assay

11.4.2 Biostatistical methods

All laboratory parameters will be listed with flags for values outside the reference ranges and values considered to be clinically significant by the investigator.

Haematology, biochemistry (excluding β-HCG and FSH) and continuous urinalysis laboratory data will be summarised for each scheduled visit, including observed values and change from each baseline. Categorical urinalysis results will be summarised for each scheduled visit using frequency tabulations.

Any available microscopic urinalysis will be listed.

Cross-tabulations (shift tables) may be presented.

11.5 Pregnancy Test and FSH

Pregnancy test data will be listed for all women of child bearing potential.

FSH data will be listed for all post-menopausal women.

11.6 Vital Signs

11.6.1 Parameters

- Systolic Blood Pressure (SBP) (mmHg)
- Diastolic Blood Pressure (DBP) (mmHg)
- Heart Rate (beats/minute)
- Tympanic Body Temperature (°C)
- Respiratory Rate (breaths/minute)

11.6.2 Biostatistical methods

All vital signs data will be listed for all participants. Any values outside of the protocol defined normal ranges (Table 1) will be flagged, with clinical significance status presented for out of range results.

Table 1: Vital Signs Normal Ranges

Parameter	Range
Systolic blood pressure	90-140 mmHg
Diastolic blood pressure	50-90 mmHg
Heart rate	50-100 bpm
Tympanic body temperature	35.0-37.5°C
Respiratory rate	10-25 breaths/min

Vital sign parameters will be summarised by presenting summary statistics for observed values and change from baseline values for each scheduled visit and timepoint, with two separate tables for:

- Vital Signs (SBP, DBP, heart rate)
- Respiratory Rate and Temperature

11.7 Physical Examination

11.7.1 Parameters

- Abdomen
- Chest
- General appearance
- Heart/Circulation
- HEENT (Head, Eyes, Ears, Nose, Throat)
- Lungs (Respiratory)
- Neck (including Thyroid)
- Neurological
- Skin
- Other (free text)

11.7.2 Biostatistical methods

Physical examination parameters will be listed for all participants and visits.

11.8 12-Lead ECG

11.8.1 Parameters

- The following ECG parameters are collected in triplicate for each timepoint:
  - PR interval (msec)
  - QRS interval (msec)
  - QT interval (msec)
  - QTcB interval (msec)
  - QTcF interval (msec)
  - Heart rate (beats/minute)
  - RR interval (msec)
- ECG result (Normal, Abnormal – Not clinically significant, Abnormal – Clinically significant)
- ECG abnormality (as appropriate)

11.8.2 Biostatistical methods

ECG parameters will be listed for all participants and time points.

Observed values, as well as changes from each baseline, will be summarised descriptively for all ECG parameters by visit.

An addition table will present the frequencies of participants who fulfill the following criteria, considering all scheduled and non-scheduled visit data:

- QTcF prolongation >30
- QTcB prolongation >30
- QTcF prolongation >60
- QTcB prolongation >60
- QTcF >450 msec
- QTcB >450 msec

All ECG data will be listed for all participants. Any values outside of the protocol defined normal ranges (Table 1) will be flagged.

Table 2: ECG Normal Ranges

Parameter	Range
PR interval	≤210 msec
QRS interval	50–120 msec
QTcB/QTcF	≤450 msec

11.9 Beck Depression Inventory

Beck Depression Inventory (BDI-II) data will be listed for all participants, including answers to the individual questions as well as the total scores.

12 HANDLING OF MISSING DATA

Only recorded data will be analysed/presented and any participants who have missing data will only have observed data reported, with no imputation for missing data.

13 CHANGES AND CLARIFICATIONS TO THE PLANNED ANALYSIS

Not applicable.

14 INTERIM ANALYSES

This trial has no formal interim analyses other than data reviews of safety and tolerability as described in the clinical study protocol.

15 SOFTWARE

The following software will be used to perform the statistical analyses: Statistical Analysis System (SAS®) Version 9.4 (SAS Institute, Cary, North Carolina, USA).

16 REFERENCES

1) MMV_Ruxolitinib_19_01 Clinical Study Protocol, v4.0, 7 September 2020

PHARMACOKINETIC ANALYSIS PLAN STUDY MMV_RUXOLITINIB_19_01

A randomised, single blind, placebo controlled, phase 1 trial to evaluate the safety, tolerability, pharmacokinetic and pharmacodynamic activity of ruxolitinib when co-administered with artemether-lumefantrine in healthy participants

Investigational drugs:	Ruxolitinib phosphate (Jakavi®) Artemether-lumefantrine (Riamet®)
Clinical study number:	MMV_RUXOLITINIB_19_01
SBQ study number:	SBQ-20251
Study director:	Paul van Giersbergen, PhD
Test Facility:	Swiss BioQuant AG Kägenstrasse 18, 4153 Reinach, Switzerland
Sponsor:	**Medicines for Malaria Venture** ICC, Route de Pre-Bois 20, 1215 Geneva 15, Switzerland
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The Sponsor's responsible person confirms by his signature on the pharmacokinetic analysis plan that all subjects signed the informed consent prior to the start of analysis. Any withdrawal of the informed consent by the subject to analyze his/her samples should be communicated to Swiss BioQuant.

2. TABLE OF CONTENTS

3. ABBREVIATIONS AND DEFINITIONS

AL	Artemether-lumefantrine
$AUC_{0-\infty}$	Area under plasma concentration-time curve from time zero, i.e., predose on Day 1, to infinity
AUC_{0-t}	Area under plasma concentration-time curve from time zero, i.e., predose on Day 1, to time t of the last measured concentration above the limit of quantification after the last dose on Day 3
AUC_{0-6h}	Area under plasma concentration-time curve from time zero to time 6h after dosing with Rux on Day 1
AUC_{0-8h}	Area under plasma concentration-time curve from time zero to time 8h after dosing with AL on Day 1
AUC_{0-10h}	Area under plasma concentration-time curve from time zero to time 6h after dosing with Rux on Day 3
AUC_{0-12h}	Area under plasma concentration-time curve from time zero to time 8h after dosing with AL on Day 3
BLQ	Below the limit of quantification
C_{max}	Maximum plasma concentration
CV	Coefficient of variation
λ_z	First order rate constant associated with the terminal log-linear portion of the plasma concentration-time curve
MMV	Medicines for Malaria Venture
P. falciparum	*Plasmodium falciparum*
PK	Pharmacokinetic(s)
R^2	Linear regression coefficient
Rux	Ruxolitinib
SD	Standard deviation
$t_{1/2}$	Apparent terminal half-life
t_{max}	Time to reach maximum plasma concentration

4. INTRODUCTION

The clinical study MMV_RUXOLITINIB_19_01 was conducted as part of the ruxolitinib (Rux)/artemether-lumefantrine (AL) clinical development program. The study population comprised of adult male and female participants aged 18 to 55 years.

In malaria volunteer infection studies, type I interferons s produced by several different cell sources were found to be important regulators of developing anti-parasitic immunity. Type I interferons are key immunomodulatory molecules in humans infected with *P. falciparum*, and targeting this pathway for clinical advantage is a promising strategy to overcome established or developing immunoregulatory networks, to improve natural, drug-mediated, or vaccine-induced immunity against malaria. Rux blocks type 1 interferon signaling, and is, therefore, a candidate for investigation in combination with established anti-malarial medications such as AL.

Study MMV_RUXOLITINIB_19_01 is the first study in humans to investigate the tolerability, safety, pharmacokinetics (PK) and pharmacodynamics of the combination of Rux and AL.

5. PERSONNEL / RESPONSIBILITY / COMMUNICATION

First choice of communication is via e-mail.

5.1. Sponsor

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5.2. Clinical Test Facility

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5.3. Pharmacokinetic Test Facility (Swiss BioQuant AG)

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6. CLINICAL STUDY OBJECTIVES

Primary objective:

- To assess the safety and tolerability of 3-day b.i.d dosing of AL+Rux and AL+placebo.

Secondary objectives:

- To assess the effect of AL+Rux and AL+placebo on pSTAT3 inhibition.
- To characterise the PK profiles of artemether and its major metabolite dihydroartemisinin [DHA], lumefantrine, and Rux.
- To assess additional safety variables (tympanic body temperature and respiration rate)

7. CLINICAL STUDY DESIGN

This study is a randomised, single-blind, placebo-controlled, single centre phase 1 trial. Subjects will be administered one of two treatments:

- AL (20 mg artemether /120 mg lumefantrine) and Rux (20 mg), or
- AL (20 mg artemether /120 mg lumefantrine) and placebo

The study will be composed of 2 groups (Group 1a and Group 1b) to be enrolled sequentially. Group 1a will participate first as the sentinel safety group.

Eight participants will be randomized to receive AL+Rux or AL+placebo in a 3:1 ratio overall (1:1 in Group 1a, and 5:1 in Group 1b). Participants will be administered oral doses of AL, with oral doses of Rux or placebo administered 2 hours later twice daily (b.i.d) for 3 consecutive days (AL at t = 0, 8, 24, 36, 48 and 60 hours, Rux at t = 2, 10, 26, 38, 50 and 62 hours).

A more detailed description of study design and study procedures is provided in the clinical study protocol [1].

7.1. Pharmacokinetic assessments

Blood samples for PK will be collected at the following times:

- Day 1 prior to commencement of dosing (pre-dose) and at t = 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 60, 62, 64, 72 and 78 hours post commencement of dosing. For time points coinciding with study drug administration, blood sampling occurs prior to study drug administration.
- Days 8, 11, 15, 21, 24 and 27 at t = 168, 240, 336, 480, 552 and 624 hours post commencement of dosing (±120 min for t = 168 hours, ± 24 hours for later timepoints).
- Day 29 at t = 672 hours (± 24 hours).

The exact date and time of blood sampling will be recorded in the Case Report Form.

The plasma concentrations of Rux, AL and the artemether metabolite dihydroartemisinin will be measured using validated liquid chromatography-tandem mass spectrometry methods at Swiss BioQuant AG, Reinach, Switzerland under phase number SBQ-20227.

8. PLANNED PHARMACOKINETIC ANALYSIS

8.1. Pharmacokinetic analysis set

All subjects who received a dose of study medication will be included in the pharmacokinetic analysis provided they have at least one available Rux and/or AL plasma concentration above the limit of quantification and who experienced no protocol deviations with relevant impact on the PK data. The number of subjects included into the PK analysis will be listed.

8.2. Data review

The exclusion of outliers, subjects and/or data points from analyses will not be done on a purely statistical basis. If a separate analysis was carried out excluding outliers, it would not normally be included in the PK report unless the conclusions differ from the primary analysis.

Concentration values excluded from the calculation of PK variables will be flagged. The pharmacokineticist will provide a reason in the PK report for excluding any points or subjects. The dataset for PK analysis will be created by Van Giersbergen Consulting (consultant for Swiss BioQuant AG) using electronic data files provided by Swiss BioQuant AG (bioanalytical data with scheduled blood sampling times) and MMV (listings of demography, protocol violations, adverse events and actual blood sampling times in hour). The dataset will be added in the report as a listing.

8.3. PK analysis plan deviations

Deviations to this PK analysis plan analysis will be listed.

8.4. Treatment compliance

Treatment compliance is assumed 100% since study drug is administered by study personel and will not be used in the analysis. A listing of dosing will, however, be provided.

8.5. Premature discontinuation and missing data

Subjects who did not receive any study drug or who did not receive the full treatment will be excluded from the PK analysis. Subjects who prematurely discontinued the study resulting in incomplete PK profiles will be included in the PK analysis but will be excluded from descriptive statistics. Missing sample concentrations will be ignored, *i.e.* no imputation of missing concentration data will be performed.

8.6. Handling of values below the limit of quantification

Samples with plasma concentrations below the limit of quantification (BLQ) will be set to zero for the PK analysis. In the dataset listing, they will be reported as BLQ. BLQ values occurring between two measurable concentrations will be set to missing.

8.7. Examination of subgroups and covariates

No subgroup/covariate PK analysis is foreseen in the protocol.

8.8. Mean pharmacokinetic plots

Nominal blood sampling times will be used to calculate the mean drug concentrations at each time point.

Comparative linear and semi-logarithmic plots of the mean concentration-time data for each analyte and corresponding tables of descriptive statistics (mean, SD, minimum, median, maximum) will be prepared.

In addition, plots of trough mean concentration-time data for AL and Rux will be prepared and used for a graphical exploration.

For plots and summary tables, BLQ values will be set to zero.

8.9. Pharmacokinetic plots

Linear and semi-logarithmic plots for each subject will be prepared using actual sample times. The time points used for the estimation of $t_{1/2}$, if applicable, will be shown on the semi-logarithmic plots as well as the coefficient of the linear regression, R^2, used to calculate $t_{1/2}$. In addition, plots on a linear and semi-logarithmic scale will be prepared showing all individual concentration-time profiles per treatment in one plot.

For individual plots, BLQ values will be handled as described in section 8.6.

8.10. Noncompartmental pharmacokinetic analysis

The PK variables of Rux, AL and the artemether metabolite dihydroartemisinin will be computed using the actual sampling times relative to the time of study drug administration.

C_{max}, t_{max}, C_{168h}

The maximum observed drug concentration (C_{max}) and the first time of its occurrence (t_{max}) will be obtained directly from the concentration-time data after the first and last administration of study drugs. For lumefantrine only, C_{168h} obtained directly from concentration-time data, will be separately listed.

λ_z, $t_{1/2}$

- The terminal phase rate constant (λ_z) will be estimated by linear regression of logarithmically transformed concentration versus time data.
- Only those data points which are judged to describe the terminal log-linear decline will be used in the regression.
- A minimum number of three data points will be used in calculating λ_z.
- λ_z will not be estimated if R^2 value of the linear regression is less than 0.8. As a consequence, λ_z -dependent pharmacokinetic variables will not be estimated.
- Further, it is preferable that the duration of time over which λ_z is estimated be at least two times the subsequently estimated terminal phase half-life ($t_{1/2}$).

The $t_{1/2}$ will be calculated as follows: $t_{1/2}=\ln 2/\lambda_z$.

The concentration-time data used for estimation of the terminal phase rate constant will be visible on the individual semi-logarithmic plasma concentration-time profiles.

AUC_{0-t}, AUC_{0-inf}, AUC_{0-6h}, AUC_{0-8h}, AUC_{0-10h}, AUC_{0-12h}

The area under the concentration-time curve (AUC) from time zero, i.e., predose AL on Day 1, to time t of last quantifiable concentration (AUC_{0-t}) after the last study drug administration on Day 3. The area from time zero extrapolated to infinite (AUC_{0-inf}) will be calculated as follows: $AUC_{0-inf} = AUC_{0-t} + C_t/\lambda_z$ where C_t is the last measured concentration above the lower limit of quantification.

On Day 1, after the first dose of study drug in the morning, AUC_{0-8h} will be calculated for AL and AUC_{0-6h} for Rux whereby time 0 refers to predose of the respective compound.

On Day 3, after the second dose of study drug in the evening, AUC_{0-12h} will be calculated for AL and AUC_{0-10h} for Rux whereby time 0 refers to predose of the respective compound.

The different AUCs will be calculated using the linear up log down trapezoidal method.

8.11. Statistics

Listings of individual PK variables for Rux, AL and the artemether metabolite dihydroartemisinin will be provided.

All PK variables (normally and log-normally distributed) will be summarized using arithmetic and geometric means, minimum, median, maximum, SD and coefficient of variation (CV%) of arithmetic and geometric means. Summary tables showing the median and range for t_{max} and geometric mean and CV% for all other PK variables will be provided by day and treatment.

8.12. Software

The data file, which will be the basis for the PK analysis, will be created using Excel. It will contain the subjects' identifier, dose administered, scheduled and actual timepoints of PK blood sampling, concentration data, etc.

The PK analysis and the statistics will be performed with Phoenix WinNonlin (version 8.2, Pharsight Corporation, Mountain View, CA, USA).

The individual plasma concentration time profiles will be generated with Phoenix WinNonlin whereas other plots will be generated with GraphPad Prism (version 5.00, GraphPad Software Inc, La Jolla, CA, USA).

9. REPORTING CONVENTIONS

The PK analysis will be reported using a Van Giersbergen Consulting report template (Word). As a rule, 3 significant digits will be used in the reporting of the results of the PK analysis.

The final report will comprise a QA statement of the Quality Assurance of Swiss BioQuant AG.

The final report will be provided in English. An electronic version (searchable, with hyperlinked table of contents and cross-references) of the PK analysis report will be provided in current PDF format to the Sponsor.

10. DATA QUALITY ASSURANCE

The Quality Assurance department of Swiss BioQuant AG (Reinach, Switzerland) will inspect the PK analysis report.

11. ARCHIVING

All documents (WinNonlin reports, QA protocols, etc.) generated by Van Giersbergen Consulting and the final PK analysis report will be filed in the Swiss BioQuant AG archives for 10 years.

At the end of the mentioned storage period Swiss BioQuant AG will ask the Sponsor for the authorization to destroy the documents of the study or to transfer them to the Sponsor's facility.

12. REFERENCES

[1] A randomised, single blind, placebo controlled, phase 1 trial to evaluate the safety, tolerability, pharmacokinetic and pharmacodynamic activity of ruxolitinib when co-administered with artemether-lumefantrine in healthy participants. Protocol number MMV_RUXOLITINIB_19_01, version 4, dated 07 September 2020.

Pharmacodynamic and Statistical Analysis Plan

Product:	Ruxolitinib phosphate Artemether-lumefantrine
Project Title:	Protocol MMV_Ruxolitinib_19_01 A randomised, single-blind, placebo controlled, phase 1 trial to evaluate the safety, tolerability, pharmacokinetic and pharmacodynamic activity of ruxolitinib when co-administered with artemether-lumefantrine in healthy participants
Sponsor:	Medicines for Malaria Venture (MMV) 20 Route de Pré-Bois 1215 Geneva 15 SWITZERLAND
PK/PD Consultant:	Stephanie Reuter Lange, PhD BSc (Hons) UniSA Clinical & Health Sciences University of South Australia CEA-19, GPO Box 2471 Adelaide, SA, 5001 Phone: +61 8 8302 1872 Email: stephanie.reuterlange@unisa.edu.au
Bioanalytical Test Facility:	TetraQ Level 7, Block 6 Royal Brisbane and Women's Hospital Herston QLD 4029
Version:	FINAL
Release Date:	16 December 2020

This Pharmacodynamic and Statistical Analysis Plan has been prepared for the study entitled "Protocol MMV_Ruxolitinib_19_01: A randomised, single blind, placebo controlled, phase 1 trial to evaluate the safety, tolerability, pharmacokinetic and pharmacodynamic activity of ruxolitinib when co-administered with artemether-lumefantrine in healthy participants". The contents of this document are confidential and reproduction, in whole or part, is not permitted without prior written permission from TetraQ.

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Dr Stephanie E Reuter Lange
Pharmacokinetic/Pharmacodynamic Consultant

This Pharmacodynamic and Statistical Analysis Plan has been reviewed and approved by representatives on behalf of the Medicines for Malaria Venture (MMV).

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Dr Farouk Chughlay
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Dr Myriam El Gaaloul
Director, Clinical Sciences

1. Introduction

Study Rationale

Medicines for Malaria Venture (MMV) is conducting a clinical trial program with ruxolitinib as a therapeutic option in the treatment of malaria. This phase I, multiple-dose study is being conducted to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of artemether-lumefantrine + ruxolitinib and artemether-lumefantrine + placebo in healthy volunteers.

Study Objectives

(i) To assess the safety and tolerability of 3-day b.i.d. dosing of artemether-lumefantrine + ruxolitinib and artemether-lumefantrine + placebo

(ii) To assess the effect of artemether-lumefantrine + ruxolitinib and artemether-lumefantrine + placebo on pSTAT3 inhibition

(iii) To characterise the pharmacokinetic profile of artemether and its major metabolite dihydroartemisinin, lumefantrine and ruxolitinib

(iv) To assess additional safety variables (tympanic body temperature and respiration rate)

The proposed pharmacodynamic analysis will be conducted to assist in addressing objective (ii).

Study Design

This is a randomised, single-blind, placebo-controlled, multiple-dose study comparing artemether-lumefantrine + ruxolitinib and artemether-lumefantrine + placebo administered twice-daily over a 3-day period to a total of 8 participants (Group 1a [Sentinel] = 2 participants, Group 1b = 6 participants).

Artemether-lumefantrine (20 mg artemether/120 mg lumefantrine) will be administered with 250 mL full-fat milk at 0, 8, 24, 36, 48 and 60 hours, and ruxolitinib (20 mg) or placebo will be administered with 250 mL water at 2, 10, 26, 38, 50 and 62 hours.

Blood samples for quantification of plasma ruxolitinib, artemether, dihydroartemisinin and lumefantrine concentrations will be collected prior to dosing (0 hr) and 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 60, 62, 64, 72, 78, 168, 240, 336, 480, 552, 624 and 672 hours after administration of artemether-lumefantrine on Day 1. Additionally, blood samples for determination of pSTAT3 levels will be collected prior to dosing (0 hr) and 1, 2, 3, 4, 5, 6, 8, 12 and 168 hours after administration of artemether-lumefantrine on Day 1. Samples scheduled for the same time as dose administration will be collected immediately prior to dosing.

2. Pharmacodynamic Analysis

pSTAT3 Data

All individual participant pSTAT3 levels and ruxolitinib concentrations will be presented within the Pharmacodynamic Consultancy Report in both tabular and graphical form. In addition, %pSTAT3 inhibition will be determined at each time-point, calculated as:

$$\%pSTAT3\ Inhibition\ = 100\ \times \frac{pSTAT3_0\ -\ pSTAT3_i}{pSTAT3_0}$$

where, $pSTAT3_0$ is the pSTAT3 level prior to treatment initiation (i.e. at 0 hr), and $pSTAT3_i$ is the pSTAT3 level at the i^{th} time-point. %pSTAT3 inhibition data will be presented within the Pharmacodynamic Consultancy Report in both tabular and graphical form

Descriptive statistics (including mean, median, standard deviation, minimum, maximum, coefficient of variation and geometric mean) will be calculated for pSTAT3 levels and %pSTAT3 inhibition at each nominal time-point. Summary data will be tabulated and presented graphically.

Pharmacodynamic Data

Pharmacodynamic analysis will be based on %pSTAT3 inhibition data. For each individual, %pSTAT3 inhibition data will be used for the calculation of:

$AUEC_T$ Area under the pharmacodynamic effect versus time profile over the ruxolitinib dosing interval on Day 1 (i.e. from 2 to 10 hours), calculated using the linear trapezoidal method. %pSTAT3 inhibition levels at 10 hours will be interpolated based on values obtained at 8 and 12 hours.

The pharmacokinetic/pharmacodynamic relationship between ruxolitinib concentrations and %pSTAT3 inhibition will also be calculated using sigmoidal curve fitting according to the following equation:

$$I = \frac{I_{max} \times C^{\gamma}}{C^{\gamma} + IC_{50}{}^{\gamma}}$$

where, I is the %pSTAT3 inhibition, C is the ruxolitinib concentration, I_{max} is the theoretical maximum %pSTAT3 inhibition, IC_{50} is the ruxolitinib concentration at which there is 50% maximal inhibition, and γ is the Hill coefficient. All %pSTAT3 inhibition values and ruxolitinib concentrations at coinciding time-points will be included in the analysis. Alternate pharmacodynamic models may be investigated at the discretion of the Pharmacokinetic/Pharmacodynamic Consultant.

All individual pharmacodynamic data will be presented within the Pharmacodynamic Consultancy Report in tabular form.

Descriptive statistics (including mean, median, standard deviation, minimum, maximum, coefficient of variation and geometric mean) will be calculated for pharmacodynamic data and will be tabulated.

Statistical Analysis

A linear mixed-effects analysis of variance (ANOVA) will be used to perform statistical comparisons of Ln-transformed $AUEC_T$, IC_{50} and I_{max} data between study treatments. The residual error (error mean square) will be used to construct the 90% confidence intervals for the ratio of treatment means.

No difference will be concluded if the 90% confidence intervals are within the standard regulatory limits of 80-125%. Significance will be set at an α-level of 0.05.

Statistical data will be presented within the Pharmacodynamic Consultancy Report in tabular form.

3. Data Handling

For graphical presentation of data, calculation of descriptive statistics and pharmacodynamic analysis, negative %pSTAT3 inhibition values will be designated a value of 0%. Plasma ruxolitinib concentrations below the limit of quantification of the assay will be designated a value of 0.00ng/mL for the pharmacokinetic/pharmacodynamic analysis.

When available, all times used in the presentation of individual pSTAT3 data and pharmacodynamic analysis will be actual times relative to first ruxolitinib administration on Day 1, with the exception of the pre-dose samples which will be designated a nominal time of 0.00 hr. In the event that actual sample collection times are not available, nominal times shall be used.

All data will be reported to 3 significant figures.

Non-rounded data will be used in descriptive, pharmacodynamic and statistical analyses.

4. Analysis Packages

Pharmacodynamic and statistical analyses will be conducted using Phoenix® WinNonlin® Version 8.0 or higher (Pharsight®, a Certara™ company). Internal validation of Phoenix® WinNonlin® will be conducted using the Phoenix® WinNonlin® Validation Suite prior to data analysis.

5. Data Transfer

Individual samples will be analysed for pSTAT3 levels by the TetraQ Analytical Laboratory. Ruxolitinib concentrations will be analysed by an external laboratory. Data will be provided to the Pharmacokinetic/Pharmacodynamic Consultant in Microsoft Excel format.

Clinical data will be exported from the locked study database and transferred to the Pharmacodynamic Consultant in Microsoft Excel format and shall include at least the following information for each participant: identification code, treatment administration details and sample collection details.

All pharmacodynamic data listings, tables and profiles will be included in the Pharmacodynamic Consultancy Report. Copies shall also be provided to the sponsor in Microsoft Word format for preparation of the Clinical Study Report.