CLINICAL STUDY PROTOCOL

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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)

PROTOCOL NO. OSCO-P2101

Sponsor:	Oscotec Inc. Korea Bio-Park, Building A, 9th Floor 700 Daewangpangyo-ro, Bundang-gu Seongnam-si, Gyeonggi-do 13488 The Republic of Korea
Sponsor Contact:	[redacted]
Medical Monitor:	[redacted]
Version of Protocol:	4.0 (Protocol Amendment 3)
Date of Protocol:	22 April 2020
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CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice.

Protocol Approval – Sponsor Signatory

Study Title	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)
Protocol Number	OSCO-P2101
Protocol Date	22 April

Protocol accepted and approved by:

[redacted]

Protocol Approval – Principal/Coordinating Investigator

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Protocol accepted and approved by:

[redacted]

Protocol Approval – Lead Statistician

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Protocol Date	22 April 2020

Protocol accepted and approved by:

Declaration of Investigator

I have read and understood all sections of the protocol entitled "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)" and the accompanying investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Protocol Amendment 3, Version 4.0, dated 22 April , the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with Oscotec Inc. or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to subjects. I agree to administer study drug only to subjects under my personal supervision or the supervision of a subinvestigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Subject identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Oscotec Inc.

[redacted]

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Protocol Synopsis

Protocol Number:	OSCO-P2101
Title:	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)
Sponsor:	Oscotec Inc. Korea Bio-Park, Building A, 9th Floor 700 Daewangpangyo-ro, Bundang-gu Seongnam-si, Gyeonggi-do 13488 The Republic of Korea
Study Phase:	Phase 2
Study Sites:	This study will be conducted at multiple sites in Korea, US, and EU.
Indication:	Immune Thrombocytopenia (ITP)
Rationale:	Primary ITP is an acquired immune mediated disorder characterized by isolated thrombocytopenia, defined as a peripheral blood platelet count less than 100,000/μL. The ITP is classified by duration into newly diagnosed (0-3 months), persistent (3-12 months' duration) and chronic (≥12 months' duration). Spleen tyrosine kinase (SYK) is a non-receptor kinase and an inflammatory signal mediator. SYK activation has been known to be involved in various autoimmune disorders. Since SYK is a key mediator of FcγR-triggered intracellular signal in various inflammatory immune cells including macrophages, it was proposed as a promising therapeutic target to treat ITP. A novel small-molecule SYK inhibitor, SKI-O-703, mesylate salt form of SKI-O-592, was designed and synthesized by Oscotec Inc. SKI-O-703 displayed high selectivity and potency against SYK in both biochemical and cell-based assays. Selective SYK inhibition by SKI-O-592 prevents FcγR mediated phagocytosis in vitro and downregulates CD63 expression on peripheral blood basophils in healthy adults. SKI-O-703 was efficacious in preventing thrombocytopenia induction in an anti-CD41 antibody induced murine ITP model. Intraperitoneal injection of anti-CD41 (integrin αIIb) antibody successfully induced immediate decrease of platelets within 24 hours. The reduced platelet numbers were normalized in 72 hours after αCD41 antibody injection. Both once daily and twice daily (BID) treatment of SKI-O-703 successfully ameliorated the thrombocytopenia in a dose dependent manner compared to vehicle treatment. The high dose

group of SKI-O-703 (42 mg/kg, equivalent to 30 mg/kg of SKI-O-592) showed better protective effect against thrombocytopenia induction than R788 (40 mg/kg, equivalent to 30 mg/kg of R406, the active compound of prodrug R788). Moreover, the low dose group of SKI-O-703 (14 mg/kg, equivalent to 10 mg of SKI-O-592) showed comparable efficacy to the high dose group of R788 (40 mg/kg).

This study will evaluate the efficacy, safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (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.

Since the 400 mg BID dose level has not been investigated in healthy volunteer studies, a safety run-in group will be implemented (ie, first 5 subjects) and an interim safety and PK data review will be performed by the DMC before remaining subjects are enrolled.

Objectives:

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.

Secondary Objectives

- 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.

Exploratory Objectives

- 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.

Study Population: **Inclusion Criteria**

Each subject must meet all the following criteria to be enrolled in this study:

a. Able to provide written informed consent and agreeable to the schedule of assessments

b. Male or female subjects, aged 18 years or older (or ≥19 years of age for Korean subjects per local regulations)

c. Diagnosis of primary ITP (persistent or chronic) made according to the American Society of Hematology 2011 evidence-based guideline

d. Failed to respond or relapsed after at least 1 prior therapy (eg, corticosteroids, IVIG, anti-D, rituximab, TPO-receptor agonists, splenectomy, and immunosuppressants such as vincristine, mycophenolate mofetil, and azathioprine), with a platelet count of <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). Response to such prior therapy is defined as platelet count of ≥30,000/μL and >2 times increase from baseline in the absence of bleeding. Failure to respond and relapse to such prior therapy are defined as failure to achieve and/or failure to maintain response on a tolerable regimen of prior therapy.

e. Adequate hematologic, hepatic, and renal function (absolute neutrophil count ≥ 1.5 x 10^9/L, hemoglobin [Hgb] ≥ 10.0 g/dL, aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≤ 2.0 x ULN, bilirubin ≤1.5 x ULN, albumin ≥ 3 g/dL, estimated glomerular filtration rate [eGFR] ≥40 mL/min/1.73m^2, and creatinine ≤ 1.5 x ULN)

f. ECOG performance status of 0, 1, or 2

g. Both male and female subjects must agree to take the following steps to reduce the potential for transmission of genetic material containing the investigational product:

   a. Both male and female subjects, the subject and their partners of childbearing potential must agree to use 2 of the following medically acceptable methods of contraception from the time of randomization, during the

study, and for 6 months following discontinuation of study drug, of which:

- One must be a highly reliable method of contraception, such as:
  - An intrauterine device or intrauterine system implanted for at least 30 days prior to Day 1
  - Surgical sterilization of one of the partners for at least 6 months prior to the date of informed consent (assuming this will be the only partner for the whole duration of the clinical trial)
  - Consistent and correct use of hormonal contraceptives (hormonal implants, injectables, contraception pills, transdermal patches, or contraceptive rings) for at least 30 days prior to Day 1
- One supplementary barrier method, such as:
  - Male or female condom always with spermicide (a spermicidal foam/gel/film/cream)
  - Diaphragm or cervical/vault caps always with spermicide (a spermicidal foam/gel/film/cream)
  - Double-barrier methods (which means a barrier method used by both partners at the same time), even when used with spermicide, are not considered to be highly reliable contraception methods, and as such, may not be the only forms of contraception used

One of the other listed highly reliable methods must be used in conjunction with a barrier method.

b. Female subjects must agree not to breastfeed starting from the time of Screening, throughout the study, and until after 6 months following the last dose of study drug.

c. Male subjects must agree not to donate sperm starting from the time of randomization, throughout the study, and until after 6 months following the last dose of study drug

d. For subjects and partners considered not of childbearing potential, the following conditions apply:

    a. Menopausal females must have experienced their last period more than 12 months prior to the date of informed consent to be classified as not of childbearing potential.

    b. Male and female subjects are in a situation of abstinence from heterosexual intercourse from Screening until after 6 months following the last dose of study drug when this is in line with the preferred lifestyle of the subject (eg, homosexual women and men or a member of a religious order such as nuns and priests).

Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. History of any clinically significant disease or disorder that in the opinion of the investigator or the sponsor may put the subject at risk due to study participation, impact the subject's ability to participate in the study, or influence the study results
2. History of current, active malignancy requiring or likely to require chemotherapeutic or surgical treatment during the study, with the exception of non-melanoma skin cancer,

carcinoma in situ of the cervix, and localized prostate cancer managed by active surveillance

3. Transfusion with blood or blood products or plasmapheresis within 2 weeks before the first administration of study drug (Day 1)
4. PT INR > 1.5
5. History of known inherited coagulopathy (including prothrombotic conditions such as Factor V Leiden, APC resistance, AT-III deficiency, and lupus anticoagulant), or recent arterial or deep venous thrombosis within the preceding 6 months
6. Change in corticosteroid or immunosuppressant (azathioprine, mycophenolate mofetil, cyclosporine) dose within 2 weeks prior to Day 1 (more than 10% variation from Day 1 daily doses)
7. Treatment with thrombopoietin (TPO) receptor agonists within 2 weeks before Day 1
8. Treatment with rituximab or splenectomy within the 8 weeks prior to Day 1
9. Treatment with intravenous immunoglobulins (IVIGs) within 4 weeks prior to Day 1
10. Infections requiring intravenous antibiotics or hospitalization within 3 months prior to Day 1
11. Subjects had positive test results at Screening for human immunodeficiency virus, hepatitis B surface antigen (HBsAg), or hepatitis C virus antibody. Subjects with past or resolved hepatitis B infection (defined as having a negative HBsAg test and a positive IgG antibody to hepatitis B core antigen [anti-HBc]) are eligible but hepatitis B virus (HBV) DNA must be obtained in these subjects prior to Cycle 1, Day 1, and must demonstrate no active infection. Subjects positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
12. Received live vaccine within 28 days prior to Day 1 or plan to receive one during the study
13. History or presence of any gastrointestinal, hepatic, or renal disease or any other condition known to interfere with the absorption, distribution, metabolism, or excretion of drugs
14. Subject has not recovered from a recent medical/surgical procedure or trauma by Day 1 as determined by the investigator

15. Uncontrolled hypertension (as defined by systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg)
16. Subject had 12-lead electrocardiogram (ECG) findings of corrected QT interval by Fridericia formula (QTcF) > 480 msec, cardiac arrhythmias, or clinically significant cardiac or ECG abnormalities
17. Subject received any investigational medication within 30 days or 5 half-lives prior to Day 1, whichever is longer
18. Concomitant use of any anticoagulants and platelet aggregation inhibiting drugs including aspirin (within 14 days of planned dosing through end of follow-up)
19. Female subject who is currently pregnant or breastfeeding
20. Prior treatment with a SYK inhibitor
21. Planned surgery in the time frame of the dosing period.

Study Design: 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 subjects are planned to participate in 3 treatment groups (24 subjects in each of the active treatment groups and 12 subjects in the placebo group). Subjects will be randomly assigned to 3 groups using a 2:2:1 ratio to receive 1 of the 2 select doses of SKI-O-703 or placebo. First 5 subjects 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). Subjects in 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 subjects are reviewed and considered satisfactory by the Data Monitoring Committee (DMC). A subset of at least 20 subjects, 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 subjects with prior TPO-receptor agonist use (yes/no) and degree of baseline thrombocytopenia (ie, baseline platelet count < or ≥15,000/μL).

The study will include a screening period of up to 4 weeks. After completing all screening assessments, subjects who meet all the inclusion and none of the exclusion criteria will proceed to the treatment period.

On Day 1, subject's eligibility will be confirmed and baseline safety evaluations will be performed (ECG, physical examination, vital sign measurements, and safety laboratory assessment). Then subjects will be randomized to receive either one of the doses of SKI-O-703 or placebo. The subjects will be administered their morning dose of study medication. The evening dose will be administered 12 hours after the morning dose. Subjects will be administered study medication with enough water to swallow the capsules. The study medication will be taken no later than 30 minutes after food.

After dosing, all subjects will be subjected to safety assessments and in addition, subjects in the safety run-in period will be subjected to PK assessments and a subset of at least 20 subjects will be subjected to PK and PD assessments. The subject will be instructed to self-administer the subsequent doses of the study medication in the morning and evening (12 hours after the morning dose) for the remaining study duration.

Estimated Study Duration:

The total study duration will be 20 weeks per subject, which consists of up to 4 weeks of screening period, 12 weeks of treatment period (split into 1-week safety run-in period and 11-week treatment period for the first 5 subjects), and 4 weeks of follow-up period.

Efficacy Assessments:

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 use of rescue medication.

Secondary Endpoints:

- Subjects 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
- Subjects 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
- Subjects 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

- Subjects 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
- Subjects able to achieve platelet counts of ≥ 50,000/μL at 3 of the last 4 visits
- Change from baseline in the average of the last 2 platelet counts during the treatment period
- Time to first platelet response (>30,000/μL and 2 x baseline)
- Number of subjects receiving rescue medication at least once during treatment period
- Subjects with at least one Grade 2 or higher non-skin bleeding event during treatment period.

Exploratory Endpoints:

- Peak platelet counts during the treatment period without use of rescue medication
- Bleeding score at select time points
- Quality of life as measured by the SF-36 score.

Pharmacokinetic Assessments: Plasma PK parameters will be calculated for SKI-O-592 and its metabolites (M2 and M4) in all subjects in the PK/PD subset on Day 1 and Week 12 using a noncompartmental approach and will include the following: C_{max}, T_{max}, $AUC_{0\text{-}tau}$, $t_{1/2}$, K_{el}, CL/F (SKI-O-592 only), V_z/F (SKI-O-592 only), R_{met}, and R_{AUC}, as applicable. Pharmacokinetic assessments will also be performed on Day 8 (±2 days) for subjects in the safety run-in period only.

Pharmacodynamic Assessments: 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 on Day 1 and Week 12. PD parameters will include the following: E_{max}, TE_{max}, $AUEC_{0\text{-}tau}$, as applicable.

Exploratory Endpoint

An assessment of PK/PD relationship between plasma concentrations of SKI-O-592, M2 and M4 and change from baseline in the percentage of activated CD63+ basophils in peripheral blood on Day 1 and Week 12

Safety Assessments: Safety variables will include physical examination findings, vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature), ECG tracings, clinical laboratory test results (hematology, coagulation, serum chemistry, and urinalysis), bleeding score, quality of life as measured by the SF-36 score, weight, body mass index, and reporting of adverse events.

	Safety monitoring will begin when subject signs the informed consent form and continue through the end-of-study visit (Week 16).
Study Drug, Dosage, and Route of Administration:	SKI-O-703 and placebo will be administered orally. Two dose levels of SKI-O-703 will be evaluated in separate groups: 200 mg BID and 400 mg BID. Third group will be of matching placebo.
Sample Size:	A minimum of 60 subjects will be enrolled in the study. Subjects 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 subjects in the active treatment group will be responders (R). A sample size of 24 subjects per active treatment group and 12 subjects in the placebo group will provide approximately 82.7% 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. Subjects 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. 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.
Statistical Methods:	Statistical analysis will be performed using SAS software Version 9.4 or later. The results for each efficacy endpoint will be summarized by visit and treatment for all subjects within the intent-to-treat (ITT) analysis set using descriptive statistical methods. Continuous variables (quantitative endpoints) will be summarized using the mean, the standard deviation, 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. The primary efficacy endpoint will be summarized as overall platelet response rate (ORR) by treatment group and analyzed using Fisher's exact test to compare the difference in ORR between each active treatment group and placebo. A logistic regression model will also be performed on platelet response and include treatment, baseline platelet count and prior TPO-receptor agonist, provided there are enough subjects in each subgroup. The odds ratio for the treatment effect compared to placebo (together with 95% confidence interval and p-value) will be provided. The analysis will be based on the ITT analysis set.

	All statistical tests will be 2-sided and performed using a 5% significance levels, leading to 95% (2-sided) confidence intervals. There will be no adjustments for multiplicity.
Version and Date of Protocol:	4.0 (Protocol Amendment 3); 22 April 2020

List of Abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
Anti-HBc	hepatitis B core antigen
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BID	Twice daily
CD-ROM	compact disk read-only memory
CFR	Code of Federal Regulations
CI(s)	confidence interval(s)
C_{max}	maximum observed concentration
CV	coefficient of variation
ECG	12-lead electrocardiogram
eCRF	electronic case report form
FcγR	Fcγ receptor
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITP	immune thrombocytopenia
ITT	Intent-to-treat
IVIG	intravenous immunoglobulin
IVRS	interactive voice response system
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no observed adverse effect level
ORR	overall platelet response rate
PCR	polymerase chain reaction

Abbreviation	Definition
PD	pharmacodynamic
PK	pharmacokinetic
QD	once daily
QTcF	corrected QT interval by Fridericia formula
SAE	serious adverse event
SD	standard deviation
TEAE	treatment-emergent adverse event
TPO	thrombopoietin
ULN	upper limit of normal

1 Introduction

Primary immune thrombocytopenia (ITP) is an acquired immune mediated disorder characterized by isolated thrombocytopenia, defined as a peripheral blood platelet count less than 100,000/µL. ITP is classified by duration into newly diagnosed (0-3 months), persistent (3-12 months' duration) and chronic (≥12 months' duration) (Mitchell et al 2013). The estimated incidence is 100 cases per 1 million persons per year, and about half of these cases occur in children. Patients with ITP have accelerated clearance of circulating immunoglobulin G-coated platelets via Fcγ receptor (FcγR)–bearing macrophages in the spleen and liver, leading to different levels of thrombocytopenia and variable degrees of mucocutaneous bleeding (Kessler et al 2017, Podolanczuk et al 2009).

Spleen tyrosine kinase (SYK) is a non-receptor kinase and an inflammatory signal mediator. A SYK activation has been known to be involved in various autoimmune disorders. Spleen tyrosine kinase is broadly involved in regulating leukocyte immune function, principally by facilitating cellular activation in response to receptor engagement of antigen or immune complex. Receptors that use SYK for signal transduction include the B-cell antigen receptor, Fc receptors, integrins, and members of the lectin and selectin families (Turner et al 2000, Mócsai et al 2002, Rogers et al 2005, and Zarbock et al 2008).

[redacted] A novel small-molecule SYK inhibitor, SKI-O-703, mesylate salt form of SKI-O-592, was designed and synthesized by Oscotec Inc. SKI-O-703 displayed high selectivity and potency against SYK in both biochemical and cell-based assays. Selective SYK inhibition by SKI-O-592 prevents FcγR mediated phagocytosis in vitro and downregulates CD63 expression on peripheral blood basophils in healthy adults.

Many patients exhibit responses to established therapies, including corticosteroids, intravenous immunoglobulin (IVIG), anti-D, splenectomy, and rituximab. Nonetheless, there are a significant minority of patients who retain persistently low platelet counts despite treatment. They consequently remain at risk of intracranial hemorrhage as well as other bleeding complications (Podolanczuk et al 2009).

Since SYK is a key mediator of FcγR-triggered intracellular signal in various inflammatory immune cells including macrophages, it was proposed as a promising therapeutic target to treat ITP.

1.1 Clinical Studies

The safety, pharmacokinetics (PK), and pharmacodynamics (PD) of SKI-O-703 have been evaluated in 2 clinical studies, a single ascending dose clinical study (OSCO-P1201) and a multiple ascending dose clinical study (OSCO-P1202) in healthy subjects.

In Study OSCO-P1201, single oral doses of SKI-O-703 ranging from 50 to 800 mg were generally safe and well tolerated by the healthy male and female subjects. There were no deaths, serious adverse events (SAEs), or treatment-emergent adverse events (TEAEs) that led to discontinuation of the study. Ten of 48 subjects (20.8%) reported a total of 18 TEAEs; of these, 3 TEAEs were reported by 3 subjects (25.0%) after receiving placebo and 15 TEAEs were reported by 7 subjects (19.4%) in the SKI-O-703 treatment groups. There were no dose-dependent trends noted in the TEAEs reported. The most commonly reported TEAE was headache, which was reported by 3 subjects (8.3%) who received SKI-O-703 and 1 subject (8.3%) who received placebo. All TEAEs across the 50 mg to 600 mg dose range were considered mild in intensity; 6 treatment-related moderate-intensity TEAEs, reported in 2 subjects, occurred at the highest dose of 800 mg SKI-O-703. All TEAEs were resolved by the end of the study. All individual hematology and coagulation, serum chemistry, and urinalysis values outside of the reference ranges were considered not clinically significant by the investigator. No TEAEs related to laboratory parameters were reported.

In Study OSCO-P1202, multiple oral doses of SKI-O-703 200 mg once daily (QD), 400 mg QD, and 200 mg twice daily (BID) were safe and well tolerated by the healthy male and female subjects. There were no deaths or SAEs; however, 1 subject reported TEAE of back pain that led to discontinuation of 200 mg SKI-O-703 BID. Overall, 7 subjects (29.2%) reported a total of 17 TEAEs; of these, 2 subjects (33.3%) reported 6 TEAEs after receiving placebo and 5 subjects (27.8%) reported 11 TEAEs after receiving SKI-O-703. The most commonly reported TEAEs were nausea and headache, each were reported by 2 subjects (33.3%) in the 200 mg SKI-O-703 BID treatment group and by 1 subject (16.7%) in the placebo group. All TEAEs were considered mild or moderate in intensity, and both moderate TEAEs occurred in the placebo group. Except for 1 subject who reported ongoing TEAEs of pyuria and chlamydial infection, all TEAEs were resolved by the end of the study. No

apparent treatment- or dose-related trends were observed in clinical laboratory values, physical examination findings, or 12-lead electrocardiogram (ECG) results. There was a slight trend in the mean increase of systolic blood pressure from baseline in the 200 mg BID group at Days 16 and 21, and diastolic blood pressure values at Days 16 and 21 also demonstrated a slight trend of a mean increase for all doses of SKI-O-703. There were no significant changes in systolic and diastolic blood pressure for all doses of SKI-O-703 versus placebo at Days 16 and 21.

1.2 Nonclinical Studies

[redacted]

[redacted]

[redacted]

1.3 Dose Rationale

SKI-O-703 was safe and well-tolerated in healthy volunteers when administered as single ascending doses over the dose range of 50 to 800 mg (Study OSCO-P1201), and multiple ascending doses at 200 mg QD, 400 mg QD and 200 mg BID for 7 days (Study OSCO-P1202). Based on the safety data from the various doses administered in these studies, there are no specific considerations that would concern the use of SKI-O-703 at doses proposed in this Phase 2 study.

Following multiple ascending doses of SKI-O-703 at 200 mg QD, 400 mg QD, and 200 mg BID (Study OSCO-P1202), a reduction in the PD endpoint "percentage of basophils expressing CD63+" was observed in healthy volunteers; on average, CD63+ expressing basophils were suppressed by 95%, 99% and 86% at steady state (Day 7) following administration at 200 mg QD, 400 mg QD, and 200 mg BID, respectively. Thereafter, the suppression of basophils expressing CD63+ was maintained at –72% or below for up to 2 and 8 hours following once-daily dosing at 200 mg and 400 mg, respectively, and up to 12 hours (ie, over a full 24-hr period) following twice-daily dosing at 200 mg. As the PD effect was sustained for longer after twice-daily dosing compared to once-daily dosing, twice-daily dosing at 200 mg and 400 mg has been selected.

As 400 mg BID has not been studied previously in humans, exposure (C_{max} and $AUC_{0\text{-}tau}$) to SKI-O-592, M2, and M4 following 400 mg BID dosing has been estimated based on data observed previously at different dose levels. To ensure that predictions are cautious and

robust, steady-state C_{max} and $AUC_{0\text{-}tau}$ following 400 mg BID have been predicted in 2 ways using data from Study OSCO-P1202:

1. $AUC_{0\text{-}12}$ (400 mg, Day 1) × Accumulation Ratio (200 mg BID)
2. PK Parameter (200 mg BID, Day 7) × 2

Systemic exposure (C_{max} and $AUC_{0\text{-}tau}$) to SKI-O-592, M2, and M4 at 400 mg BID is predicted to be higher using the second approach [PK Parameter (200 mg BID, Day 7) × 2]. For SKI-O-592, C_{max} and $AUC_{0\text{-}tau}$ are predicted to be 6160 ng/mL and 14600 h ng/mL, respectively, and for M2 C_{max} and $AUC_{0\text{-}tau}$ are predicted to be 994 ng/mL and 10000 h ng/mL, respectively, which is well within exposure levels calculated at the NOAEL in rats, and comparable to levels previously observed at 800 mg in Study OSCO-P1201. However, due to the very low M4 metabolite ratios observed in rats compared to healthy volunteers, predicted exposure to M4 (644 ng/mL and 1970 h ng/mL for C_{max} and $AUC_{0\text{-}tau}$, respectively) is higher than the NOAEL exposure. Therefore, the dosing regimens proposed for this study (200 mg BID and 400 mg BID) have been carefully selected to ensure that exposure to M4 does not exceed levels observed previously in healthy volunteers (Study OSCO-P1201, 800 mg).

*Note: Because increases in systemic exposure to M4 were less than proportional to the dose of SKI-O-703 in Studies OSCO-P1201 and OSCO-P1202, and a reduction in M4 levels was observed over time in Study OSCO-P1202, both means of estimating C_{max} and $AUC_{0\text{-}tau}$ for M4 at 400 mg BID are considered to be cautious approaches, potentially overestimating exposure at 400 mg BID. An interim safety and PK data review will be performed by the DMC for the first 5 subjects dosed (including 2 subjects dosed with 400 mg BID) before the remaining subjects are treated.

Following single oral administration of 400 mg SKI-O-703 (Study OSCO-P1203), overall systemic exposure to SKI-O-592, M2 and M4 ($AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$) was comparable between the fed and fasted state, with 90% CI for the ratio (Fed / Fasted) contained entirely within the BE limits (0.80, 1.25) for SKI-O-592 and M4. By contrast, when administered in the fed state there was an approximate 56%, 43% and 46% reduction in maximum exposure (C_{max}) for SKI-O-592, M2 and M4, respectively, with an associated 2.5 to 4 hours delay in median T_{max} across all analytes. Since the overall extent of absorption is unaffected by the intake of food, but peak exposure is reduced, dosing is recommended with food in this

Phase 2 study to reduce the potential for AEs which may be associated with spikes (i.e. high C_{max}) in SKI-O-592, M2 and M4.

1.4 Placebo Rationale

The proposed study is a double-blind, placebo-controlled, randomized trial of two doses of oral SKI-O-703 for patients with persistent and chronic ITP. Subjects will be allowed to receive stable doses of background medications including corticosteroids and immunosuppressive drugs, in line with the current standard of care. Any subject who cannot adhere to the protocol or who discontinues treatment will have an end-of-treatment visit and will be followed for the intended duration of the study.

1.5 Benefits and Risks Assessments

In the clinical development program, the safety, tolerability, and PK of SKI-O-703 have been evaluated in 2 clinical studies, a single ascending dose clinical study (OSCO-P1201) and a multiple ascending dose clinical study (OSCO-P1202) in healthy subjects. No deaths and SAEs were reported in these studies; however, 1 subject reported TEAE of back pain that led to discontinuation of SKI-O-703. All adverse events (AEs) were mild to moderate in intensity.

As described in Section 1.2, SKI-O-703 was efficacious in preventing thrombocytopenia induction in an anti-CD41 antibody induced murine ITP model.

There are no important identified risks with SKI-O-703. The identified potential risks associated with SKI-O-703 included immune system effects, gastrointestinal effects, liver enzyme changes, cardiovascular effects, and headache.

Gastrointestinal effects and headache have been observed clinically, while immune system effects, liver enzyme changes, and cardiovascular effects are considered important potential risks based on non-clinical data and the SKI-O-703 mechanism of action. Considering the measures to minimize the risks to patients participating in the SKI-O-703 clinical development program, and the nonclinical and clinical evidence highlighted above, the benefits of the conduct of the proposed clinical study outweigh the associated risks.

2 Study 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.

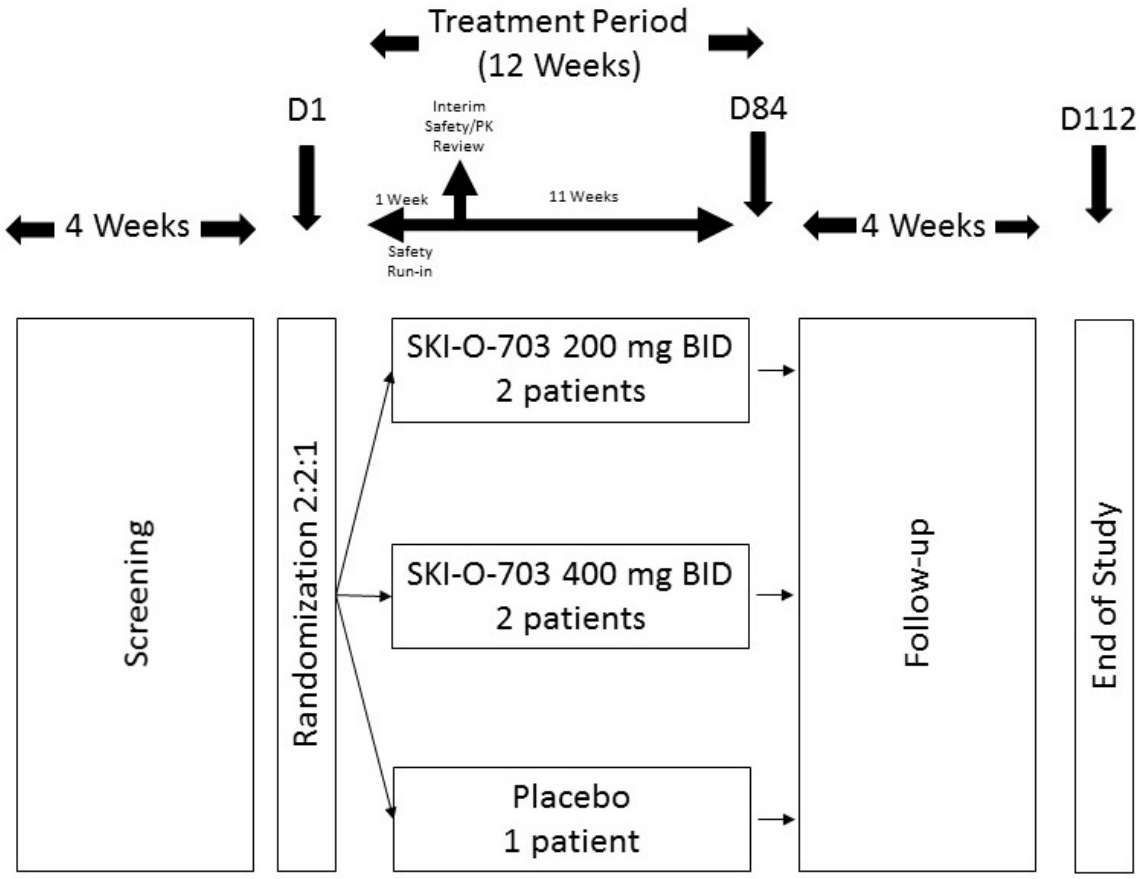
3 Investigational Plan

3.1 Study Design

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 subjects are planned to enroll in 3 treatment groups (24 subjects in each of the active treatment groups and 12 subjects in the placebo group). Subjects 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 subjects 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). Subjects 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 subjects are reviewed and considered satisfactory by the Data Monitoring Committee (DMC). A subset of at least 20 subjects, 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 subjects 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 1 and Figure 2.

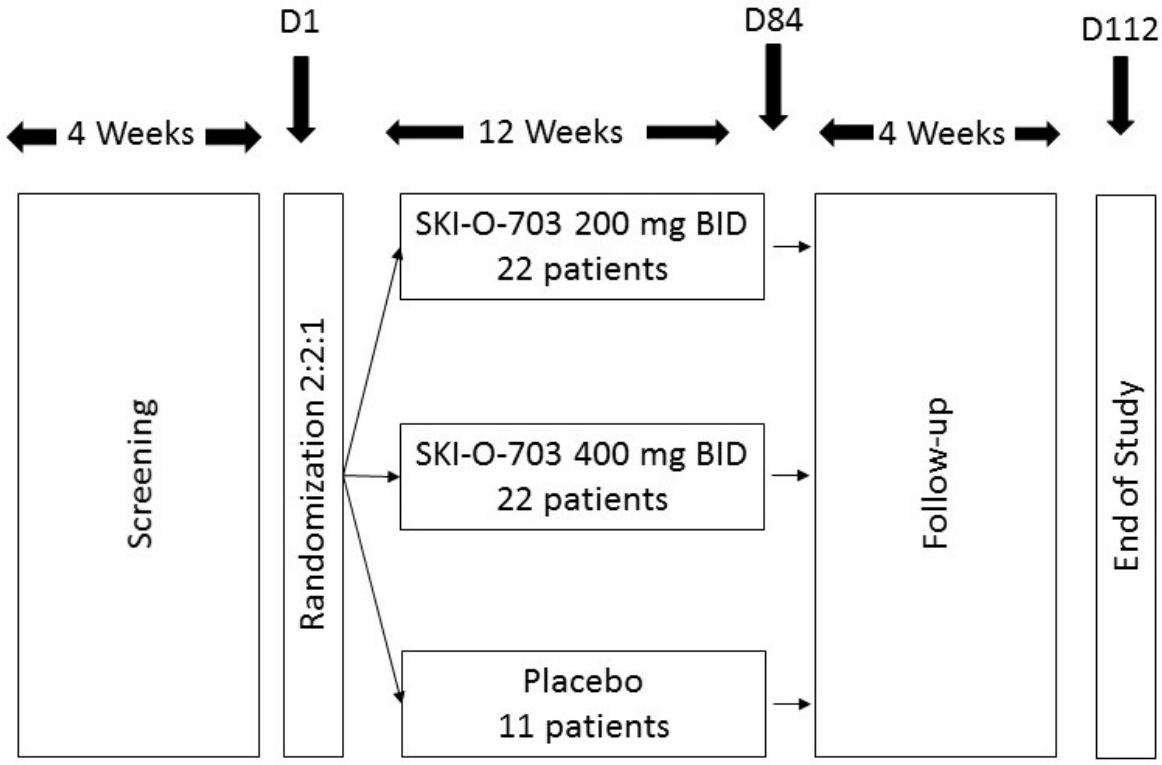
Figure 1 Study Design Schematic (for the First 5 Subjects in the Safety Run-in Period only)



Abbreviation: BID, twice daily

Note: First 5 subjects 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). Subjects 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 subjects are reviewed and considered satisfactory by the Data Monitoring Committee.

Figure 2 **Study Design Schematic (For Subjects 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 subjects will sign and date the informed consent form (ICF) prior to any study assessments or procedures. These subjects will be assessed as per the eligibility criteria at Screening. After completing all screening assessments, subjects 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 subjects only):* First 5 subjects 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). Subjects 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 subjects are reviewed and considered satisfactory by the DMC.

For all subjects, on Day 1, subject's eligibility will be confirmed and baseline safety evaluations will be performed (ECG, physical examination, vital sign measurements, and safety laboratory assessment). Eligible subjects 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. Subjects will be administered the study medication with enough water to swallow the capsule. The study medication will be taken no later than 30 minutes after food.

After dosing, all subjects will be subjected to safety assessments and a subset of at least 20 subjects, who are not included in the safety run-in period, will be subjected to PK and PD assessments according to the Schedule of Events (Table 2). Subjects enrolled in the safety run-in period will be admitted for 24 hours on Days 1, 8, and 84 or 85 of the study. Subjects selected for the PK/PD portion of the study will be admitted for 24 hours on Days 1 and 84 or 85 of the study.

The maximum duration of study participation for a subject 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.

3.1.1 Dose Interruption and Reduction

It is recognized that some AEs may require dose adjustment or study drug discontinuation. Intra-subject dose reduction or escalation is permitted and based upon treatment-related adverse events observed (Table 1).

After experiencing an AE, subjects 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.

Table 1 Guidelines for Dose Interruption or Reduction[a]

AE	Occurrence	Action
ALT elevations (range 3 to 5 × ULN) Alkaline Phosphatase > 3 × ULN and > 2 × baseline	First	• If asymptomatic (no nausea, anorexia, vomiting), repeat test within 72 hours[b] and, if stable or lower, may continue dosing of study drug. • If on repeat test value has increased further but remains < 5 × ULN and asymptomatic, withhold study drug and retest weekly until values becomes stable. When stabilized to < 5 × ULN, continue dosing with the study drug. • If symptomatic or > 5 × ULN, withhold study drug. Follow the subject weekly until symptoms abate and values return to baseline per confirmation from central laboratory; at which time study drug may be restarted at a 50% reduced dose by taking only one daily dose. **Note: Discontinue study drug permanently if the ALT elevation is accompanied by an elevation in direct bilirubin to > 2 mg/dL (34.2 mmol/L).**
	Second	Discontinue study drug permanently.
ANC <1,000/mm^3 or febrile neutropenia	First	Withhold dose until ANC ≥ 1000/mm3, or has returned to baseline, then reduce the dose by skipping one of the daily dose and increase to previous dose if ANC remains stable for 2 weeks on reduced dose.
	Second	Discontinue study drug permanently if the intolerance reoccurs or persists.
Sustained increased systolic (> 160 mmHg) or sustained increased diastolic (> 100 mmHg) blood pressure in a previously normotensive subject	First	Study drug may be withheld for 5 to 7 days and then restarted at a reduced dose by skipping one of the daily dose. **Irrespective of study drug dose adjustment, subjects who develop a sustained increased systolic (>140 mmHg) or a sustained increased diastolic (>90 mmHg) blood pressure should be started on antihypertensive medications (e.g. lisinopril 5mg daily) or have their antihypertensive regimen adjusted if already on any antihypertensive agent.**
	Second	Discontinue study drug permanently if the hypertension reoccurs or persists.
Intolerable nausea or vomiting (see Section 5.8.2 for further details)	First	Study drug may be withheld for 5-7 days and then restarted at a reduced dose by skipping evening dose.
	Second	Discontinue study drug permanently if the intolerance reoccurs or persist.

AE	Occurrence	Action
QTcF >500 ms for female subject OR >480 ms for male subject, at any time point	-	The ECG should be repeated as triplicate (all three within 2 minutes) and a cardiology consult may be obtained as medically necessary. • If the repeat ECG confirms QTcF >500 ms (females) or >480 ms (males), dosing must be interrupted for up to 14 days • If the QTcF resolves to ≤480 ms (males and females)/they may resume dosing at the reduced dose by skipping one of the doses (ie, morning or evening) • If the QTcF remains >480 ms (males and females) after 14 days of dose interruption, the study drug must be permanently discontinued.
QTcF change of >30 ms from baseline	-	If the QTcF has increased >30 ms when compared to the baseline with no other known etiology, and the principal investigator considers it clinically significant then a confirmatory ECG (single) will be performed and dose should be reduced by skipping one of the doses (ie, morning or evening) for the remainder of the study.

Abbreviations: ACE, angiotensin-converting-enzyme; AE, adverse event; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; ECG, electrocardiogram; LFTs, liver function tests; MOA, mechanism of action; QTcF, corrected QT interval by Fridericia formula; ULN, upper limit of normal

[a] These are examples based on previously observed AEs for agents with similar MOA (ie, fostamatinib). All other potential/spontaneous Grade 3/4 AEs that can warrant dose reduction or interruption are not excluded and will be assessed on an ongoing basis during the study. Those would be evaluated upon judgment by the principal investigator and the safety operations team.

[b] A central laboratory must be used for repeat ALT, AST, ALP, or ANC.

3.1.2 Rationale of Study Design

This double-blind, placebo-controlled study is designed to evaluate the efficacy, safety, tolerability, PK, and PD of SKI-O-703 in persistent and chronic ITP patients. The results of this study will guide on further clinical evaluation of SKI-O-703 patients with ITP. The double-blind placebo-controlled design has been selected to minimize bias in the evaluation of the safety, efficacy, PK, and PD.

Since the 400 mg BID dose level has not been investigated in healthy volunteer studies, a safety run-in group will be implemented. To protect the study blind, 5 subjects will be included in the safety run-in period to reflect the overall 2:2:1 randomization, resulting in 2 subjects each being dosed at 400 mg and 200 mg BID and 1 subject being dosed with placebo. An interim safety and PK data review will be performed by the DMC once the subjects in the safety run-in period complete their Day 8 (±2 days) assessments. Further

enrollment in each treatment group will only resume after safety and PK data of the first week for the first 5 subjects are reviewed and considered satisfactory by the DMC.

Serial blood samples (5 mL) for PK assessment of SKI-O-592 and its metabolites (M2 and M4) from all subjects in the PK/PD subset will be obtained from this study, which in turn would help refine the sparse sampling approaches needed for later Phase 3 studies leading to a better population PK analysis in Phase 3.

The power of a statistical test is typically a function of the magnitude of the treatment effect, the designated Type I error rate (α, risk of false-positive result) and the sample size (n). When designing a trial, it is important to decide upon the desired study power (typically 80% for a Phase 2 study) and calculate the necessary sample size to achieve this goal. Since it is often not feasible to conduct large trials during early stage of development, it is necessary to identify the strategies to optimize the statistical power of smaller studies.

In this study, platelet response, 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 use of rescue medication, is selected as the primary endpoint.

4 Subject Selection and Withdrawal Criteria

4.1 Selection of Study Population

A minimum of 60 subjects will be enrolled at multiple sites in Korea, US, and EU. Subjects will be assigned to study drug only if they meet all of the inclusion criteria and none of the exclusion criteria. Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or patient safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.1.1 Inclusion Criteria

Each subject must meet all of the following criteria to be enrolled in this study:

1. Able to provide written informed consent and agreeable to the schedule of assessments
2. Male or female subjects, aged 18 years or older (or ≥19 years of age for Korean subjects per local regulations)
3. Diagnosis of primary ITP (persistent or chronic) made according to the American Society of Hematology 2011 evidence-based guideline
4. Failed to respond or relapsed after at least 1 prior therapy (eg, corticosteroids, IVIG, anti-D, rituximab, TPO-receptor agonists, splenectomy, and immunosuppressants such as vincristine, mycophenolate mofetil, and azathioprine), with a platelet count of <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). Response to such prior therapy is defined as platelet count of ≥30,000/μL and >2 times increase from baseline in the absence of bleeding. Failure to respond and relapse to such prior therapy are defined as failure to achieve and/or failure to maintain response on a tolerable regimen of prior therapy.
5. Adequate hematologic, hepatic, and renal function (absolute neutrophil count ≥ 1.5 x 10^9/L, hemoglobin [Hgb] ≥ 10.0 g/dL, aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≤ 2.0 x ULN, bilirubin ≤1.5 x ULN, albumin ≥ 3 g/dL, estimated glomerular filtration rate [eGFR] ≥40 mL/min/1.73m^2, and creatinine ≤ 1.5 x ULN)

6. ECOG performance status of 0, 1, or 2
7. Both male and female subjects must agree to take the following steps to reduce the potential for transmission of genetic material containing the investigational product:
    a. Both male and female subjects, the subject and their partners of childbearing potential must agree to use 2 of the following medically acceptable methods of contraception from the time of randomization, during the study, and for 6 months following discontinuation of study drug, of which:
        - One must be a highly reliable method of contraception, such as:
            - An intrauterine device or intrauterine system implanted for at least 30 days prior to Day 1
            - Surgical sterilization of one of the partners for at least 6 months prior to the date of informed consent (assuming this will be the only partner for the whole duration of the clinical trial)
            - Consistent and correct use of hormonal contraceptives (hormonal implants, injectables, contraception pills, transdermal patches, or contraceptive rings) for at least 30 days prior to Day 1
        - One supplementary barrier method, such as:
            - Male or female condom always with spermicide (a spermicidal foam/gel/film/cream)
            - Diaphragm or cervical/vault caps always with spermicide (a spermicidal foam/gel/film/cream)
            - Double-barrier methods (which means a barrier method used by both partners at the same time), even when used with spermicide, are not considered to be highly reliable contraception methods, and as such, may not be the only forms of contraception used

        One of the other listed highly reliable methods must be used in conjunction with a barrier method.
    b. Female subjects must agree not to breastfeed starting from the time of Screening, throughout the study, and until after 6 months following the last dose of study drug.

c. Male subjects must agree not to donate sperm starting from the time of randomization, throughout the study, and until after 6 months following the last dose of study drug

d. For subjects and partners considered not of childbearing potential, the following conditions apply:

    a. Menopausal females must have experienced their last period more than 12 months prior to the date of informed consent to be classified as not of childbearing potential.

    b. Male and female subjects are in a situation of abstinence from heterosexual intercourse from Screening until after 6 months following the last dose of study drug when this is in line with the preferred lifestyle of the subject (eg, homosexual women and men or a member of a religious order such as nuns and priests).

4.1.2 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. History of any clinically significant disease or disorder that in the opinion of the investigator or the sponsor may put the subject at risk due to study participation, impact the subject's ability to participate in the study, or influence the study results
2. History of current, active malignancy requiring or likely to require chemotherapeutic or surgical treatment during the study, with the exception of non-melanoma skin cancer, carcinoma in situ of the cervix, and localized prostate cancer managed by active surveillance
3. Transfusion with blood or blood products or plasmapheresis within 2 weeks before the first administration of study drug (Day 1)
4. PT INR > 1.5
5. History of known inherited coagulopathy (including prothrombotic conditions such as Factor V Leiden, APC resistance, AT-III deficiency, and lupus anticoagulant), or recent arterial or deep venous thrombosis within the preceding 6 months

6. Change in corticosteroid or immunosuppressant (azathioprine, mycophenolate mofetil, cyclosporine) dose within 2 weeks prior to Day 1 (more than 10% variation from Day 1 daily doses)
7. Treatment with thrombopoietin (TPO) receptor agonists within 2 weeks before Day 1
8. Treatment with rituximab or splenectomy within the 8 weeks prior to Day 1
9. Treatment with IVIGs within 4 weeks prior to Day 1
10. Infections requiring intravenous antibiotics or hospitalization within 3 months prior to Day 1
11. Subject had positive test results at Screening for human immunodeficiency virus, hepatitis B surface antigen (HBsAg), or hepatitis C virus antibody. Subjects with past or resolved hepatitis B infection (defined as having a negative HBsAg test and a positive IgG antibody to hepatitis B core antigen [anti-HBc]) are eligible but hepatitis B virus (HBV) DNA must be obtained in these subject prior to Cycle 1, Day 1, and must demonstrate no active infection. Subjects positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
12. Live vaccine within 28 days prior to Day 1 or plan to receive one during the study
13. History or presence of any gastrointestinal, hepatic, or renal disease or any other condition known to interfere with the absorption, distribution, metabolism, or excretion of drugs
14. Subject has not recovered from a recent medical/surgical procedure or trauma by Day 1 as determined by the investigator
15. Uncontrolled hypertension (as defined by systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg)
16. Subject had ECG findings of corrected QT interval by Fridericia formula (QTcF) > 480 msec, cardiac arrhythmias, or clinically significant cardiac or ECG abnormalities
17. Subject have received any investigational medication within 30 days or 5 half-lives prior to Day 1, whichever was longer

18. Concomitant use of any anticoagulants and platelet aggregation inhibiting drugs including aspirin (within 14 days of planned dosing through end of follow-up)
19. Female subject who is currently pregnant or breastfeeding
20. Prior treatment with a SYK inhibitor
21. Planned surgery in the time frame of the dosing period.

4.2 Withdrawal of Subjects From Study Drug and/or the Study

The duration of the study is defined for each subject as the date signed informed consent is provided through date of the last follow-up visit on Week 16.

4.2.1 Reasons for Withdrawal/Discontinuation

Subjects may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. Every effort should be made to keep subjects in the study. The reasons for subjects not completing the study will be recorded. A subject may be withdrawn from the study for any of the following reasons:

1. Noncompliance with the protocol
2. A serious or intolerable adverse event(s) (AE[s]) that in the investigator's opinion requires withdrawal from the study
3. Central nervous system bleeding or life-threatening gastro-intestinal bleeding. Please also refer to the additional information in the 'Note' at the bottom of this section.
4. Laboratory safety results that reveal clinically significant hematological or biochemical changes from the baseline values
5. Symptoms of an intercurrent illness not consistent with the protocol requirements or that justify withdrawal
6. Lost to follow-up. Subjects that are considered lost to follow-up, reasonable attempts must be made to obtain information on the final status of the subject. At a minimum, 2 phone calls must be made and 1 certified letter must be sent for documentation
7. Other reasons (eg, pregnancy, development of contraindications of use of study drug, breakthrough bleeding)

8. The subject withdraws consent or the investigator or sponsor decides to discontinue the subject's participation in the study
9. Death of the subject.

Note: Bleeding events in the ITP studies are common during the first few weeks of the study before the drug has a chance to take effect; hence, all the bleeding events in this study should be recorded as an AE or SAE (based on seriousness criteria). These events should not result in removal of the subjects from the study, at least during the first 4 weeks of treatment. As the standard of care among the participating countries may differ, platelet transfusions are allowed as a rescue therapy for such events; however, these therapies may be reserved for serious or life-threatening bleeding events.

The investigator will also withdraw a subject if Oscotec Inc. terminates the study. Upon occurrence of a serious or intolerable AE, the investigator will confer with the sponsor. If a subject is discontinued because of an AE, the event will be followed until it is resolved. Any subject may withdraw his or her consent at any time. Although Oscotec Inc. has every intention of completing the study, Oscotec Inc. reserves the right to discontinue the study at any time for clinical or administrative reasons, please refer to Section 11.3 for further details.

4.2.2 Handling of Withdrawals

Subjects are free to withdraw from the study or study drug at any time upon request. Subject participation in the study may be stopped at any time at the discretion of the investigator or at the request of the sponsor.

Subjects who discontinue study drug or active participation in the study will no longer receive study drug. When a subject withdraws from the study drug or active participation in the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the electronic case report form (eCRF). Whenever possible, all subjects who discontinue study drug permanently or withdraw from the study prematurely will undergo all end-of-study assessments. Subjects who fail to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol. Following a minimum of 2 documented unsuccessful telephone calls, a registered letter will be sent to the subject in a final attempt to ensure protocol compliance.

It is vital to obtain follow-up data on any subject withdrawn because of an AE or SAE. In every case, efforts must be made to undertake protocol-specified safety follow-up procedures.

4.2.3 Replacements

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

5 Study drugs

Two dose levels of SKI-O-703 will be evaluated: 200 mg BID and 400 mg BID. The SKI-O-703 capsules will contain 100 mg of drug substance. Placebo capsules are filled with microcrystalline cellulose.

5.1 Method of Assigning Subjects to Treatment Groups

Subjects 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 subjects 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 subject randomization numbers to treatment codes. The randomization will be stratified to balance subjects with 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.

5.2 Treatments Administered

Subject specific doses will be prepared and checked by blinded pharmacy staff and administered by appropriately trained blinded clinic staff as delegated by the principal investigator at the study site. The study drugs will be identical in number and appearance for each group. The following dosing scheme will be performed:

- 200 mg BID group: 2 capsules of 100 mg SKI-O-703 + 2 capsule of placebo
- 400 mg BID group: 4 capsules of 100 mg SKI-O-703 + 0 capsules of placebo
- Placebo group: 4 capsules of 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 of study medication. The evening dose will be administered 12 hours after the morning dose. Subjects will be administered the study medication with enough water to swallow the capsules. The investigative site staff will check the subject's mouth to ensure the study drug and entire volume of water was swallowed. The study medication will be taken no later than 30 minutes after food. Subjects enrolled in the safety run in period will be admitted for 24 hours on Days 1, 8, and 84 or 85

of the study. Subjects selected for the PK/PD portion of the study will be admitted for 24 hours on Days 1 and 84 or 85 of the study. The subject will be instructed to self-administer the subsequent doses of the study medication in the morning and evening (12 hours after the morning dose) for the remaining study duration.

Dosing of the study medication that occur on study visit days, subjects will take the morning dose of study drug in the office under the guidance of study site personnel after all specified study tests and procedures have been completed. However, if the visit cannot be scheduled in the morning, the subject will be instructed to take the morning dose at the regular schedule on that visit day.

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

If the subjects forget to take their study drug dose at their regularly scheduled dosing time, they should take the forgotten dose as soon as they remember the dose was missed, within 4 hours of scheduled timepoint or at least 8 hours before the next scheduled dose. If the subjects experience any drug interruption(s), they should notify their study site physician. Such protocol violations may result in data that are not deemed evaluable (by the investigator) for a protocol analysis and/or may require subject(s) to be discontinued.

5.3 Identity of Investigational Product

SKI-O-703 capsule is a Swedish orange capsule. Oscotec Inc. will provide adequate supplies of blinded SKI-O-703 and placebo capsules to the study site.

SKI-O-703 capsules will contain the active ingredient SKI-O-703 (100 mg).

Placebo capsules will be identical in appearance to the SKI-O-703 capsule and contain only microcrystalline cellulose and magnesium stearate.

5.4 Management of Clinical Supplies

5.4.1 Study Drug Packaging and Storage

SKI-O-703 (100 mg) capsules and matching placebo capsules will be manufactured using a ProFill® capsule filler, packaged 70 counts each into high density polyethylene bottles, and

shipped to the study site. Study drug will be packaged and labelled according to applicable local and regulatory requirements.

Study drug must be stored in accordance with the manufacturer's instructions. The storage conditions and expiry date will be indicated on the label. At the study site, study drug must be stored in a securely locked area and kept at a controlled room temperature with excursions between 15°C and 30°C.

5.4.2 Test Article Accountability

The sponsor or affiliate will ship a sufficient supply of study drug to the study site. The investigator will maintain accurate records of receipt of all test articles, including dates of receipt. In addition, accurate records will be kept regarding when and how much test article is dispensed and used by each subject in the study. Subjects will be instructed to return all drug containers (even if empty) to the study site personnel at each clinic visit. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drug will be reconciled and retained or destroyed according to applicable regulations.

Subject dosing will be recorded on eCRF. Study drug will be dispensed bi-weekly (34 doses, 17 days' worth of drug at a time) to the subjects. Subjects will be instructed to return all drug containers (even if empty) to the study site personnel at each clinic visit. Site personnel will document compliance in the study source documents.

5.5 Overdose Management

An overdose is any dose of study drug given to a subject or taken by a subject that exceeds the dose described in the protocol. A medication error is a preparation, dispensing, or administration error. Any overdose or medication error, with or without associated AEs, must be promptly reported to the investigator, medical monitor, and sponsor. Overdoses and medication errors without signs or symptoms do not need to be recorded as AEs; in case of any AEs associated with the overdose or medication error, these should be reported on relevant AE/SAE sections in the eCRF.

Overdoses and medication errors will be documented as protocol deviations and communicated to the clinical study manager and/or safety manager.

No specific therapy for an overdose of SKI-O-703 exists. In the event of an overdose or medication error, therapy appropriate for the subject's symptoms and clinical status should be provided.

5.6 Blinding

This is a double-blind study. Neither the subjects nor the investigator/site personnel will be aware of the treatment assignment for the subjects 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 subjects enrolled in the safety run-in period from an independent statistician for review, which have to be handled strictly confidentially. None of these reports can be delivered to unauthorized persons.

5.6.1 Breaking the Blind

A subject's treatment assignment will not be broken until the end of the study unless medical treatment of the subject depends on knowing the study treatment the subject received, eg, bleeding events requiring rescue medication do not require breaking the blind unless knowing the treatment allocation may result in different management.

In the event that the blind needs to be broken because of a medical emergency, the investigator may unblind an individual subject's treatment allocation. As soon as possible, the investigator should first contact the medical monitor to discuss the medical emergency and the reason for revealing the actual treatment received by that subject. The treatment assignment will be unblinded through IVRS. Reasons for treatment unblinding must be clearly explained and justified in the eCRF. The date on which the code was broken together with the identity of the person responsible must also be documented.

5.7 Treatment Compliance

Day 1 doses of the study drug will be administered and recorded by study site personnel, and any deviations from the dosing schedule will be entered into the subject's eCRF. From Day 2 onwards, subjects will be instructed to self-administer their morning dose of study medication. The subject will be instructed to self-administer their evening dose 12 hours after the morning dose. Treatment compliance will be determined from subject dosing data in eCRF.

5.8 Prior and Concomitant Therapy

Use of all concomitant medications that the subject is receiving at the time of Screening or receives during the study must be recorded in the subject's eCRF. The minimum requirement is the reason for drug use, drug name, and the dates of administration (including start and end dates), dosage information including dose, route, and frequency are to be recorded in the eCRF. This will include all prescription drugs, herbal products, vitamins, minerals, vaccines, and over-the-counter medications (including folic acid). Any changes in concomitant medications also will be recorded in the subject's eCRF.

Any concomitant medication, except the prohibited medications listed in Section 5.8.3, deemed necessary for the welfare of the subject during the study may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding the medication are recorded in full in the eCRF.

Subjects will be allowed to receive stable doses of background medications in line with the current standard of care. The background medications allowed include corticosteroids (<20 mg prednisone equivalent per day) and immunosuppressive drugs such as azathioprine (≤50 mg twice daily), mycophenolate mofetil (≤500 mg twice daily), and cyclosporine (≤100 mg twice daily). The dose of such background medications should be fixed for at least 2 weeks before Day 1 and remain unchanged until 12 weeks of treatment have been completed or unless rescue therapy is required.

5.8.1 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.

Subjects should be withdrawn in case of CNS bleeding or life-threatening GI bleeding (see Section 4.2.1).

5.8.2 Management of Nausea and Vomiting

Based on Investigator's discretion, nausea and vomiting can be managed based the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grades as described below.

- Grade 1: No routine anti-emetics are necessary. Consider oral domperidone 20 mg three times a day as needed or oral metoclopramide 20 mg three times a day as needed
- Grade 2: Oral domperidone 20 mg three times a day as needed or oral metoclopramide 20 mg three times a day as needed
- Grade 3: Oral domperidone 20 mg three times a day as needed or oral metoclopramide 20 mg three times a day as needed and consider levomepromazine 6 mg at night as needed
- Grade 4: Oral aprepitant 80 mg QD or oral domperidone 20 mg three times a day or oral metoclopramide 20 mg three times a day

5.8.3 Prohibited Concomitant Medications

The medical monitor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited medications are administered. Prohibited medications during the study include:

- Any biological agents for the treatment of ITP
- Any rescue medications other than those described in Section 5.8.1
- Any immunosuppressant drugs other than those described in Section 5.8
- Change in corticosteroid and immunosuppressants dose as detailed in the exclusion criteria

- Use of IVIGs within 4 weeks prior to Day 1
- Treatment with rituximab or splenectomy within the 8 weeks prior to Day 1
- Any parenteral antibiotics as specified in the exclusion criteria
- Any live vaccine taken within 28 days prior to Day 1 or plan to receive one during the study
- Concomitant use of any anticoagulants and platelet aggregation inhibiting drugs including aspirin (within 14 days of planned dosing through end of follow-up)
- Known CYP1A2 and UGT1A1 inhibitors and inducers (See Appendix 13.1 for a list of suggested named CYP1A2 and UGT1A1 inhibitors and inducers). These medications must be discontinued within 5 half-lives or 4 weeks prior to Day 1, whichever is longer.

6 Study Assessments and Procedures

Before performing any study procedures, all potential subjects will sign an ICF. Subjects will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the subject. The investigator will also sign the ICF.

6.1 Study Visits

The total study duration will be 20 weeks per subject, 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 subjects). 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 2.

Table 2 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 day)**	**W2D8 (±2 days)**	**W3, 7, 11 (±3 days)**	**W12 (D84 or D85) (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, HBV DNA, HCV RNA	X							
Pregnancy test/ FSH[d]	X	X				X	X	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		
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		

		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 day)**	**W2D8 (±2 days)**	**W3, 7, 11 (±3 days)**	**W12 (D84 or D85) (EOT) (±3 days)**	**End of Study W16 (±1 week)**	
Bleeding Score[i]		X		X*		X	X	X
Quality of life using SF-36 score		X				X	X	X
Pharmacogenomic screening		X[j]						

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

* Subjects 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 subjects, 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 or D85 (EOT) visit should be performed while on therapy.

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

c For all subjects: predose ECG on the first day of dosing and on Day 1 of each subsequent week as specified in the table above. For subjects in the safety run-in subsets and PK/PD subset who are in safety run-in subset only: ECG on the first day of dosing at predose, 1, 2, 4, 8, and 12 hours (±10 min) after the study drug administration.

d For women of childbearing potential only: Serum pregnancy tests are performed at Screening. To confirm pregnancy, urine pregnancy test will be performed locally on Day 1 prior to randomization and prior to study drug administration on clinic visit days at mentioned timepoints. If urine pregnancy test is negative, dosing will be started; if urine pregnancy test is positive then with-hold dosing and perform a serum pregnancy test. FSH testing is needed at Screening for post-menopausal female subjects only.

e Laboratory only visits will be performed on Day 4 ±1 day (Week 1) for all subjects and on Week 2/Day 8 (±2 days) for subjects 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 subjects in the safety run-in period only (for PK only; no PD assessments):

- Day 1: morning predose, 0.25 (+5 min), 0.5 (±5min), 1, 2, 4, 8, and 12 hours (±10 min) (evening predose).
- Day 8 (±2 days): morning predose, 0.25 (+5 min), 0.5 (±5min), 1, 2, 4, 8, and 12 hours (±10 min) (evening predose).
- Week 12: morning predose, 0.25 (+5 min), 0.5 (±5min), 1, 2, 4, 8, and 12 hours (±10 min).

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

- Day 1: morning predose, 0.25 (+5 min), 0.5 (±5min), 1, 2, 4, 8, and 12 hours (±10 min) (evening predose).
- Week 12: morning predose, 0.25 (+5 min), 0.5 (±5min), 1, 2, 4, 8, and 12 hours (±10 min).

For other subjects 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 once at any clinic visit from Day 1 (Week 1) to the end-of-treatment visit, only from subjects who have consented to participate in the genetic analysis component of the study.

6.2 Demographic and Medical History

Demographic data and a complete medical history (including prior and concomitant medical conditions and procedures; drug, alcohol, and tobacco use; current use of herbal remedies, vitamin supplements, grapefruit juice, and caffeine- and xanthine-containing products) will be collected at Screening.

6.3 Efficacy Assessments

Efficacy will be assessed based on the laboratory and clinical assessments/bleeding score. See Section 7.

6.4 Safety Assessments

Safety variables will include physical examination findings, vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature), ECG tracings, clinical laboratory test results (hematology, coagulation, serum chemistry, and urinalysis), bleeding score, quality of life as measured by the SF-36 score, weight, body mass index, and reporting of AEs.

Bleeding will be assessed according to the bleeding score as described by Page et al 2007. These assessments will be carried out at the time points indicated in the schedule of events. Safety assessments will be conducted as shown in the schedule of events (Table 2).

6.4.1 Physical Examination

A complete physical examination will be performed at the screening visit and an abbreviated physical examination at other time points indicated in the schedule of events (Table 2). 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. Interim physical examinations can be performed at the discretion of the investigator, if deemed necessary to evaluate AEs or clinical laboratory abnormalities.

6.4.2 Vital Sign Measurements, Height, and Weight

Vital sign measurements will include systolic and diastolic blood pressures, pulse rate, respiratory rate, and temperature. The subject will be seated for at least 5 minutes before all measurements are taken. Vital signs will be measured at the time points indicated in the schedule of events (Table 2).

Height will be measured at Screening only. Weight will be measured at the time points indicated in the schedule of events (Table 2).

When procedures are overlapping and occurring at the same time point, the order in which procedures are performed should be vital sign measurements followed by blood collection.

The investigator will determine whether any of the vital sign measurements 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). If a clinically significant change from the screening values is noted, the clinically significant value and the reason for clinical significance will be documented on the AE page of the subject's eCRF. The investigator will continue to monitor the subject with additional assessments until the value has reached either the reference range or the value at Screening or until the investigator determines that follow-up is no longer medically necessary.

6.4.3 Electrocardiograms

For all subjects, single ECG (predose) will be obtained, after the subject has been in the supine position for at least 5 minutes, on the first day of dosing and on Day 1 of each subsequent week at the time points indicated in the schedule of events (Table 2). For subjects in the safety run-in subsets and PK/PD subset subjects who are in safety run-in subset only, ECGs will be obtained on the first day of dosing at predose, 1, 2, 4, 8, and 12 hours (±10 min) after the study drug administration. Electrocardiogram 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). If a clinically significant change from screening is noted, the clinically significant value and the reason for clinical significance will be documented on the AE page of the subject's eCRF. The investigator will continue to monitor the subject with additional assessments until the values have reached either the reference range or the values at Screening or until the investigator determines that follow-up is no longer medically necessary.

6.4.4 Clinical Laboratory Tests

Clinical laboratory tests will be performed by PPD's central laboratory. Blood and urine samples will be collected under fasted conditions and at the time points indicated in the schedule of events (Table 2).

For women of childbearing potential only: Serum pregnancy tests will be performed at Screening. To confirm pregnancy, urine pregnancy test will be performed locally. For post-menopausal female subjects only, FSH testing will be performed at Screening.

The following hematology, coagulation, serum chemistry, and urinalysis assessments will be performed:

Hematology:	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
Coagulation:	International normalized ratio, partial thromboplastin time, and prothrombin time, ABO and Rh Blood Type
Serum Chemistry:	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
Urinalysis:	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

Abnormal clinical laboratory values will be flagged as either high or low (or normal or abnormal) based on the reference ranges for each laboratory parameter. The investigator will determine whether any abnormally high or low 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). If a clinically significant change from the screening value is noted, the clinically significant value and the reason for clinical significance will be documented on the AE page of the subject's eCRF. The investigator will continue to monitor the subject with additional assessments until the values have reached either the reference range or the values at Screening or until the investigator determines that follow-up is no longer medically necessary.

The FDA guidance for industry on Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009) will be used as a guideline for the assessment of liver enzymes/liver function tests (DHHS 2009).

Clinically significant laboratory values for individual subjects will be listed. A summary for the numbers and percentages of subjects with clinically significant laboratory values at any time point will be presented.

6.4.5 Adverse Events

6.4.5.1 Definitions of Adverse Events

The investigator is responsible for reporting all TEAEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

An AE is defined as any untoward medical occurrence in a subject enrolled into this study regardless of its causal relationship to study drug. Subjects will be instructed to contact the investigator at any time after randomization if any symptoms develop.

A 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.

6.4.5.2 Serious Adverse Events

An SAE is defined as any event 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

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Note: The AE terms neutropenia and hypertension should be used only when reporting events that meet the following criteria:

- The term neutropenia is reserved for reporting an absolute neutrophil count $<1000/mm^3$ or $<1.0 \times 10^9/L$ and may or may not be associated with fever or concurrent infection.
- The term hypertension is reserved for reporting an increase in systolic blood pressure ≥160 mmHg, or diastolic blood pressure ≥100 mmHg, or any clinically significant increase in blood pressure that requires modification of the subject's antihypertensive regimen.

6.4.5.3 Eliciting and Documenting Adverse Events

Adverse events will be assessed from the time the subject signs the informed consent form until end of study visit (Week 16).

If the investigator becomes aware of an SAE that occurs after the end of study visit and is assessed by the investigator as at least possibly related to the study drug, they need to report the SAE.

At every study visit, subjects will be asked a standard nonleading question to explore a response regarding any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

In addition to subject observations, AEs identified from any study data (eg, laboratory values, physical examination findings, ECG changes) or identified from review of other documents that are relevant to subject safety will be documented on the AE page in the eCRF.

6.4.5.4 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF. Information to be collected includes drug treatment, dose, event term, time of onset, investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, any required treatment or evaluations, and outcome. Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA v20.0) will be used to code all AEs. All AEs, SAEs, drug-related AEs, and drug-related SAEs will be summarized using the worst grade per NCI CTCAE v5.0 by system organ class and preferred term.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

6.4.5.5 Reporting Serious Adverse Events

Any AE that meets SAE criteria (Section 6.4.5.2) must be reported to PPD immediately (ie, within 24 hours) after the time that site personnel first learn about the event. The nonserious adverse event of special interest (AESI) defined in Section 6.4.5.6 should be recorded on the SAE report form in addition to the eCRF and faxed using the same process as for reporting SAEs.

Pharmacovigilance

[redacted]

[redacted]

6.4.5.6 Suspected Unexpected Serious Adverse Reactions and Nonserious Adverse Events of Special Interest

The following nonserious AESI should be recorded on the SAE report form in addition to the eCRF and faxed using the same process as for reporting SAEs.

- **Neutropenia** with fever defined as absolute neutrophil count <1000/mm^3 or <1.0 × 10^9/L on the most recent complete blood count with fever equal to or greater than 38°C that does not fulfill any of the serious criteria, ie, hospitalization.
- **Hepatotoxicity** defined as ALT >3 × ULN plus total bilirubin >2 × ULN that does not fulfill any of the serious criteria, ie, hospitalization. This information should be recorded on the drug induced liver injury eCRF each time the elevated laboratory parameters are met during the study

Oscotec Inc. will promptly evaluate all suspected unexpected serious adverse reactions (SUSARs) and nonserious AESI against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and applicable health authorities based on applicable legislation.

To determine reporting requirements for single AE cases, Oscotec Inc. will assess the expectedness of these events using the study drug investigator’s brochure.

Oscotec Inc. will compare the severity of each SUSAR and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by Oscotec Inc. as needed.

6.4.5.7 Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the subject's daily activities. The intensity of the AE will be rated using the NCI CTCAE v5.0.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of the onset and duration of each episode.

6.4.5.8 Assessment of Causality

The investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. The relationship or association of the study drug in causing or contributing to the AE will be characterized using the following classification and criteria:

Unrelated:	This relationship suggests that there is no association between the study drug and the reported event.
Possible:	This relationship suggests that treatment with the study drug caused or contributed to the AE, ie, the event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the study drug but could also have been produced by other factors.
Probable:	This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the study drug seems likely. The event disappears or decreases on cessation or reduction of the dose of study drug.
Definite:	This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or reaction to concurrent medication) do not appear to explain the event. The event reappears or worsens if the study drug is re-administered.

6.4.5.9 Follow-Up of Subjects Reporting Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF and followed to satisfactory resolution, until the investigator deems the event to be chronic or not clinically significant, or until the subject is considered to be stable.

6.5 Pharmacokinetic and Pharmacodynamic Assessments

6.5.1 Pharmacokinetic Blood Samples

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 (+5 min), 0.5 (±5min), 1, 2, 4, 8 and 12 hours (±10 min) morning post-dose (12-hr sample should be collected prior to the evening dose).
- Week 12 (Day 84 or 85): 0 hour (morning pre-dose), and 0.25 (+5 min), 0.5 (±5min), 1, 2, 4, 8, and 12 hours (±10 min).

In addition, PK samples will also be collected at the following time points on Day 8 (±2 days) from subjects in the safety run-in period only:

- Day 8 (±2 days): 0 hour (morning pre-dose), and at 0.25 (+5 min), 0.5 (±5min), 1, 2, 4, 8 and 12 hours (±10 min) morning post-dose (12-hr sample should be collected prior to the evening dose).

For other subjects not included in the safety run-in period or PK/PD subset, morning pre-dose PK samples will be collected during Week 12 only.

When the PK blood sample collection coincides with safety assessments, PK blood samples should be collected as close to the scheduled time point as possible, and safety assessments should be performed before PK blood samples are taken.

For each sample collected, separated plasma will be transferred in approximately equal portions into 2 tubes that are labeled for sets A and B for SKI-O-592 and metabolites. Labels will include the study number, the subject identification number, an indication that they are PK samples, the nominal day and collection time, the analyte(s), and the set (A or B). Plasma samples will be stored at approximately –70°C in an upright position.

Set A samples will be transported, frozen with sufficient dry ice for several days, to the bioanalytical facility.

Set B samples will be retained at the study center until the study is completed and the clinical study report is issued, unless shipment to another facility is requested by the Oscotec Inc.

Instructions regarding the disposition of the B samples will be provided by the Oscotec Inc. Specific details and the full protocol for analysis of PK samples can be found in the study laboratory manual.

6.5.2 Pharmacokinetic Variables

Plasma PK parameters will be calculated for SKI-O-592 and its metabolites M2 and M4 in the PK/PD subset using a noncompartmental approach and will include the following, where applicable:

C_{max}	maximum observed concentration
T_{max}	time to reach the maximum observed concentration
$AUC_{0\text{-}tau}$	area under the concentration versus time curve within a dosing interval
$t_{1/2}$	apparent terminal elimination half-life
K_{el}	terminal elimination rate constant
CL/F	apparent oral clearance (SKI-O-592 only)
V_z/F	apparent oral volume of distribution (SKI-O-592 only)
R_{met}	metabolite ratio
R_{AUC}	accumulation ratio based on $AUC_{0\text{-}tau}$

Additional PK parameters may be estimated, as deemed appropriate.

6.5.3 Pharmacodynamic Blood Samples

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 (+5 min), 0.5 (±5 min), 1, 2, 4, 8 and 12 hours (±10 min) morning post-dose (12-hr sample should be collected prior to the evening dose).
- Day 84 or 85 (Week 12): 0 hour (morning pre-dose), and at 0.25 (+5 min), 0.5 (±5 min), 1, 2, 4, 8, and 12 hours (±10 min).

Blood samples must be dispatched to the processing laboratory as quickly as possible to ensure transport, cataloguing, and processing time is complete within the required timeframe

for the selected assay. All blood collection systems must be pyrogen free. Blood samples (0.5 mL) will be collected into tubes containing dipotassium ethylene diamine tetra acetic acid (K2 EDTA) anticoagulant. Tubes containing ethylene diamine tetra acetic acid or citric acid as anticoagulant are prohibited. Samples are to be stored at 2°C to 8°C prior to shipping and packed with ice pack for shipping.

Specific details and the full protocol for analysis of PD samples can be found in the study laboratory manual.

6.5.4 Pharmacodynamic Variables

The primary PD endpoint will be the change in the percentage of activated CD63+ basophils in peripheral blood. The PD parameters will include the following:

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

Additional PD endpoints/parameters may be evaluated, as deemed appropriate.

6.6 Safety Monitoring Committee

An independent DMC appointed by the Sponsor will review the interim safety and PK data of the first 5 subjects enrolled in the safety run-in period. Further details will be provided in the DMC charter.

6.7 Pregnancy

Pregnancy is not regarded as an AE unless it is suspected that study drug interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during study participation must be reported using a clinical study pregnancy form. To ensure subject safety, each pregnancy must be reported to the sponsor within 2 weeks of learning of its occurrence. The pregnancy must be followed up at least 30 days after birth or the first well-baby visit to determine the outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and the status of mother and child, even if the subject was discontinued from the study. Pregnancy complications and elective

terminations for medical reasons must be reported as AEs or SAEs. Spontaneous miscarriages must be reported as SAEs.

Any SAE occurring in association with a pregnancy that is brought to the investigator's attention after the subject has completed the study and that is considered by the investigator as possibly related to the study drug must be promptly reported to the sponsor.

Contraception status will be monitored at each visit and documented appropriately.

6.8 Laboratory Analyses

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, vital sign measurements), including those that worsen from baseline, felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as AEs or SAEs.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.

6.9 Sample Collections

The total volume of blood collected for each assessment is discussed in each specific laboratory manual.

6.10 Pharmacogenomic Screening

A 6-mL whole blood sample for genotyping will be drawn at Baseline (Day 1, before dosing) from subjects who have consented to participate in the genetic analysis component of the study to potentially explore genetic polymorphisms of the enzymes (eg, UGT1A1) responsible for the metabolism of SKI-O-703 and the association of these genetic polymorphisms with the PK of SKI-O-703. Further details of blood collection and processing will be provided in the laboratory manual.

7 Statistical and Analytical Plan

7.1 Primary Endpoint - Platelet Response

- 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

7.2 Secondary Endpoints

7.2.1 Subjects Achieving Two or More Pre-specified Platelet Counts

- Subjects 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
- Subjects 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
- Subjects 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
- Subjects 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
- Subjects able to achieve platelet counts of ≥ 50,000/μL at 3 of the last 4 visits.

7.2.2 Change from Baseline in Platelet Counts

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

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

7.2.3 Time to First Platelet Response

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

For each subject, 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.

7.2.4 Others

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

For each endpoint, a subject 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.

7.3 Exploratory Endpoints

7.3.1 Peak Platelet Count

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

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

7.3.2 Bleeding Score

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

Table 3 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
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

Site	Bleeding Grade		
	0	1	2
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

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

7.3.3 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 the schedule of events (Table 2).

7.4 Sample Size Calculations

A minimum of 60 subjects will be enrolled in the study. Subjects 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 subjects in the active treatment group will be responders (R). A sample size of 24 subjects per active treatment group and 12 subjects in the placebo group will provide approximately 82.7% 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.

Subjects 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.

7.5 Analysis Sets

The following analysis sets will be used in the statistical analyses.

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

Intent-to-Treat (ITT) set: The ITT set will consist of all randomized subjects who receive at least 1 dose of study drug (SKI-O-703 or placebo) and have at least 1 post-baseline platelet assessments. Subjects 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.

Per-protocol (PP) set: The PP set will consist of all subjects in ITT set with no major protocol violations. Major protocol violations will be identified during the study. Subjects 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.

Pharmacokinetic (PK) set: The PK set will consist of all subjects who receive SKI-O-703 and have at least 1 measurable plasma concentration. Subjects who have partial data and/or major protocol deviations that may impact PK, and subjects 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.

Pharmacodynamic (PD) set: The PD set will consist of all subjects who receive at least 1 dose of study drug (SKI-O-703 or placebo) and have at least 1 evaluable postdose PD value. Subjects 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.

Pharmacokinetic (PK)/pharmacodynamic (PD) set: All subjects included in the PK and PD analysis sets. This analysis set will be used for the PK/PD analyses.

7.6 Description of Subgroups to be Analyzed

The primary endpoint will be summarized using the following subgroups of interest:

- Number of previous lines of therapy (0-2 vs. ≥3)
- Response to previous treatment (non-responders vs. relapsed)
- Splenectomized subjects vs. non-splenectomized subjects and
- Subjects with baseline platelet count < 15,000/μL versus subjects with platelet count between 15,000/μL to 30,000/μL.
- Subjects with prior TPO-receptor agonist use versus subjects without prior TPO-receptor agonist use.

7.7 Statistical Analysis Methodology

Statistical analysis will be performed using SAS software Version 9.4 or later. The results for each efficacy endpoint will be summarized by visit and treatment for all subjects within the ITT analysis set using descriptive statistical methods. 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.

Details of the statistical analyses, methods, and data conventions will be described in the statistical analysis plan.

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.

7.7.1 Subject Disposition

Subject disposition will be summarized by treatment group and will include subjects that enrolled, were randomly assigned, discontinued, and completed the study. For discontinued subjects, the reasons for discontinuation will be summarized.

7.7.2 Analyses of Demographic and Baseline Characteristics

Demographic and baseline characteristics such as age, gender, race, body weight, height, body mass index, and medical history will be summarized by treatment group using descriptive statistics.

7.7.3 Analysis of Platelet Response

The primary efficacy endpoint will be summarized as overall platelet response rate (ORR) by treatment group and analyzed using Fisher's exact test to compare the difference in ORR between each active treatment group and placebo. A logistic regression model will also be performed on platelet response and include treatment, baseline platelet count and prior TPO-receptor agonist use, provided there are enough subjects in each subgroup. The odds ratio for the treatment effect compared to placebo (together with 95% CI and p-value) will be provided.

Summary statistics will be provided on the number (%) of subjects achieving platelet response by each treatment group and the combined active treatment group. Fisher's exact test on the differences in the ORR 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.

Furthermore, summary statistics will be provided on the number (%) of subjects achieving platelet response by each treatment group and the subgroups defined in Section 7.6.

A subject will be classified as a platelet responder if subject shows at least 1 platelet count ≥ 30,000/μL and doubling the baseline (average of 2 previous counts), at any visit during treatment period, without use of rescue medication. The ITT analysis set will be used in the analysis of the primary endpoint.

7.7.4 Analysis of Secondary Endpoints

For each binary endpoint (ie, definition of subject achieving 2 or more consecutive platelet counts), a logistic regression model will be performed and include treatment, baseline platelet count and prior TPO-receptor agonist use, provided there are enough subjects in each

subgroup. The odds ratio for the treatment effect compared to placebo (together with 95% CI and p-value) will be provided.

Time to platelet response will be estimated using the Kaplan-Meier method. Each active treatment group curve will be 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.

Change from baseline in the average of the last 2 platelet counts will be analyzed using an analysis of covariance with baseline platelets count as covariate, treatment, and prior TPO-receptor agonist use. Each active treatment group will be compared with placebo.

Summary statistics of the following subjects will be provided by each treatment group:

- Subjects receiving rescue medication during the treatment period
- Subjects with Grade 2 or higher non-skin bleeding event during the treatment or follow-up period

A subject will be considered to have an event if the event was observed at least once during the treatment period or follow-up period as mentioned above.

7.7.5 Analyses of Exploratory Endpoints

Peak platelet will be summarized by treatment groups. The median peak platelet, and the lower and upper quartile 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

Bleeding score will be summarized by treatment group and the combined active treatment groups.

7.7.6 Pharmacokinetic/Pharmacodynamic Analyses

7.7.6.1 Pharmacokinetic Analyses

Plasma concentrations of SKI-O-592 and its metabolites (M2 and M4) will be listed and summarized separately for each treatment and day at each nominal time point using descriptive statistics (number of observations [n], mean, SD, coefficient of variation [CV], minimum, median, and maximum). Individual and mean plasma concentration versus time profiles will be plotted for each treatment and day.

PK parameters for SKI-O-592 and its metabolites will be calculated using noncompartmental methods. Descriptive statistics (n, geometric mean, geometric CV, mean, SD, CV, minimum, median, and maximum) for the PK parameters for SKI-O-592 and its metabolites will be presented for each treatment and day. Treatment comparisons will be performed as deemed appropriate.

7.7.6.2 Pharmacodynamic Analyses

Absolute and percentage change from baseline in the percentage of activated CD63+ basophils in peripheral blood will be listed and summarized separately for each treatment and day at each nominal time point using descriptive statistics (number of observations [n], mean, SD, CV, minimum, median, and maximum). Individual, mean absolute and percentage change from baseline in the percentage of activated CD63+ basophils will be plotted versus time for each treatment and day.

PD parameters for the percentage of activated CD63+ basophils will be calculated using non-compartmental methods. Descriptive statistics (n, mean, SD, CV, minimum, median, and maximum) for the PD parameters will be presented for each treatment and day. Treatment comparisons will be performed as deemed appropriate.

7.7.6.3 Exploratory PK/PD Analyses

PK/PD relationship between plasma concentrations of SKI-O-592, M2, and M4 and change from baseline in the percentage of activated CD63+ basophils in peripheral blood on Day 1 and Week 12 will be assessed. Individual and mean plasma concentrations of SKI-O-592, M2, and M4 will be plotted versus change from baseline in the percentage of activated CD63+ basophils in peripheral blood on Day 1 and Week 12.

Exploratory PK/PD modeling may also be performed; full details will be provided in a separate Statistical Analysis Plan.

7.7.7 Safety Analyses

Continuous parameters (such as laboratory measurements, ECG results, and vital signs) will be summarized separately for each treatment at each nominal time point using descriptive statistics (mean, SD, minimum, median, and maximum).

Discrete parameters (such as deaths, SAEs, AEs, concomitant medications, and physical examination results) will be summarized separately for each treatment at each nominal time point using frequency counts and percentages. All AEs, SAEs, drug-related AEs, and drug-related SAEs will be summarized using the worst grade per NCI CTCAE v5.0 by system organ class and preferred term. All safety data will be listed.

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

7.7.8 Interim Analyses

An unblinded interim safety and PK data review will be performed by the DMC once the subjects in the safety run-in period complete their Day 8 (±2 days) assessments. Subjects 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 subjects are reviewed and considered satisfactory by the DMC.

8 Data Quality Assurance

This study will be conducted according to the ICH E6(R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management (ICH 2005).

8.1 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports and ECG strips.

Investigative site personnel will enter subject data into Oracle™Clinical Remote Data Capture. The analysis data sets will be a combination of these data and data from other sources (eg, laboratory data).

Clinical data management will be performed in accordance with applicable sponsor standards and data cleaning procedures to ensure the integrity of the data, eg, removing errors and inconsistencies in the data. Adverse events and concomitant medication terms will be coded using MedDRA Version 20.0 or later, an internal validated medication dictionary.

After database lock, each study site will receive a CD-ROM containing all of their site specific eCRF data as entered into Oracle Clinical Remote Data Capture for the study, including full discrepancy and audit history. Additionally, a CD-ROM copy of all of the study site's data from the study will be created and sent to the sponsor for storage. PPD will maintain a duplicate CD-ROM copy for their records. In all cases, subject initials will not be collected or transmitted to the sponsor.

9 Ethics

9.1 Independent Ethics Committee or Institutional Review Board

Federal regulations and the ICH guidelines require that approval be obtained from an IRB/IEC before participation of human subjects in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject or the subject's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R2): Good Clinical Practice (GCP) will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

9.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, the protocol, and all applicable regulations.

9.3 Subject Information and Consent

A written informed consent in compliance with the respective applicable regulatory authority regulations shall be obtained from each subject before entering the study or performing any unusual or nonroutine procedure that involves risk to the subject. An informed consent template may be provided by the sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the sponsor or its designee or both before IRB/IEC submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB/IEC for review

and approval before the start of the study. If the ICF is revised during the course of the study, all active participating subjects must sign the revised form.

Before recruitment and enrollment, each prospective subject or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the subject/legal guardian understands the implications of participating in the study, the subject/legal guardian will be asked to give consent to participate in the study by signing the ICF.

The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the subject or legal guardian.

10 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be changed based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

10.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, the US FDA, or the IRB/IEC.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

10.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 Code of Federal Regulations (CFR) 54. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor PPD is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor PPD is financially responsible for further treatment of the subject's disease.

10.3 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB/IEC approval
- Original investigator-signed investigator agreement page of the protocol
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- Curriculum vitae for the investigator and each subinvestigator listed on Form FDA 1572
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IRB/IEC-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject or legal guardian, and
- Laboratory certifications and normal ranges for any local laboratories used by the site, in accordance with 42 CFR 493.

10.4 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.5 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

10.6 Adverse Events and Study Report Requirements

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

10.7 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports required.

10.8 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period; however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10.9 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld.

11 Study Management

11.1 Monitoring

11.1.1 External Data Monitoring Committee

An independent DMC appointed by the Sponsor will review the interim safety and PK data of the first 5 subjects enrolled in the safety run-in period (See Section 7.7.8). Further details will be provided in the DMC charter.

11.1.2 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and personnel.

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

11.1.3 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency (eg, FDA) access to all study records.

The investigator should promptly notify the sponsor and PPD of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

11.2 Management of Protocol Amendments and Deviations

11.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator's IRB/IEC for approval before subjects can be enrolled into an amended protocol.

11.2.2 Protocol Deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study subjects without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the subject or investigator that results in a significant, additional risk to the subject. Significant deviations can include nonadherence to inclusion or exclusion criteria, or nonadherence to FDA regulations or ICH GCP guidelines, and will lead to the subject being withdrawn from the study (Section 4.2).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal investigators will be notified in writing by the monitor of deviations. The IRB/IEC should be notified of all protocol deviations in a timely manner.

11.3 Study Termination

Although Oscotec Inc. has every intention of completing the study, Oscotec Inc. reserves the right to discontinue the study at any time for clinical or administrative reasons which may include (but not limited to) the followings:

- Unacceptable risk to a subject participating in the study
- The decision on the Sponsor to suspend or discontinue evaluation of the study drug
- Insufficient adherence to protocol
- Failure to comply with regulation, etc.

The end of the study is defined as the date on which the last subject completes the last visit (includes follow-up visit).

11.4 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the clinical study reports are prepared and provided to the regulatory agencies as required by the applicable regulatory requirement(s). The sponsor will also ensure that the clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study report, Oscotec Inc. will provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate. The study results will be posted on publicly available clinical trial registers.

12 Reference List

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