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Oscotec Inc.

OSCO-P2101

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Dose Study to Evaluate the Efficacy and Safety of Oral SKI-O-703, SYK Inhibitor, in Patients with Persistent and Chronic Immune Thrombocytopenia (ITP)

14FEB2023

Final Statistical Analysis Plan

Version *2.0*

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List of Abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration versus time curve
$AUC_{0\text{-}tau}$	area under the plasma concentration-time curve within a dosing interval
AUEC	area under the effect versus time curve
$AUEC_{0\text{-}tau}$	area under the effect versus time curve within a dosing interval
BID	twice daily
BLQ	below the limit of quantification
BMI	body mass index
CI	confidence interval
CL/F	apparent oral clearance
C_{max}	maximum observed concentration
eCRF	electronic case report form
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration observed at steady state
CV	coefficient of variation
ECG	electrocardiogram
EOT	end-of-treatment
ITP	immune thrombocytopenia
ITT	Intent to treat
IVRS	interactive voice response system
K_{el}	terminal phase elimination rate constant
K_{el} lower	lower bound used for the estimation of K_{el}
K_{el} upper	upper bound used for the estimation of K_{el}
K-M	Kaplan-Meier
LS	least-square
MedDRA	Medical Dictionary for Regulatory Activities
ORR	overall platelet response rate
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	per protocol
PT	preferred term
QTcF	corrected QT interval by Fridericia formula
R_{AUC}	accumulation ratio

Abbreviation	Definition
R_{met}	metabolite ratio
Rsq (r^2)	coefficient of determination
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	system organ class
$t_{1/2}$	apparent terminal elimination half-life
$t_{1/2,eff}$	effective half-life
TEAE	treatment-emergent adverse event
TE_{max}	Time to achieve maximum effect
T_{max}	time to reach maximum observed concentration
V_z/F	apparent volume of distribution
WHODD	World Health Organization Drug Dictionary

1. Introduction

This Statistical Analysis Plan (SAP) describes the analyses and data presentations for Oscotec Inc.'s protocol OSCO-P2101 Version 4.0 (Amendment 3, dated 22 Apr 2020) "A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Dose Study to Evaluate the Efficacy and Safety of Oral SKI-O-703, SYK Inhibitor, in Patients with Persistent and Chronic Immune Thrombocytopenia (ITP)" which was originally issued on 09 Jan 2019. It contains definitions of analysis populations, derived variables and statistical methods for the analysis of efficacy, safety, pharmacokinetics (PK) and pharmacodynamics (PD).

There is one final analysis and one interim analysis planned for this study. This SAP is prepared for final analysis, and interim analysis is planned in a separate interim analysis SAP. Throughout these SAPs, the treatment groups will be referred to as the 200 mg twice daily (BID) group, the 400 mg BID group, and the placebo group. The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to any data analysis prior to database lock. This SAP will be finalized and signed prior to the final database lock.

All statistical analyses detailed in this SAP will be conducted using SAS® 9.4 or later (SAS Institute Inc., Cary, North Carolina).

2. Objectives

2.1. Primary Objective

To evaluate the safety and efficacy on the primary endpoint (platelet response) of select (200 mg BID and 400 mg BID) doses of SKI-O-703 compared to placebo in patients with persistent and chronic ITP, with a platelet count <30,000/μL on 2 occasions at least 7 days apart with the confirmatory count being taken during Screening.

2.2. Secondary Objectives

The secondary objectives of this study are as below:

- To evaluate the efficacy on the secondary endpoints of select (200 mg BID and 400 mg BID) doses of SKI-O-703 compared to placebo in patients with persistent and chronic ITP
- To investigate the PK profile of SKI-O-592 (the free base of SKI-O-703) and its metabolites (M2 and M4) in patients with persistent and chronic ITP
- To evaluate the effects of SKI-O-703 on PD biomarkers in patients with persistent and chronic ITP.

2.3. Exploratory Objectives

The exploratory objectives of this study are as below:

- To evaluate the PK/PD relationship between plasma concentrations of SKI-O-592, M2, and M4 and the percent change in activated CD63+ basophils in peripheral blood in patients with persistent and chronic ITP
- To evaluate the changes of the exploratory endpoints of select (200 mg BID and 400 mg BID) doses of SKI-O-703 compared to placebo.

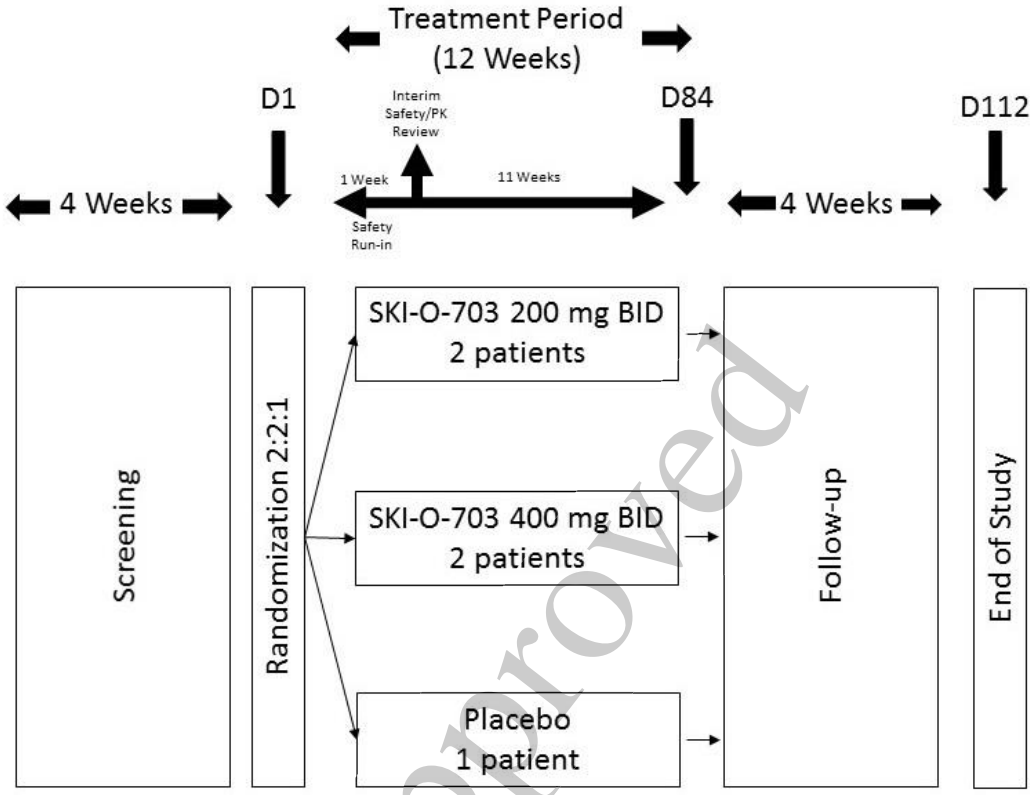
3. Investigational Plan

3.1. Overall Study Design and Plan

This is a randomized, double-blind, multicenter, placebo-controlled, parallel dose study to evaluate the efficacy, safety, tolerability, PK, and PD of select (200 mg BID and 400 mg BID) doses of SKI-O-703 in persistent and chronic ITP patients who have failed to respond or relapsed after prior therapy, with a platelet count <30,000/μL on 2 occasions at least 7 days apart with the confirmatory count being taken during Screening (the most recent result from the central laboratory will be considered as the confirmatory platelet count, when an unscheduled visit(s) is performed during the screening period).

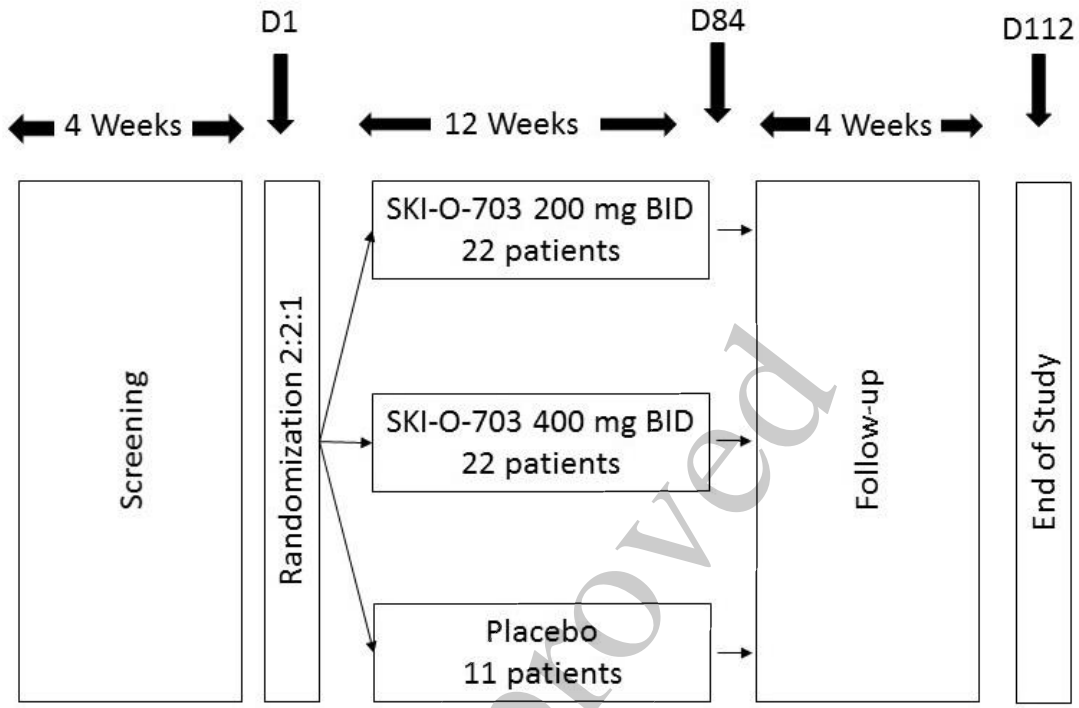
A minimum of 60 patients are planned to enroll in 3 treatment groups (24 patients in each of the active treatment groups and 12 patients in the placebo group). Patients will be randomly assigned to the 3 groups using a 2:2:1 ratio to receive one of the 2 select doses of SKI-O-703 or placebo. First 5 patients randomly assigned in the study will have the safety run-in period for the first 1 week with interim safety and PK assessments on Day 8 (±2 days). Patients in the safety run-in period will continue to be dosed whilst the interim analysis is being conducted. However, further enrollment in each treatment group will only resume after safety and PK data of the first week for the first 5 patients are reviewed and considered satisfactory by the Data Monitoring Committee (DMC). A subset of at least 20 patients, who are not included in the safety run-in period, will be randomized to undergo PK/PD assessments at a selected number of sites. Randomization will be stratified to balance patients with respect to prior TPO-receptor agonist use (yes/no) and degree of baseline thrombocytopenia (ie, baseline platelet count < or ≥15,000/μL). A schematic diagram of the overall study design is presented in Figure 3-1 and Figure 3-2.

Figure 3-1 Study Design Schematic (for the First 5 Patients in the Safety Run-in Period only)



Abbreviation: BID, twice daily
Note: First 5 patients randomly assigned in the study will have safety run-in period for the first 1 week with interim safety and PK assessments on Day 8 (±2 days). Patients in the safety run-in period will continue to be dosed whilst the interim analysis is being conducted. However, further enrollment in each treatment group will only resume after safety and PK data of the first week for the first 5 patients are reviewed and considered satisfactory by the Data Monitoring Committee.

Figure 3-2 Study Design Schematic (For Patients Other Than Enrolled in the Safety Run-in Period)



Abbreviation: BID, twice daily

Screening Period

The study will include up to 4 weeks of screening period. All potential patients will sign and date the informed consent form (ICF) prior to any study assessments or procedures. These patients will be assessed as per the eligibility criteria at Screening. After completing all screening assessments, patients who meet all the inclusion and none of the exclusion criteria will proceed to the treatment period.

12-week Treatment Period

- *1-week Safety Run-in Period (for the first 5 patients only):* First 5 patients randomly assigned in the study will have the safety run-in period for the first 1 week with interim safety and PK assessments on Day 8 (±2 days). Patients in the safety run-in period will continue to be dosed whilst the interim analysis is being conducted. However, further enrollment in each treatment group will only resume after safety and PK data of the first week for the first 5 patients are reviewed and considered satisfactory by the DMC.

For all patients, on Day 1, patient's eligibility will be confirmed and baseline safety evaluations will be performed (ECG, physical examination, vital sign measurements, and

safety laboratory assessment). Eligible patients will be randomly assigned to receive either one of the doses of SKI-O-703 or placebo. On Day 1, the investigative site staff will administer the morning dose. The evening dose of study medication will be administered 12 hours after the morning dose. Patients will be administered the study medication with enough water to swallow the capsule.

After dosing, all patients will be subjected to safety assessments and a subset of at least 20 patients, who are not included in the safety run-in period, will be subjected to PK and PD assessments according to the Schedule of Events (Appendix 15.1). Patients enrolled in the safety run-in period will be admitted for 24 hours on Days 1, 8, and 84 of the study. Patients selected for the PK/PD portion of the study will be admitted for 24 hours on Days 1 and 84 of the study.

The maximum duration of study participation for a patient will be 20 weeks, which consists of up to 4 weeks of screening period, 12 weeks of treatment period, and 4 weeks of follow-up period.

3.2. Study Endpoints

3.2.1. Primary Endpoint

The primary endpoint, patient platelet response, is defined as platelet count ≥ 30,000/μL and doubling the baseline (average of 2 previous counts), at any visit during the treatment period and without the use of rescue medication. Refer baseline definition to Section 4.2.

3.2.2. Secondary Endpoints

3.2.2.1. Patients Achieving Two or More Pre-specified Platelet Counts

- Patients able to achieve 2 or more consecutive platelet counts of ≥ 30,000/μL separated by at least 5 days and without use of rescue medication
- Patients able to achieve 2 or more consecutive platelet counts of ≥ 30,000/μL with an increase of platelet count of ≥ 20,000/μL from baseline separated by at least 5 days and without use of rescue medication
- Patients able to achieve 2 or more consecutive platelet counts of ≥ 50,000/μL separated by at least 5 days and without use of rescue medication
- Patients able to achieve 2 or more consecutive platelet counts of ≥ 100,000/μL during the treatment period, separated by at least 5 days and without use of rescue medication
- Patients able to achieve platelet counts of ≥ 50,000/μL at 3 of the last 4 visits.

3.2.2.2. Change from Baseline in Platelet Counts

- Change from baseline in the average of the last 2 platelet counts during the treatment period.

For each patient, the change from baseline in the mean of the last 2 platelet counts during the treatment period will be calculated. For those patients with only 1 platelet count during treatment period, the change from baseline in the single platelet count will be used.

3.2.2.3. Time to First Platelet Response

- Time to first platelet response (>30,000/μL and 2 × baseline)

For each patient, the time of the first platelet response is the first visit during treatment period in which platelet count ≥ 30,000/μL without use of rescue medication.

3.2.2.4. Others

- Number of patients receiving rescue medication at least once during treatment period
- Patients with at least one Grade 2 or higher non-skin bleeding event during treatment period.

For each endpoint, a patient will be considered to have had an event if the event was observed at least once during the treatment period for rescue medication, and during treatment or follow-up period for bleeding event.

3.2.3. Exploratory Endpoints

3.2.3.1. Peak Platelet Count

- Peak platelet counts during the treatment period without use of rescue medication

For each patient, peak platelet count is patient's highest platelet count during the treatment period, without use of rescue medication.

3.2.3.2. Bleeding Score

The ITP bleeding assessment score as described by Page et al. 2007 will be used to characterize bleeding tendency.

Table 3-1 The ITP Bleeding Score Assessment

Site	Bleeding Grade		
	0	1	2
Skin [physical Examination (PE)]	None	1–5 bruises and/or scattered petechiae	>5 bruises with size >2 cm and/or diffuse petechiae
Oral (PE)	None	1 blood blister or >5 petechiae or gum bleeding that clears easily with rinsing	Multiple blood blisters and/or gum bleeding

Site	Bleeding Grade		
	0	1	2
Skin (Hx)	None	1–5 bruises and/or scattered petechiae	>5 bruises with size >2 cm and/or diffuse petechiae
Oral (Hx)	None	1 blood blister or >5 petechiae and/or gum bleeding <5 min	Multiple blood blisters and/or gum bleeding >5 min
Epistaxis	None	Blood when blowing nose and/or epistaxis <5 min (per episode)	Bleeding >5 min (per episode)
Gastrointestinal	None	Occult blood	Gross blood
Urinary	None	Microscopic (+ve dipstick)	Macroscopic
Gynecological	None (normal period)	Spotting not at time of normal period	Bleeding >spotting not at time of period or very heavy period
Pulmonary	None	N/A	Yes
Intracranial haemorrhage	None	N/A	Yes
Subconjunctival haemorrhage	None	Yes	N/A

- abbreviation: ITP, immune thrombocytopenia; PE, physical examination; N/A, not applicable
- Note: In case of a breakthrough bleeding, the patients will discontinue the trial.

3.2.3.3. Quality of Life as Measured by the SF-36 Score

The Short Form (36) Health Survey is a 36-item, patient-reported survey of patient health. The SF-36 is a measure of health status and the survey will be conducted according to the SF-36 quality of life questionnaire Version 2.0.

The assessments will be performed at time points indicated in Schedule of Events (Appendix 15.1).

3.3. Dose Interruption and Reduction

It is recognized that some AEs may require dose adjustment or study drug discontinuation. Intra-patient dose reduction or escalation is permitted and based upon treatment-related adverse events observed. Guidelines for dose interruption or reduction are specified in Protocol Section 3.1.1.

After experiencing an AE, patients whose laboratory results return to baseline values and remain stable for 4 consecutive weeks have the option to increase the dose of SKI-O-703 1 dose level up to the randomized dose level.

4. General Statistical Considerations

4.1. Reporting Convention

Continuous variables (quantitative endpoints) will be summarized using the mean, the standard deviation (SD), median, range (minimum value and maximum value), and interquartile. Categorical variables (qualitative endpoints) will be summarized using frequency counts (number) and percentages, unless otherwise specified.

For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean, median and interquartile will be displayed to one level of precision greater than the data collected. Standard deviation / standard error will be displayed to two levels of precision greater than the data collected. All percentages will be rounded to one decimal place. If the percentage is 100, no decimal is required.

P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001." If a p-value is greater than 0.999 it will be reported as ">0.999."

All statistical tests will be 2-sided using a 5% significance levels, leading to 95% (2-sided) confidence intervals (CIs). This will be used for each pairwise comparison with placebo, i.e., there will be no adjustments for multiplicity since this is a Phase 2 study, and interim analysis will only be performed on safety and PK analysis.

Patients will be identified in the listings by the subject identifier. Data will be displayed in all listings sorted by treatment group.

4.2. Baseline Definition and Study Day

For platelet count related endpoints, baseline will be defined as the lowest platelet count within 1 month prior to or on the date that the first dose of study drug (SKI-O-703 or placebo) is taken. Data from Central lab will be used first. Otherwise, baseline will be defined as the last non-missing evaluation prior to or on the date that the first dose of study drug (SKI-O-703 or placebo) is taken.

The study day will be calculated as:

- Study day = assessment date - first dose of study drug (SKI-O-703 or placebo) date + 1, if assessment date is on or after the first dose date.
- Study day = assessment date – first dose of study drug (SKI-O-703 or placebo) date, if assessment date is prior to the first dose date.

4.3. Analysis Visit Window

No analysis visit window is assigned. All data are summarized based on the visit name collected on the CRF page.

4.4. Sample Size

A minimum of 60 patients will be enrolled in the study. Patients will receive either 200 mg BID or 400 mg BID of SKI-O-703 or placebo in a 2:2:1 ratio.

Based on Podolanczuk et al (2009) at least 50% of patients in the active treatment group will be responders (R). A sample size of 24 patients per active treatment group and 12 patients in the placebo group will provide approximately 82.74% power to detect a difference between response rates of 50% and 1% in the active treatment and placebo groups, respectively, at the 2-sided 5% significance level. The test statistic used in the sample size calculation was the 2-sided Fisher's Exact test using the normal approximation method.

Patients that do not receive the study drug or do not provide at least 1 post baseline measurement will be excluded from the analysis above and replaced.

There will be no adjustment for multiple comparisons. The sample size calculation was performed using PASS 15 Power Analysis and Sample Size Software (2017). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.

4.5. Randomization, Stratification, and Blinding

Patients will be randomly assigned in a 2:2:1 ratio to receive SKI-O-703 200 mg BID, SKI-O-703 400 mg BID, or matching placebo. A subset of at least 20 patients will be randomized to undergo PK/PD assessments at a selected number of sites. An interactive voice response system (IVRS) will be used to administer the randomization schedule. The randomization schedule will be generated using SAS software Version 9.4 or later (SAS Institute Inc., Cary, North Carolina) for IVRS, which will link sequential patients randomization numbers to treatment codes. The randomization will be stratified by prior TPO-receptor agonist use (yes/no) and degree of baseline thrombocytopenia (ie, baseline platelet count < or ≥15,000/μL). It will also use an appropriate block size, which will not be revealed.

Patients who are randomly assigned and not dosed will be replaced. Patients who discontinue the study for any reason after dosing will not be replaced.

This is a double-blind study. Neither the patients nor the investigator/site personnel will be aware of the treatment assignment for the patients in each cohort. Additionally, the study drugs will be identical in number and appearance for each cohort. Blinding will be

maintained throughout the study by use of active or placebo dosage forms of similar appearance.

The DMC will receive first 1-week safety and PK unblinded data by treatment group or unblinded (if necessary) confidential reports of the first 5 patients enrolled in the safety run-in period from an independent statistician for review, which has to be handled strictly confidentially. None of these reports can be delivered to unauthorized persons.

4.6. Analysis Set

4.6.1. Safety set

The Safety set will consist of all patients who receive at least 1 dose of study drug (SKI-O-703 or placebo). Patients will be analyzed according to the treatment they received. This analysis set will be used in the analysis of demographic and safety data.

4.6.2. Intent-to-Treat (ITT) set

The ITT set will consist of all randomized patients who receive at least 1 dose of study drug (SKI-O-703 or placebo) and have at least 1 post-baseline platelet assessments. Patients will be analyzed according to the treatment arm to which they were randomized. This analysis set will be used for efficacy summaries, including the analysis of the primary endpoint.

4.6.3. Per-protocol (PP) set

The PP set will consist of all patients in ITT set with no major protocol violations that may impact the analysis. Major protocol violations will be identified during the study according to the protocol deviation list and treatment compliance defined in Section 7.4.2. Patients will be analyzed according to the treatment arm to which they were randomized. This analysis set will be used for efficacy summaries, including the analysis of the primary endpoint.

4.6.4. Pharmacokinetic (PK) set

The PK set will consist of all patients who receive SKI-O-703 and have at least 1 measurable plasma concentration. Patients who have partial data and/or major protocol deviations that may impact PK, and patients who experience emesis, will be evaluated on a case-by-case basis and may be excluded from the PK analysis set. This analysis set will be used for summaries of PK data.

4.6.5. Pharmacodynamic (PD) set

The PD set will consist of all patients who receive at least 1 dose of study drug (SKI-O-703 or placebo) and have at least 1 evaluable postdose PD value. Patients who have partial data and/or major protocol deviations that may impact PD will be evaluated on a case-by-case basis and may be excluded from the PD analysis set. This analysis set will be used for summaries of PD data.

4.6.6. Pharmacokinetic (PK)/pharmacodynamic (PD) set

All patients included in the PK and PD analysis sets. This analysis set will be used for the PK/PD analyses.

4.7. Imputation of Missing Date

Incomplete Start and Stop Date of Concomitant Medications and Adverse Events:
For the purpose of inclusion in prior and/or concomitant medication tables and treatment-emergent adverse events (TEAE), incomplete medication/AE start and stop dates will be imputed as follows:
Missing start dates (where UK, UKN and UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY: If the month and year are different from the month and year of the first dose of study drug, assume 01-MMM-YYYY. If the month and year are the same as the first dose of study drug month and year and the end date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the month and year are the same as the first dose of study drug month and year and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the start date;
- DD-UKN-YYYY/UK-UKN-YYYY: If the year is different from the year of the first dose of study drug, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of study drug year and the end date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the year is the same as the first dose of study drug and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the start date.

Missing stop dates (where UK, UKN and UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY: Assume the last day of the month;
- DD-UKN-YYYY/UK-UKN-YYYY: Assume 31-DEC-YYYY.

If start date is completely missing and end date is not prior to the first dose, then the medication will be classified as both prior and concomitant. If the start date is completely missing and the end date is prior to the first dose of study drug, then the medication will be classified as prior. If the end date is missing, then the medication will be classified as ongoing. Medications for which the start and end dates are missing will be classified as prior and concomitant.

If start date is completely missing and end date is not prior to the first dose, then the AE will be classified as TEAE. AEs for which the start and end dates are missing will be classified as TEAEs.

5. Patient Disposition

5.1. Disposition

The number of patients screened, the number and percentage of patients who failed screening, and the violated eligibility criteria will be summarized. The above percentages will be based on the number of patients screened.

A summary of the analysis sets includes the number and percentage of patients for the following categories: Safety set, ITT set, and PP set. The above percentages will be based on the number of patients randomized.

Patient disposition will be summarized for the ITT set. A disposition of patients includes the number and percentage of patients who completed study treatment, discontinued study treatment, completed the study, and discontinued from the study. The reasons for study discontinuation, the reasons for study treatment discontinuation will also be summarized in this table, as collected on eCRF pages.

The number and percentage of patients by region, study site and treatment group will be tabulated based on all randomized patients.

Patient disposition data will be presented in listings.

5.2. Protocol Deviations

The protocol deviations/violations will be identified and assessed by clinical research physician or designee following institution standard operational procedures. The protocol deviations/violations will be summarized for all randomized patients by treatment group and overall based on all randomized patients.

A listing of patients with protocol deviations/violations will be provided with detail protocol deviation category and description presented.

6. Demographics and Baseline Characteristics

The demographics and baseline characteristics will be summarized by treatment group based on ITT set, unless otherwise specified. The patient data will also be presented in listings.

6.1. Demographics

The following demographics and baseline characteristics will be summarized based on ITT set, and repeated on Safety set:

- Age (years)

- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)

Body mass index is calculated as (body weight in kilograms) / (height in meters)^2. A patient's age in years is calculated using the date of the informed consent and date of birth.

Patient demographic and baseline characteristics will be presented in a listing.

6.2. Baseline Disease Characteristics

The following disease characteristics will be summarized:

- Number of previous lines of therapy
- Number of previous lines of therapy categories (0-2 vs. ≥3)
- Response to previous treatment (non-responders vs. relapsed)
- Previous splenectomy (yes vs. no)
- Baseline platelet count
- Baseline platelet count categories (<15,000/µL vs. 15,000/µL-30,000/µL)
- TPO-receptor agonist use (yes vs. no)

Patient baseline and disease characteristics will be presented in a listing.

6.3. Alcohol, Nicotine and Drug Usage

The following characteristics will be summarized based on ITT set, and repeated on Safety set:

- Alcohol status (never a drinker, current drinker, ex-drinker)
- Nicotine status (never smoked, smoker, ex-smoker)
- Drug status (never, current, former)

6.4. Genetic Analysis

The following genetic analysis components will be summarized based on ITT set, and repeated on Safety set:

- CYP1A2 Genotype
- CYP1A2 Phenotype
- UGT1A1 Genotype
- UGT1A1 Phenotype

6.5. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA v21.0 or later). The number and percentage of patients with any medical history will be summarized overall and by treatment for each system organ class (SOC) and preferred term (PT). SOCs and PTs will be presented in a descending order of overall patient frequency, then the patient frequency within treatment groups from high dose to low dose and placebo group, if applicable.

Patient medical history data including specific details will be presented in a listing.

6.6. Prior and Concomitant Procedure

6.5.1. Prior Procedure

Procedures collected on the Prior and Concomitant Procedures eCRF pages will be coded to SOC and PT terms using MedDRA (v21.0 or later). The procedures with the date prior to the start of study drug (SKI-O-703 or placebo) will be counted as prior procedures. The number and percentage of patients who had any prior procedures will be presented, and summaries will be provided overall and by treatment for each SOC and PT.

A listing will be generated for all procedures (including prior and concomitant) collected.

6.5.2. Concomitant Procedure

The procedures with the date on or after the start of study drug (SKI-O-703 or placebo) will be counted as concomitant procedures. The number of patients having concomitant procedures will be summarized overall and by treatment for each SOC and PT.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

Use of all concomitant medications that the patient is receiving at the time of Screening or receives during the study must be recorded in the patient's eCRF. All medications will be coded according to the World Health Organization Drug Dictionary (WHODD) Enhanced B3 March 2018 or later.

A prior medication is defined as any medication that has a stop date prior to the first dose of study drug (SKI-O-703 or placebo). Concomitant medications are defined as medications that are started between the first dose of study drug (SKI-O-703 or placebo) date and the last dose of study drug (SKI-O-703 or placebo) date, both inclusive, or started before the first dose of study drug (SKI-O-703 or placebo) date but ended or remain ongoing while on treatment. Incomplete medication start and stop dates will be imputed as per Section 4.7.

The frequency table will be provided by treatment group and overall on ITT set. The number and percentages of patients who had any prior medications will be summarized overall and by treatment groups, therapeutic drug classes (ATC level 2) and generic drug names. Therapeutic drug classes and generic drug names will be presented in a descending order of overall patient frequency, then the patient frequency within treatment groups from high dose to low dose and placebo group, if applicable. Similar frequency tables will be provided for permitted concomitant medications and prohibited concomitant medications on ITT set. The prohibited concomitant medications are defined in protocol Section 5.8.3.

The list of prohibited concomitant medications should be reviewed and finalized by sponsor designee before final database lock.

A listing of prior and concomitant medications by patient will be provided, with an indicator to identify the prior and concomitant medications.

7.2. Rescue Medications

In case of bleeding events requiring rescue medication, the following rescue medications are permitted: IVIG 1 g/kg/day for 2 days (ie, 2 g/kg), romiplostim 2 to 5 µg/kg, dexamethasone 40 mg/day for 4 days, other high dose parenteral steroids (ie, solumedrol 1 g IV), platelet transfusions (these may be reserved for serious or life threatening bleeding events), or standard of care as per participating countries. Patients should be withdrawn in case of CNS bleeding or life-threatening GI bleeding (see protocol Section 4.2.1).

Rescue medications will be coded to therapeutic drug classes (ATC level 2) and generic drug names using WHODD Enhanced B3 March 2018 or later. The number and percentages of patients who had any rescue medications will be summarized overall and by treatment, therapeutic drug classes (ATC level 2) and generic drug names based on ITT set. Therapeutic drug classes and generic drug names will be presented in a descending order of overall patient frequency, then the patient frequency within treatment groups from high dose to low dose and placebo group, if applicable.

A listing with all rescue medications will be generated.

7.3. Prior Therapy

Therapies collected on the Prior Therapy eCRF pages will be coded to therapeutic drug classes (ATC level 2) and generic drug names using WHODD Enhanced B3 March 2018 or later. The number and percentages of patients who had any prior therapy will be summarized overall and by treatment, therapeutic drug classes (ATC level 2) and generic drug names based on ITT set. Therapeutic drug classes and generic drug names will be presented in a descending order of overall patient frequency, then the patient frequency within treatment groups from high dose to low dose and placebo group, if applicable.

A listing with all prior therapies will be generated.

7.4. Study Treatments

On Day 1, eligible patients will be randomly assigned to receive either SKI-O-703 200 mg BID, SKI-O-703 400 mg BID or placebo. SKI-O-703 200 mg BID, 400 mg BID, and placebo will be administered orally. On Day 1, the investigative site staff will administer the morning dose. The evening dose of study medication will be administered 12 hours after the morning dose. Patients will be administered the study medication with enough water to swallow the capsule. From Day 2 to Week 12, patients will self-administer study drug.

7.4.1. Extent of Exposure

Duration of exposure is defined as the total number of days a patient is exposed to study drug (SKI-O-703 or placebo) and will be presented as the total number of days from the first dose date (Day 1) to the last dose date (date of last dose minus the date of first dose + 1) as recorded on the End of Treatment page on the CRF.

The duration of exposure to study drug by treatment will be summarized for all patients in the Safety set and will be presented in a table by summary statistics. The duration of exposure will then be classified into one of the following categories: < 2 weeks, 2 to <4 weeks, 4 to <6 weeks, 6 to <8 weeks, 8 to <10 weeks, 10 to 12 weeks and will be presented as the number and percentage of patients in each duration category. Percentages will be computed from the number of patients in the Safety set.

7.4.2. Treatment Compliance and Modifications

Each patient's dosing schedule should be closely monitored by the site at each study visit. This will ensure that all patients enrolled into the study maintain their original dosing schedule beginning with the first dose of study drug.

Study drug compliance will be calculated for each patient by taking into account whether a patient takes all doses of study drug as instructed. The number of tablets taken will be calculated from subject dosing data in eCRF.

The overall study drug compliance (%) will be calculated by dividing the total number of tablets taken by the total number of tablets prescribed and then multiplying by 100.
Compliance (%) = [(total no. of tablets taken) / (No. of days exposure× No. of tablets prescribed per day)] × 100

The overall study drug compliance will be summarized by treatment based on Safety set.

A patient is considered compliant if overall study drug compliance is between 80% - 120%.

Summary statistics on percentage of treatment compliance as well as the number and percentage of patients in each compliance category (<80%, 80%-120%, and >120% compliant) will be presented overall. Percentages will be calculated out of the number of patients who were dosed at that dosing period in the Safety set.

Patients drug accountability data will be provided in a listing.

8. Efficacy Analysis

The results for each efficacy endpoint will be summarized by treatment for all patients within the ITT set using descriptive statistical methods, and repeated within the PP set. Continuous variables (quantitative endpoints) will be summarized using the mean, the standard deviation (SD), median, range (minimum value and maximum value), and interquartile. Categorical variables (qualitative endpoints) will be summarized using frequency counts (number) and percentages. Data will be listed in data listings.

All statistical tests will be 2-sided using a 5% significance levels, leading to 95% (2-sided) confidence intervals (CIs). This will be used for each pairwise comparison with placebo, ie, there will be no adjustments for multiplicity since this is a Phase 2 study, and interim analysis will only be performed on safety and PK analysis.

If there are multiple post-baseline platelet count results in the same visit, the result from central lab will be used first. If there are more than one central lab result in the same visit, the result with larger platelet count will be used. However, if only local lab results exist, the local lab result with larger platelet count will be used.

8.1. Primary Efficacy Endpoint

The primary efficacy endpoint, patient platelet response, is defined as platelet count ≥ 30,000/μL and doubling the baseline (average of 2 previous counts), at any visit during the treatment period and without a use of rescue medication. Refer baseline definition to Section 4.2. The average based on last 2 platelet counts at the time of evaluation.

8.1.1. Primary Analysis

The platelet responses after using rescue medication during treatment period will be set to missing and will be imputed as the average of the last 2 previous non-missing platelet counts. For example, if platelet count in Week 2 Day 8, Week 3 and Week 5 are 45,000, missing, and 48,000 respectively, the average will be calculated by results from Week 2 Day 8 and Week 5.

The primary efficacy endpoint will be summarized as overall platelet response rate (ORR) with exact unconditional 95% confidence intervals (CI) by treatment group. The ORR difference and exact unconditional 95% CI will be provided between each of active treatment groups and placebo group, and between two active treatment groups. The p-value from Fisher's exact test will be presented.

For patients whose ORR cannot be adequately determined, their ORR will be imputed using a non-responder imputation (NRI) approach.

Summary statistics will be provided on the number (%) of patients achieving platelet response by each treatment and the combined active treatment groups. The differences in the ORR, 95% CI and p-value from a Fisher's exact test will therefore be provided for:

- Each active treatment group (200 mg BID, 400 mg BID) vs. placebo
- Combine active treatment groups vs. placebo
- 200 mg BID vs. 400 mg BID.

A logistic regression model will also be performed on platelet response as dependent variable and treatment group, baseline platelet count and prior TPO-receptor agonist use as covariates. The odds ratio for the treatment effect compared to placebo (together with 95% CI and p-value) will be provided.

Bar plots on difference in proportions of ORR and exact unconditional 95% CI will be provided by treatment group and combined active treatment group.

8.1.2. Sensitivity Analysis

Sensitivity analysis based on rescue medication with 28-day effective window:

The primary analysis will be repeated applying a 28-day window on rescue medication. Specifically, if a patient meets platelet response definition before a rescue therapy or after 28 days since a use of rescue medication, the patient will be considered as a responder.

The same analysis on ORR including summary statistics and logistic regression described in the primary analysis above will be carried out.

Sensitivity analysis based on treatment-policy strategy:

The primary analysis will be repeated on assessments in all scheduled visits from post-baseline until Week 12, regardless of patients using rescue medication or discontinuation. The missing platelet count values will be imputed by Multiple Imputation (MI) method for all treatment groups, under the missing at random (MAR) framework.

The SAS procedure MI will be used to impute missing platelet count at the scheduled analysis visits (up to Week 12) to create 25 complete data sets. The missing data patterns

will be checked by treatment and at the scheduled visits for the platelet count. If there are non-monotone missing patterns, two separate imputation procedures will be used to complete the imputation process.

In the first step, the Markov Chain Monte Carlo (MCMC) method will be used to impute missing values by treatment to create 25 imputed data sets with monotone missing patterns. The seed will be set to 7032101, the imputed values will be rounded to 3 decimals with 10^9/L unit and a single chain will be used to produce imputations.

In the second step, the monotone regression method will be used to impute the remaining missing values for the 25 data sets with monotone missing patterns. The MONOTONE REG statement will be used with seed 2101703. The missing values at each visit will be imputed based on treatment, values at baseline and previous visits, and prior TPO-receptor agonist use.

If model fail to converge because the number of visits is more than number of subjects, the model will be reformed. The nearest visits (Week 1 Day 1 to Week 2 Day 8, Week 3 to Week 7, and Week 9 to Week 12) will be imputed by two steps imputation procedures described above separately with unique seed. For visits Week 1 Day 1 to Week 2 Day 8, the seed used in first step is 7032101 and in second step is 2101703. For visits Week 3 to Week 7, the seed used in first step is 1021984 and in second step is 1984102. For visits Week 9 to Week 12, the seed used in first step is 1072018 and in second step is 2018107.

After the completion of two steps imputations, the response will be defined based on platelet counts in the 25 complete datasets and the same logistic regression model described in Section 8.1.1 will be used to analyze the 25 complete datasets. The SAS procedure MIANALYZE will be used to combine the results for the statistical inferences.

8.2. Secondary Efficacy Endpoint

8.2.1. Patients Achieving Two or More Pre-specified Platelet Count

When considering the achieving two or more pre-specified platelet count, the visit with missing result will be excluded.

A logistic regression model will be performed on each endpoint defined in Section 3.2.2.1 and include treatment, baseline platelet count and prior TPO-receptor agonist use, provided there are enough patients in each subgroup determined by each factor. The odds ratio for each active treatment effect compared to placebo (together with 95% CI and p-value) will be provided. Each endpoint will be summarized in number (%) of patients by treatment group.

For patients whose pre-specified platelet count achievement cannot be adequately determined, their achievement will be imputed using the same NRI approach as described in Section 8.1.

Bar plots on proportions of patients achieving two or more pre-specified platelet counts on each defined endpoint and exact unconditional 95% CI will be provided by treatment group and combined active treatment group.

8.2.2. Change from Baseline in Platelet Counts

Primary Analysis

The primary Analysis will be performed on all observed data until Week 12, regardless of rescue medication and discontinuation.

Change from baseline in the average of the last 2 platelet counts will be analyzed using an analysis of covariance (ANCOVA) model with covariates including baseline platelets count, treatment, rescue medication use, and prior TPO-receptor agonist use.

The within-group least-square (LS) means, the associate standard errors (SE), and the treatment differences in LS means, the associated SE, 95% CIs and p-values will be derived from the model to compare each active treatment group against placebo. Descriptive statistics of baseline value, observed value and change from baseline will be presented by treatment group.

Sensitivity Analysis based on treatment-policy strategy

The primary analysis will be repeated based on assessments in all scheduled visits from post-baseline until Week 12, regardless of patients using rescue medication or discontinuation. The same MI method will be applied as outlined in Section 8.1.2.

For each of m=25 imputed datasets, same ANCOVA model as defined in primary analysis will be carried out. Results from each of imputed datasets will be combined to generate the adjusted mean of change from baseline in platelet counts for each treatment group, as well as between-group difference (comparing each active treatment group against placebo) and the 95% CI for the difference.

Sensitivity analysis based on hypothetical strategy

The primary analysis will be repeated based on a hypothetical scenario if the rescue medication had not occurred. Specifically, applying the same rescue medication window, all assessments happened within 28 days of the use of rescue medication will be considered as missing, regardless if they are collected or not. Then all missing data will be imputed until Week 12 by Multiple Imputation (MI) method for all treatment groups, under:

- Missing at random (MAR) framework:
  Under this framework, the same MI method will be applied as outlined in Section 8.1.2.
- Missing not at random (MNAR) framework:

Two imputation steps will be performed under this assumption. First step for arbitrary missing is MCMC monotone imputation which is the same as described in Section 8.1.2. The second step is control-based pattern imputation using monotone regression method with seed 2010703, in which the missing data in all active treatment groups and placebo group will be imputed based on placebo group using the neighboring-case missing values method with k=2.

If model fail to converge because the number of visit is more than number of subjects, the same approach in Section 8.1.2 will be applied. When imputed value out of range (ie value <0), the value will be replaced by min value in dataset.

The same ANCOVA model defined in primary analysis will be carried out to analyze the 25 complete datasets. The SAS procedure MIANALYZE will be used to combine the results for the statistical inferences

8.2.3. Time to First Platelet Response

Time to platelet response based on the non-response imputation defined in Section 8.1.1 will be summarized by treatment group using Kaplan-Meier (K-M) methods with median time to platelet response (including two-sided 95% CI). K-M estimates of platelet response rates at 2-week intervals (e.g., 2-week, 4-week, etc) will be provided with corresponding two-sided 95% CIs by treatment group. The K-M curve for time to platelet response (later visit meet criteria) will be presented graphically and compared against placebo curve using log-rank test.

In addition, a proportional hazard model will be implemented as well with treatment, baseline platelet count, and prior TPO-receptor agonist use. The hazard ratios, 95% CIs and p-values will be provided to compare each active treatment group against placebo.

A listing of time to platelet response will also be provided.

8.2.4. Others

Summary statistics will be provided to each endpoint listed in Section 3.2.2.4 by each treatment group.

8.3. Exploratory Endpoints

8.3.1. Peak Platelet Count

Descriptive statistics of peak platelet count will be provided by treatment group. The difference in median peak platelet will be calculated for:

- Each active treatment group (200 mg BID, 400 mg BID) vs. placebo
- Combined active treatment groups vs. placebo
- 200 mg BID vs. 400 mg BID

Box plots will be provided to display the distribution of peak platelet count by treatment group and combined active treatment group.

8.4. Subgroup Analysis

The primary endpoint will be summarized using the number (%) of patients achieving platelet response by each treatment group and the following subgroups of interest:

- Number of previous lines of therapy (0-2 vs. ≥3)
- Response to previous treatment (non-responders vs. relapsed)
- Splenectomized patients vs. non-splenectomized patients and
- Patients with baseline platelet count < 15,000/µL versus patients with platelet count between 15,000/µL to 30,000/µL.
- Patients with prior TPO-receptor agonist use versus patients without prior TPO-receptor agonist use.
- Patients with background medication (defined in protocol Section 5.8) vs. patients without background medication.

9. Safety Analysis

Continuous parameters will be summarized separately for each treatment at each scheduled visit using descriptive statistics (mean, SD, minimum, median, and maximum). Discrete parameters will be summarized separately for each treatment at each nominal time point using frequency counts and percentages.

Safety results will be summarized using the Safety set by treatment groups and the combined active treatment group, unless otherwise specified.

9.1. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA v21.0 or later) will be used to code all adverse events (AE). All AEs, serious AEs (SAE), drug-related AEs, and drug-related SAEs will be summarized using the worst grade per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) by system organ class and preferred term. The intensity of the AE will be rated using the NCI CTCAE v5.0.

An AE is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to study drug. For the purpose of inclusion in TEAE tables, incomplete AE onset and end dates will be imputed according to Section 4.7.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

A treatment-related TEAE is defined as an TEAE which is considered to be related to the study drug and reported as "Possible", "Probable" or "Definite" on the eCRF. Any TEAE with a missing relationship will be classified as a treatment-related TEAE.

A SAE is defined as an AE that

- Results in death
- Is immediately life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

An overall summary of the following AE categories will be provided by treatment group and combined active treatment group:

- Patients with any TEAE
- Patients with any treatment-related TEAE
- Patients with any serious adverse event (SAE)
- Patients with any treatment-related SAE
- Patients with any grade 3 or 4 TEAE
- Patients with any grade 3 or 4 treatment-related TEAE
- Patients with any TEAE leading to Dose Reduced or Drug Interrupted
- Patients with any TEAE leading to Drug Withdrawn
- Patients with any TEAE leading to death

Tables summarizing the incidence of TEAEs by treatment group and combined active treatment group in SOC and PT will be provided for each of the following AE categories:

- All TEAEs
- Treatment-related TEAEs
- Grade 3 or 4 TEAEs
- Grade 3 or 4 treatment-related TEAEs
- TEAEs leading to Dose Reduced or Drug Interrupted
- TEAEs leading to Drug Withdrawn
- All SAEs
- Treatment-related SAEs
- TEAEs leading to death

The number and percentage of patients who experience any TEAE categories will be summarized by treatment group and combined active treatment group for each system organ class (SOC) and preferred term (PT), with SOCs and PTs within each SOC presented in a descending order of patient incidence within combined active treatment groups, then from high dose to low dose and placebo group if applicable.

Summary table of All TEAEs by maximum toxicity grade will also be provided. If patient reports multiple occurrences of a specific AE, the patient will be counted only once on the maximum grade.

Separated listings will be prepared for All AEs, SAEs, Grade 3 or 4 TEAEs, TEAEs leading to treatment modification or discontinuation and TEAEs leading to death. The verbatim term, PT and SOC, as well as event dates and other attributes that were collected on eCRF will be included in the listing.

9.2. Adverse Events of Special Interest

Adverse events of special interest (AESI) as listed below will be summarized by treatment group and combined active treatment group:

- Neutropenia
- Hepatotoxicity

The number and percentage of patients who experience any TEAE of special interest will be presented for each preferred term in a descending order of frequency within combined treatment group, then from high dose to low dose and placebo group if applicable. If patient reports multiple occurrences of an AESI, the patient will be counted only once.

A listing of AESI will be provided with verbatim term, PT and SOC presented, as well as other relevant event attributes collected on eCRF.

9.3. Clinical Laboratory Evaluations

Clinical laboratory tests will be performed by both central and local laboratory. All summaries will be based on the standard international (SI) units provided by both central and local lab.

The laboratory values will be graded using CTCAE version 5.0. For hematologic and chemistry laboratory values that fall outside of the grade criteria of CTCAE version 5.0, the grade of 0 will be assigned.

Abnormal clinical laboratory values will be flagged as either high or low based on the reference ranges for each laboratory parameter.

Summary statistics of observed values, change and percent changes from baseline in numeric laboratory parameters will be provided by treatment group and combined active treatment group, and scheduled visit indicated in the schedule of events in Appendix 15.1. Numeric values reported as less than (<) or greater than (>) a laboratory-defined limit will be included with the "<" or ">" signs ignored.

For relevant laboratory parameter, frequency summaries of categorical shifts from baseline grade to each post-baseline visit grade, and to the worst post-baseline grade during treatment will be provided in the graded hematology and serum chemistry parameters by treatment group and combined active treatment group.

Line plots of means and SEs will be created to display actual values and change from baseline by scheduled visit.

When there are multiple values within a post-baseline visit for a particular laboratory parameter (except platelet; refer rule of platelet to Section 8), the worst value will be taken (worst being the smallest value for criteria below a certain threshold or the largest value for criteria above a certain threshold). If a patient has a value below the threshold and above the threshold, the value furthest from the threshold will be chosen. If the distances are the same, the value with the recent date/time will be chosen.

All laboratory data will be listed, including unscheduled/repeat visits.

All laboratory data outside the normal range will be listed. For each laboratory test, individual patients with any values outside the standard reference range will have all their test results listed.

9.3.1. Hematology

Hematology will be collected at visits indicated in the schedule of events (Appendix 15.1).

The following hematology assessments will be performed:
Hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count, red blood cell count, total and differential (absolute and percent) leukocyte count, and erythrocyte sedimentation rate.

9.3.2. Serum Chemistry

Serum chemistry will be collected at visits indicated in the schedule of events (Appendix 15.1).

The following serum chemistry assessments will be performed:
Alanine aminotransferase, albumin, alkaline phosphatase, AST, bilirubin (total and direct if clinically indicated), blood urea nitrogen, calcium, creatinine, gamma-glutamyltransferase, glucose, lactate dehydrogenase, serum electrolytes (sodium, potassium, chlorine, magnesium, phosphate) and total protein.

9.3.3. Urinalysis

Urinalysis will be collected at visits indicated in the schedule of events (Appendix 15.1).

The following urinalysis assessments will be performed:
Appearance, bilirubin, color, glucose, ketones, leukocyte esterase, microscopy (performed if dipstick is positive; includes bacteria, casts, crystals, epithelial cells, red blood cells, and white blood cells), nitrites, occult blood, pH, protein, specific gravity, turbidity, and urobilinogen.

9.4. Vital Sign Measurements

Vital sign measurements will include systolic and diastolic blood pressures, pulse rate, respiratory rate, and temperature. Vital signs will be measured at visits indicated in the schedule of events (Appendix 15.1).

Height will be measured at Screening only. Weight will be measured at visits indicated in the schedule of events (Appendix 15.1).

Summary tables presenting observed values and changes from baseline will be provided for vital sign data by treatment group and combined active treatment group. Changes from baseline to each scheduled post-baseline visit will be presented.

The relevant vital sign values at each visit will be classified into the categories of low, normal, and high based on the reference ranges defined as: 60 to 100 beats/minute for pulse rate, 12 to 20 breaths/minute for respiratory rate, 36.5 to 37.5 ºC for oral temperature, 90 to 140 mmHg for systolic blood pressure, and 60 to 90 mmHg for diastolic blood pressure.

Shift tables from baseline to post-baseline visits in terms of low, normal and high will be provided for pulse rate, respiratory rate and blood pressure by treatment group and combined active treatment group.

When there are multiple values within a visit for a particular vital sign variable, the worst value will be taken (worst being the smallest value for criteria below a certain threshold or the largest value for criteria above a certain threshold). If a patient has a value below the threshold and above the threshold, the value furthest from the threshold will be chosen. If the distances are the same, the value with the recent date/time will be chosen.

Unscheduled visits will be included in the calculation of baseline.

All vital sign data by patient and parameter will be presented in a listing.

9.5. Physical Examination

A complete physical examination will be performed at the screening visit and an abbreviated physical examination at visits indicated in the schedule of events (Appendix 15.1).

An abbreviated physical examination will include checks of general appearance, head and neck, abdomen, lymph nodes, skin, cardiovascular system, respiratory system, and musculoskeletal system. A complete physical examination will include assessments of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, cardiovascular system, abdomen, lymph nodes, and musculoskeletal system/extremities.

Physical examination data by patient and parameter will be presented in a listing.

9.6. Electrocardiogram

Electrocardiogram (ECG) assessments will include comments on the rhythm; presence of arrhythmia or conduction defects; morphology; or ST segment, T wave, and U wave abnormalities; as well as whether the tracings are normal or abnormal and if there is any evidence of myocardial infarction. In addition, the following parameters will be measured and reported: RR interval, PR interval, QRS width, QT interval, and QTcF.

The investigator will determine whether any of the ECG results are normal or abnormal and whether any abnormal results are clinically significant or not clinically significant. Clinical significance is defined as any variation in results that has medical relevance and may result in an alteration in medical care (eg, active observation, diagnostic measures, or therapeutic measures).

Summary tables will be presented for ECG data and change from baseline by treatment group and combined active treatment group. The ECG investigator interpretations will be summarized in shift tables comparing the ECG value interpretation categories of each post-baseline visit with the value at the baseline visit. In addition, the worst post-baseline ECG value will be compared with the value at the baseline visit (with worst of all being Abnormal Clinically Significant and best being Normal).

ECG data by patient and ECG parameter will be presented in a listing.

9.7. Bleeding Score

Bleeding score will be summarized at visits indicated in the schedule of events (Appendix 15.1) by treatment group and the combined active treatment groups.

9.8. Quality of Life as Measured by the SF-36 Score

The SF-36 Score consists of 8 scales: physical function scale, role physical scale, bodily pain scale, general health scale, vitality scale, social functioning scale, role emotional scale, and mental health scale. Scale scores range from 0 to 100, with higher scores indicating better health.

Three overall scores will be further derived: physical component summary, mental component summary, and health utility score (SF-6D). The SF-6D provides a single index for use in economic evaluation or for determination of quality adjusted life years, derived from seven of the eight scales in SF-36.

All 8 scale scores, 3 overall scores, and the answer to the Global Health questionnaire item (SF-36 question 1) will be summarized by scheduled visit. Change from baseline in scale scores, physical health summary measure, mental health summary measures, SF-6D, and the Global Health questionnaire item will be analyzed and reported using the same ANCOVA model as specified for change from baseline in platelet counts in Section 8.2.2, using observed cases.

10. Pharmacokinetics

10.1. Pharmacokinetic Data Handling

Plasma concentrations that are below the limit of quantification (BLQ) will be treated as zero for calculation of descriptive statistics and all PK analyses. Missing concentrations will be excluded from all calculations.

All concentrations and PK parameters will be rounded to 3 significant figures for reporting purposes. The only exceptions will be actual sampling times and T_{max} (which will be rounded to 2 decimal places) and the number of data points (which will be reported as integers). Summary statistics will be rounded to the same precision as individual data, with the exception of n (which will be reported as an integer). Estimates and confidence intervals from all statistical comparisons will be reported to 2 decimal places, and associated p-values will be reported to 4 decimal places.

10.2. Plasma Pharmacokinetic Concentrations

Serial blood samples (5 mL) for PK assessment of SKI-O-592 and its metabolites (M2 and M4) will be collected from all subjects in the PK/PD subset at the following time points:

- Day 1: 0 hour (morning pre-dose), and at 0.25, 0.5, 1, 2, 4, 8 and 12 hours morning post-dose (12-hr sample should be collected prior to the evening dose).
- Week 12 (Day 84): 0 hour (morning pre-dose), and 0.25, 0.5, 1, 2, 4, 8, and 12 hours.

In addition, PK samples will also be collected at the following time points on Day 8 from subjects in the safety run-in period only:

- Day 8: 0 hour (morning pre-dose), and at 0.25, 0.5, 1, 2, 4, 8 and 12 hours morning post-dose (12-hr sample should be collected prior to the evening dose).

In all non-PK/PD subset subjects, trough PK samples will be collected during Week 12 only, for these samples plasma concentrations of SKI-O-592, M2, and M4 will be presented in data listings.

Individual plasma concentrations of SKI-O-592, M2, and M4 will be presented from the PK/PD subset in data listings and presented graphically versus actual time by treatment and analyte on both linear and semi-logarithmic scales.

Plasma concentrations of SKI-O-592, M2, and M4 will be summarized using descriptive statistics (n, mean, SD, CV, minimum, median, and maximum) by time point for each treatment and day separately. Mean plasma concentrations will be plotted by treatment for each analyte versus nominal time on both linear and semi-logarithmic scales.

10.3. Plasma Pharmacokinetic Parameters

The following plasma PK parameters will, where possible, be estimated on Days 1, 84 and 8 (for the first 5 subjects enrolled in the safety run-in period) for SKI-O-592, M2, and M4 using actual sampling times via non-compartment analysis using Phoenix WinNonlin version 6.4 or higher:

C_{trough} Trough concentration observed at steady state (Day 8 and 84 only).

C_{max} Maximum observed concentration.

T_{max} Time of the maximum observed concentration.

$AUC_{0\text{-}tau}$ Area under the concentration versus time curve within a dosing interval (τ), calculated using the linear trapezoidal rule.

$t_{1/2,eff}$ Effective half-life, calculated as $[\ln(2)/((-\ln(1-(1/R_{AUC}))/\tau))]$ (Day 8 and 84 only).

R_{met} Metabolite ratio, calculated as [($AUC_{0\text{-}tau}$ (metabolite)/ ($AUC_{0\text{-}tau}$ (parent)].

R_{AUC} Accumulation ratio based, calculated as [$AUC_{0\text{-}tau}$ (Day 8 and 84)/ $AUC_{0\text{-}tau}$ (Day 1)].

Actual PK blood sampling times will be used for the assessment of all PK parameters. Plasma PK parameters for SKI-O-592, M2, and M4 will be presented in data listings and summarized separately using the following descriptive statistics for each treatment and analyte (n, geometric mean, geometric CV, mean, SD, CV, minimum, median, and maximum). For T_{max}, only n, median, minimum and maximum will be reported.

Note: due to the limited duration of sampling after each dose (i.e. 12 hours), parameters associated with the estimation of a terminal elimination phase (e.g., K_{el}, $t_{1/2}$, CL/F, V_z/F, $AUC_{0-\infty}$, etc.) will not be presented.

10.4. Pharmacokinetic Statistical Analyses

10.4.1. Assessment of Accumulation

The accumulation ratio will be estimated by making comparisons of AUC_{0-tau} and C_{max} on Day 84 with corresponding estimates on Day 1 for each treatment separately; a mixed-effects model will be fitted to log-transformed AUC_{0-tau} and C_{max} including day (Day 1 or 84) as a fixed effect and subject as a random effect. This model will be used to estimate the accumulation ratio (Day 84 / Day 1) with 95% CIs for each treatment. The geometric least squares means and ratio with 95% CIs will be tabulated by treatment and parameter.

11. Pharmacodynamics

11.1. Pharmacodynamic Data Handling

Subjects with baseline CD63+ values below the limit of detection will be defined as low responders and excluded from the PD set and all summaries of PD data. Baseline will be defined as the percentage of activated CD63+ cells at predose samples on Day 1.

All PD data will be rounded to 3 significant figures for reporting purposes. The only exceptions will be actual sampling times and TE_{max} (which will be rounded to 2 decimal places). Summary statistics will be rounded to the same precision as individual data, with the exception of n (which will be reported as an integer).

11.2. Pharmacodynamic Data

Serial blood samples for assessment of the percentage of activated CD63+ basophils in peripheral blood will be collected in all subjects in the PK/PD subset at the following times:

- Day 1: 0 hour (morning pre-dose), and 0.25, 0.5, 1, 2, 4, 8 and 12 hours morning post-dose (12-hr sample should be collected prior to the evening dose).

- Day 84 (Week 12): 0 hour (morning pre-dose), and at 0.25, 0.5, 1, 2, 4, 8, and 12 hours.

Absolute and percentage change from baseline (CFB) in activated CD63+ basophils will be listed by treatment, day and sampling time. Individual change from baseline in CD63+ data will be plotted for each treatment versus time on linear scales using actual times.

Absolute and percentage change from baseline in CD63+ basophils will be summarized by time point for each treatment and day using the following descriptive statistics: n, mean, SD, CV, median, minimum and maximum. Mean percentage change from baseline in CD63+ basophils will be plotted versus time by treatment and day using nominal times on linear scales.

11.3. Pharmacodynamic Parameters

The following PD parameters will be estimated on Day 1 and 84 using change from baseline in activated CD63+ basophils in peripheral blood using actual sampling times via non-compartment analysis using Phoenix WinNonlin version 6.4 or higher:

E_{max} Maximum effect

TE_{max} Time to achieve maximum effect

$AUEC_{0\text{-}tau}$ Area under the effect versus time curve within a dosing interval

Actual PK blood sampling times will be used for the assessment of all PD parameters, and negative baseline-adjusted values will be included in the analysis.

PD parameters will be presented in data listings and summarized separately using the following descriptive statistics for each treatment and analyte (n, mean, SD, CV, minimum, median, and maximum). For TE_{max}, only n, median, minimum and maximum will be reported.

11. Interim Analysis

An unblinded interim safety and PK data review will be performed by the DMC once the patients in the safety run-in period complete their Day 8 (±2 days) assessments. Patients in the safety run-in period will continue to be dosed whilst the interim analysis is being conducted. However, further enrollment in each treatment group will only resume after safety and PK data of the first week for the first 5 patients are reviewed and considered satisfactory by the DMC.

An independent DMC appointed by the Sponsor will review the interim safety and PK data of the first 5 patients enrolled in the safety run-in period. Further details will be provided in the DMC charter, and a separate Interim Analysis SAP.

12. Changes in the Planned Analysis

Change from v0.2 (sponsor mail approved version):

- General: for coding dictionary (MEDDRA, WHODrug), add "or later" wording to apply newest version if needed.
- General: applied changes in Protocol Amendment 3.
- Section 4.2: added baseline definition for platelet count related endpoints
- Section 4.6.3:
  - specified the PD that may impact the analysis will be excluded from PP set.
  - fixed typo for incorrected referring link (Section 7.2.2 -> Section 7.4.2)
- Section 7.4.2: change the source of dose taken
- Section 8: specified the priority of using result when multiple
- Section 8.1.1: specified the scenario when there are missing visit result.
- Section 8.1.2:
  - correct the value round
  - specified the scenario that model fail to converge due to more visits then subjects
- Section 8.2.1: specified the scenario when there is missing visit result.
- Section 8.2.2: specified the scenario that model fail to converge due to more visits then subjects or imputed value out of range.
- Section 8.2.3: specified the visit/date used for time to response.
- Section 9.3:
  - corrected used results. Both central and local lab results will be used.
  - removed the clinically significant since it's not applicable for this study.
  - removed the platelet count in choosing records when multiple.
  - removed the redundant description
- Section 9.4: removed the clinically significant since it's not applicable for this study.

Change from v1.0 (sponsor approved version)

- Section 7.4.2: Aligned compliance calculation using Subject Diary as resource

13. References

Podolanczuk A, Lazarus AH, Crow AR, et al. Of mice and men: an open-label pilot study for treatment of immune thrombocytopenic purpura by an inhibitor of Syk. Blood. 2009;113(14):3154-60.

Page LK, Psaila B, Provan D, et al. The immune thrombocytopenic purpura (ITP) bleeding score: assessment of bleeding in patients with ITP. Br J Haematol. 2007;138(2):245-8.

14. Appendices

15.1. Schedule of Events

The total study duration will be 20 weeks per patients, which consists of up to 4 weeks of screening period. The treatment period will be 12 weeks (split into 1-week safety run-in period and 11-week treatment period for the first 5 patients). The post-treatment follow-up period will be of 4 weeks. Each assessment will be carried out at timepoints indicated in the Schedule of Events table and clarified in the footnotes presented below the table. The schedule of events is summarized in Table 15-1.

Table 15-1 Schedule of Events

		On-treatment Visits					**Follow-up Clinic Visits**	**Early Withdrawal/ Unscheduled visit**
	Screening (D-28 to D-1)	**W1 (D1), W5 and 9 (±3 days)**	**W1D4 (±1 days)**	**W2D8 (±2 days)**	**W3, 7, 11 (±3 days)**	**W12 (D84) (EOT) (±3 days)**	**End of Study W16 (±1 week)**	
Clinic visits	X	X[a]		X[a]*	X[a]	X[a]	X[a]	X
Informed consent	X							
Inclusion/Exclusion criteria	X	X[h]						
AEs	<----------							X
Concomitant medications	X	X		X*	X	X	X	X
Height	X							
Weight	X	X		X*		X	X	X
Physical examination/medical history[b]	X	X		X*	X	X	X	X
ECG[c]	X	X		X		X	X	X
Vital signs	X	X		X*	X	X	X	X
Urinalysis	X	X		X*	X	X	X	X
Hep B & C, HIV	X							
Pregnancy test/ FSH[d]	X							
Contraception status	X	X		X*		X	X	X
ABO and Rh blood type	X							
Serum chemistry	X	X		X*	X	X	X	X
Hematology, differential	X	X	X[a,e]	X[a,e]	X	X	X	X
PT/INR PTT	X					X		

		On-treatment Visits					Follow-up Clinic Visits	Early Withdrawal/ Unscheduled visit
	Screening (D-28 to D-1)	**W1 (D1), W5 and 9 (±3 days)**	**W1D4 (±1 days)**	**W2D8 (±2 days)**	**W3, 7, 11 (±3 days)**	**W12 (D84) (EOT) (±3 days)**	**End of Study W16 (±1 week)**	
Study drug dispensing		X			X			X[f]
Study drug administration		X	X	X*	X	X		X[f]
Blood samples for PK and PD assessments[g]		X[h]		X*		X		
Bleeding Score[i]		X		X*		X	X	X
Quality of life using SF-36 score		X				X	X	X
Pharmacogenomic screening[j]		X						

Abbreviations: AEs, adverse events; D, Day; ECG, 12-lead electrocardiogram; EOT, end-of-treatment; FSH, follicle stimulating hormone; hep, hepatitis; HIV, human immunodeficiency virus; PD, pharmacodynamics; PK, pharmacokinetics; PT/INR, prothrombin time/international normalized ratio, PTT, partial thromboplastin time; W, Week

* Patients in the safety run-in period will have clinic visit on Week 2/Day 8 (±2 days) for the mentioned assessments including hematology (differential) tests. For other patients, this visit will be laboratory only visit to perform hematology (differential) tests only.

a Clinic / laboratory visit windows are about ± 3 days for all dosing period and laboratory visits and about ± 1 week for clinic follow-up visits. The W12/D84 (EOT) visit should be performed while on therapy.

b Complete physical examination at Screening and abbreviated physical examination at other visits.

c For all patients: ECG on the first day of dosing and on Day 1 of each subsequent week as specified in the table above. For patients in the safety run-in only: ECG on the first day of dosing at 1, 2, 4, 8, and 12 hours after the study drug administration.

d For women of childbearing potential only: Serum pregnancy tests are performed at Screening. FSH testing is needed for post-menopausal female patients only.

e Laboratory only visits will be performed on Day 4 (Week 1) for all patients and on Week 2/Day 8 (±2 days) for patients other than those enrolled in the safety run-in period.

f Study drug dispensing and administration can occur at unscheduled visit.

g Samples to be collected as follows:

For the patients in the safety run-in period only (for PK only; no PD assessments):

- Day 1: morning predose, 0.25, 0.5, 1, 2, 4, 8, and 12 hours (evening predose).
- Day 8 (±2 days): morning predose, 0.25, 0.5, 1, 2, 4, 8, and 12 hours (evening predose).
- Week 12: morning predose, 0.25, 0.5, 1, 2, 4, 8, and 12 hours.

For the patients in the PK/PD subset only (for PK/PD):

- Day 1: morning predose, 0.25, 0.5, 1, 2, 4, 8, and 12 hours (evening predose).
- Week 12: morning predose, 0.25, 0.5, 1, 2, 4, 8, and 12 hours.

For other patients not included in the safety run-in period or PK/PD subset (for PK only):

- Week 12: morning predose.

h Only on Day 1 (Week 1).

i Bleeding score assessment as described by Page et al 2007 should be performed on Day 1 of each week specified in the above table and at follow-up visit.

j A blood sample for genotyping will be drawn at baseline (Day 1, before dosing) from patients who have consented to participate in the genetic analysis component of the study.