CLINICAL STUDY PROTOCOL

IND 125357

EUDRA-CT 2018-003330-32

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Dose Study to Evaluate the Efficacy and Safety of Oral SKI-O-703 in Patients With Active Rheumatoid Arthritis Despite Treatment With Conventional Therapies

OSCO-P2201

Sponsor:	Oscotec Inc. Korea Bio-Park, Building A, 9th Floor 700 Daewangpangyo-ro, Bundang-gu Seongnam-si, Gyeonggi-do 13488 The Republic of Korea
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Medical Monitor:	
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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 in Patients With Active Rheumatoid Arthritis Despite Treatment With Conventional Therapies
Protocol Number	OSCO-P2201
Protocol Date	19 Oct 2020

Protocol accepted and approved by:

[redacted]

[redacted]

Protocol Approval – Principal/Coordinating Investigator

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[redacted]

Protocol Approval – Lead Statistician

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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 in Patients With Active Rheumatoid Arthritis Despite Treatment With Conventional Therapies" 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 Final Protocol version 5.0, Amendment 4, 19 Oct 2020, 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 treatment 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.

Signature of Principal Investigator	Date

Printed Name of Principal Investigator

Protocol Synopsis

Protocol Number	OSCO-P2201
Title	A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Dose Study to Evaluate the Efficacy and Safety of Oral SKI-O-703 in Patients With Active Rheumatoid Arthritis Despite Treatment With Conventional Therapies
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 the United States, Europe, and South Korea.
Indication	Rheumatoid Arthritis
Rationale	Spleen tyrosine kinase (SYK) is a nonreceptor tyrosine kinase known to have a crucial role in immune receptor signaling. A number of studies have revealed that aberrant SYK activation is associated with diverse allergic disorders and antibody-mediated autoimmune diseases such as rheumatoid arthritis (RA), asthma, and allergic rhinitis. The novel small-molecule SYK inhibitor SKI-O-592 (the free base of SKI-O-703) has demonstrated high selectivity and potency against SYK in a biochemical assay. For immunoreceptor activation linked to SYK, the effect of SKI-O-592 on the anti-inflammatory response consisting of tumor necrosis factor alpha (TNFα), β-hexosaminidase, and cluster of differentiation 69 (CD69) expression was greater than the effects of first-generation SYK inhibitors (eg, R406) in several immune cell lines and in human primary cells. This anti-inflammatory activity was responsible for the selective inhibition of p-SYK (Y525/526), which led to the sequential inhibition of downstream effectors. More importantly, the inhibitory activity of SKI-O-592 was more potent than that of R406 in human CD14+ monocytes (38 and 106 nM in half-maximal inhibitory concentration [IC_{50}], respectively). SKI-O-592 also inhibited CD69 expression in Ramos with an IC_{50} value of 189 nM and was more potent than R406, which had an IC_{50} value of 978 nM. Hence, excellent SYK selectivity of SKI-O-592 led to no inhibition of SYK-independent

signal pathways, indicating that SKI-O-592 shows more potent anti-inflammatory activity to allow continuous administration of SKI-O-703 compared with the first-generation SYK inhibitors.

This study will evaluate the safety and efficacy of SKI-O-703 compared with placebo in subjects with active RA who have had an inadequate response to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) or previous 1, 2 or more TNFα inhibitors.

Objectives

Primary Objective

- To evaluate the efficacy of select (100 mg twice daily [BID], 200 mg BID, and 400 mg BID) doses of SKI-O-703 compared with placebo

Secondary Objectives

- To evaluate the efficacy on other clinical endpoints of select (100 mg BID, 200 mg BID, and 400 mg BID) doses of SKI-O-703 compared with placebo
- To evaluate the safety and tolerability of select (100 mg BID, 200 mg BID, and 400 mg BID) doses of SKI-O-703 compared with placebo
- To investigate the pharmacokinetic (PK) profile of SKI-O-592 (the free base of SKI-O-703) and its metabolites (M2 and M4)
- To evaluate the effects of SKI-O-703 on exploratory pharmacodynamic (PD) biomarkers

Exploratory Objectives

- To evaluate the PK/PD relationship between plasma concentrations of SKI-O-592, M2, and M4 and the percent change in activated gp53/CD63+ basophils in peripheral blood

Subject Population

Inclusion Criteria

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

1. Subject is an adult male or female aged ≥18 years old at time of signing the informed consent (or per local customs for ≥19 years of age for Korean subjects).
2. Subject with Body Mass Index (BMI) of ≥18 and <40 kg/m^2 at screening.
3. Subject who has a diagnosis of RA according to the 1987

American College of Rheumatology (ACR) criteria or the 2010 ACR/European League Against Rheumatism classification criteria for at least 6 months prior to Day 1.

4. Subject who has active disease at screening and baseline following treatment of RA with inadequate response to csDMARDs or anti-TNFα biological agent(s) as per 2012 update of the 2008 ACR RA treatment recommendations.
   a. Active disease defined as:
      - presence of ≥5 swollen joints (of 28 assessed) and presence of ≥5 tender joints (of 28 assessed), and
      - serum high sensitivity C-reactive protein (hsCRP) concentration ≥0.6 mg/dL (or ≥6.0 mg/L; 1 mg/L = 9.524 nmol/L) at screening (based on the upper limit of normal [ULN] of laboratory normal range). Repeat may be allowed once during screening period (after an approval from medical monitor), if the result is considered unexplained/unexpected (eg, not corresponding with clinical disease activity or discordant with recent local result).
   b. At least ONE of the following treatments for RA must have been received:
      - anti-TNFα biological agent(s): Includes at least 1 of the following treatments, with completed washout period indicated prior to Day 1 dosing

adalimumab (Humira®)	60 days washout
etanercept (Enbrel®)	30 days washout
infliximab (Remicade®)	60 days washout
certolizumab pegol (Cinzia®)	60 days washout
golimumab (Simponi®)	60 days washout

      - csDMARD therapy: Includes at least 1 of the following dosing regimen for at least 90 days of continuous use (prior to Day 1 dosing)*:
        - MTX 15 to 25 mg/week. If the current MTX dose is <15 mg/week, the subject's intolerance to ≥7.5 mg dose must be documented in the subject's medical history
        - ≤3000 mg/day (3 g/day) sulfasalazine

- ≤400 mg/day hydroxychloroquine
- ≤200 mg/day minocycline
- ≤20 mg/day leflunomide

*Note: Combinations of up to 2 csDMARDs are allowed. However, combination of MTX and leflunomide is not allowed. Subjects are allowed to continue taking csDMARDs therapy at stable doses (initiated ≥4 weeks prior to the first dose of study drug) throughout the study period.

a) If subjects have to discontinue csDMARDs therapy (except for leflunomide), the washout windows of 30 days prior to Day 1 dosing must be observed.

b) If subjects have to discontinue leflunomide due to combination use with MTX before enrollment, the following washout windows must be observed: subjects who discontinued leflunomide and have had successful chelation with 8 g of cholestyramine (3 times daily) for 3 days must wait for 4 weeks prior Day 1 dosing. Subjects who discontinued leflunomide and did not have cholestyramine washout must wait 12 weeks after last dose of leflunomide prior to Day 1 dosing.

5. Subject taking MTX while on study must be willing to take dietary supplement of oral folic acid (or equivalent, such as folinic acid) at a stable dose.
6. Subject who has adequate renal and hepatic function at screening as defined by the following clinical chemistry results:
   a. Serum creatinine <1.5 × ULN or an estimated creatinine clearance level ≤50 mL/min (by MDRD GFR equation)
   b. Serum alanine aminotransferase <2.5 × ULN
   c. Serum aspartate aminotransferase <2.5 × ULN
   d. Serum total bilirubin <2 × ULN

   Repeat of clinical chemistry laboratory tests may be allowed once during screening period (after an approval from medical monitor), if the initial result is unexpected/unexplained (not due to a known underlying condition or concomitant medications or other known cause).

7. Subject who has the following hematology laboratory test results at screening:
    a. Hemoglobin ≥8.5 g/dL (International System of Units [SI] units: ≥85 g/L or 5.28 mmol/L)
    b. White blood cell count ≥3.5 × 103 cells/µL (SI units: ≥3.5 × 109 cells/L)
    c. Neutrophil count ≥1.5 × 103 cells/µL (SI units: ≥1.5 × 109 cells/L)
    d. Platelet count ≥100 × 103 cells/µL (SI units: ≥100 × 109 cells/L)

    Repeat of hematology laboratory tests may be allowed once during screening period (after an approval from medical monitor), if the initial result is unexpected/unexplained (not due to a known underlying condition or concomitant medications or other known cause).
8. Subject who can comprehend the full nature and purpose of the study, including possible risks and side effects, to cooperate with the investigator, to understand verbal and/or written instructions, and to comply with the requirements of the entire study.
9. Subject is informed of the full nature and purpose of the study, including possible risks and side effects, and given ample time and opportunity to read or understand this information, signed and dated the written informed consent before inclusion in the study.
10. A) For both male and female subjects (except subjects in Czech Republic and Republic of Korea), the subject and their partners of childbearing potential must agree to use one of the following medically acceptable methods of contraception during the study and for 6 months following discontinuation of study drug:
    a. Barrier contraceptives (male condom, female condom, or diaphragm with a spermicidal gel)
    b. Hormonal contraceptives (implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings)
    c. Intrauterine device

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 and their partners who have been surgically sterilized for less than 6 months prior to the date of informed consent must agree to use any medically acceptable methods of contraception.

B) For subjects in Czech Republic and Republic of Korea, both male and female subjects must agree to take the following steps to reduce the potential for the 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.

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. Subject is receiving or has previously received any treatment for RA other than the medications listed in the inclusion criteria for the treatment of RA. This includes but not limited to:
   a. Prior exposure to any biological agent other than TNFα inhibitor(s)
   b. Any prior use of SYK or Janus kinase inhibitors
   c. Alkylating agents used within 6 months prior to Day 1 dosing
   d. Prior treatment with intra-articular, intramuscular, intravenous, trigger point or tender point, intra-bursa, or intra-tendon sheath corticosteroids in the proceeding 8 weeks prior to Day 1 dosing.
   e. Any surgical procedure, including bone or joint surgery or synovectomy (including joint fusion or replacement)

within 12 weeks prior to Day 1 dosing.

2. Live or live-attenuated vaccine within 4 weeks prior to Day 1 dosing or expected need for live vaccination during study participation including at least 4 weeks after the last dose of study drug.
3. Subject has had treatment with any other investigational device or medical product within 4 weeks or 5 half-lives prior to Day 1 dosing, whichever is longer.
4. Subject who (based on the investigator's clinical assessment, makes the subject an unsuitable candidate for the study) has any active or recurrent or history of any of the following infections:
    a. Hepatitis B virus (HBV): Serologic evidence of current/previous HBV infection based on the results of testing for hepatitis B surface antigen (HBsAg) and anti-hepatitis B core (anti-HBc) antibody as follows within 6 weeks of Day 1:
        - Subjects positive for HBsAg and/or positive for anti-HBc antibody (regardless of anti-HBs antibody status) are excluded.
    b. Hepatitis C virus (HCV): Positive test for antibody confirmed on a subsequent blood sample by RNA-polymerase chain reaction (PCR) assay within 6 weeks of Day 1.
        - Subjects who are positive for hepatitis C antibody and negative for hepatitis C RNA-PCR assay performed on a subsequent sample will be eligible to participate.
        - Subjects who are positive for hepatitis C antibody and have a positive result for hepatitis C RNA-PCR assay performed on the subsequent sample will not be eligible to participate.
    c. Human immunodeficiency virus (HIV) 1 or 2: Positive test at screening.
    d. Mycobacterium tuberculosis (TB):
        - For subjects with a history of TB, they may be enrolled if the following conditions met:
            - documented evidence of appropriate treatment, which must have been completed at least 4 weeks or 5 half-lives, whichever is longer, prior to Day 1

of dosing,
- have no history of re-exposure since their treatment was completed,
- have no clinical features of active TB, and
- have a screening chest x-ray with no evidence of active TB.

- For subjects with an indeterminate result for interferon-gamma release assay (IGRA) or latent TB (defined as a positive result of IGRA with a negative examination of chest x-ray) at screening, the following conditions must be met:
  - If the result of the IGRA is indeterminate at screening, retest can be performed once during the screening period.
    - If the repeated IGRA result is indeterminate again or positive, the subject will be excluded from the study.
    - If the repeated IGRA result is negative, the subject can be enrolled in the study.
    - Note: QuantiFERON Gold will be tested in central laboratories for all subjects and will determine subject's eligibility with regards to TB.
  - If subjects present with a history of latent TB, they may be enrolled if all of the following conditions are met:
    - have documented evidence of appropriate treatment (TB prophylaxis must have been completed at least 4 weeks or 5 half-lives, whichever is longer, prior to Day 1 of dosing),
    - have no history of re-exposure since their treatment was completed,
    - have no clinical features of active TB, and
    - have a screening chest x-ray with no evidence of active TB.

e. Interstitial pneumonia that is judged by the investigator/subinvestigator to be inappropriate for the subject to participate in this study.

f. Granulomatous infections or other severe or chronic infection (such as sepsis, abscess or opportunistic infections, or invasive fungal infection such as histoplasmosis). A subject who has a past diagnosis with sufficient documentation of complete resolution >6 months prior to Day 1 can be enrolled.

g. Chronic or recurrent infection (including herpes zoster) within 6 weeks prior to Day 1.

h. Acute infection requiring oral antibiotics within 2 weeks or parenteral injection of antibiotics within 4 weeks prior to Day 1.

i. Other serious infection as assessed by the investigator within 6 months prior to Day 1 (such as sepsis, abscess or opportunistic infections, or invasive fungal infection such as histoplasmosis).

5. Subject who has any condition that could confound the evaluation of the data or the effect of the study drug, such as:

   a. Any other inflammatory or rheumatic diseases, including but not limited to psoriatic arthritis, ankylosing spondylitis, spondyloarthritis, systemic lupus erythematosus, Lyme disease, or uncontrolled fibromyalgia. Subjects with inactive or well-controlled fibromyalgia will be allowed to be enrolled in this study if the disease does not impact the study assessments, as per the investigator's judgment. Subjects with Sjogren's disease secondary to RA are eligible.

   b. Any conditions significantly affecting the nervous system (ie, neuropathic conditions or nervous system damage) if it may interfere with the investigator's assessment on disease activity scores including joint counts.

   c. Severe physical incapacitation (unable to perform routine self-care, has RA ACR functional status class 4, or who cannot benefit from medication).

   d. Any other serious acute or chronic medical or psychiatric condition that may increase the risk associated with study participation or study drug administration or that may interfere with the interpretation of study.

6. Subject who currently has one or more of the following medical conditions which in the opinion of the investigator would put the subject at risk by participating in the protocol:

a. Uncontrolled diabetes mellitus, even after insulin treatment.
b. Uncontrolled hypertension (as defined by systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg on >1 occurrence or as judged by investigator).
c. Clinically significant finding meeting any protocol exclusion criteria on chest x-ray. Chest x-ray must be obtained during the screening period, unless a radiograph lung imaging (ultrasound not acceptable) was obtained within 12 weeks prior to the screening visit.
d. Evidence of cardiac conditions as defined by the following:
   - New York Heart Association (NYHA) class III or IV heart failure, severe uncontrolled cardiac disease (unstable angina), or myocardial infarction within the 6 months prior to Day 1.
   - Clinically relevant or significant ECG abnormalities, including ECG and QT interval correction for heart rate (QTc) using Fridericia's correction formula (QTcF). Subject with prolonged QT interval (using QTcF) defined as QTc >450 ms for male and >470 ms for female at retest will be excluded at screening.
e. Any uncontrolled, clinically significant respiratory disease (in the opinion of the investigator), including but not limited to chronic obstructive pulmonary disease, asthma, bronchiectasis, or pleural effusion.

7. Subject who has a history of any of the following medical conditions
   a. Any malignancy within the 5 years prior to Day 1 except completely excised and cured squamous cell carcinoma, carcinoma of the cervix in situ, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma.
   b. Lymphoma or lymphoproliferative disease or bone marrow hyperplasia.
   c. Organ transplantation, including corneal graft/transplantation.
   d. Previous diagnosis or symptoms suggestive of demyelinating disorders, including multiple sclerosis and

Guillain-Barré syndrome.

8. Subject who has planned to receive any of the following prohibited medications or treatment(s) from the time of informed consent through any additional time periods indicated below:
   a. Live or live-attenuated vaccination.
   b. Any surgical procedure, including bone or joint surgery or synovectomy (including joint fusion or replacement) within 6 months after Day 1.
   c. High potency opiates including (but not limited to): oxycodone, oxymorphone, fentanyl, levorphanol, buprenorphine, methadone, hydromorphone, morphine, and meperidine. Subject should discontinue at least 4 weeks prior to Day 1.
9. Subject who has clinically significant (per investigator's judgement) history of drug or alcohol abuse within the last 6 months.
10. Female subject who is currently pregnant, breastfeeding, or planning to become pregnant or breastfeed during the study or within 6 months after the last dose of study drug.

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 (100 mg BID, 200 mg BID, and 400 mg BID) doses of SKI-O-703 in subjects with RA who have had an inadequate response to csDMARDs or anti-TNFα biologic agents. The proportion of subjects who have received previous biologics will be dependent on the enrollment metrics for the study since there are geographic factors that may influence this proportion. Ratio will be approximately 70% csDMARDs to 30% biological therapy.

Approximately 148 subjects are planned to participate in 4 cohorts (37 subjects each). Subjects will be randomly assigned using a 1:1:1:1 ratio to receive one of the three doses of SKI-O-703 (100 mg BID, 200 mg BID, or 400 mg BID) or placebo. Dosing will be twice daily for 12 weeks.

The study will include a 28-day screening period. 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 (12-

lead ECG, physical examination, vital sign measurements, urine pregnancy test, and safety laboratory assessment).

Following predose study procedures, the subject will be randomly assigned to receive either SKI-O-703 or placebo. On Day 1, subjects will undergo predose study procedures and will be randomly assigned to receive either SKI-O-703 or placebo. On Day 1, subject will be administered his/her first dose of study medication no later than 30 minutes after food with approximately 8 ounces (240 mL) of water by the site personnel. The study site personnel will check the subject's mouth to ensure the study drug and entire volume of water was swallowed.

The second dose will be administered approximately 12 hours (±2 hours) after the first dose. The second dose and all subsequent doses will be self-administered by the subject. The subjects will be instructed to take study medication no later than 30 minutes after food.

Estimated Study Duration

The maximum duration of study participation for a subject will be 143 days (approximately 20 weeks), which consists of a screening period of up to 4 weeks (28 days), 12 weeks of dosing (84 days), and a 4-week follow-up period (28 days ± 3 days).

Efficacy Assessments

Primary Endpoints

- Mean change from baseline in disease activity score for 28 joints (DAS28) using hsCRP score (based on 3 individual components including TJC, SJC, and hsCRP) at Week 12

Secondary Endpoints

Secondary endpoints will be evaluated at Weeks 2, 4, 8 and 12 unless otherwise stated.

- Percentage of subjects who would achieve ACR20, ACR50 and ACR70 response over time
- Change from baseline in DAS28-hsCRP score (based on 3 individual components including TJC, SJC, and hsCRP)
- Change from baseline in the tender/painful and swollen joint count (28)
- Change from baseline in the physician global assessment of disease activity by visual analog scale (VAS)
- Change from baseline in the subject global assessment of disease activity by VAS
- Change from baseline in the subject's assessment of

	arthritis pain by VAS • Change from baseline in the health assessment questionnaire - disability index (HAQ-DI) • Change from baseline in median hsCRP values at each visit
Pharmacokinetic Assessments	**Secondary Endpoints** PK parameters of SKI-O-592 and its metabolites (M2 and M4) from a subset of subjects per cohort on Day 1 and at Week 12, including: observed maximum plasma or serum concentration after administration (C_{max}), time to reach the observed maximum (peak) concentration (T_{max}), area under the concentration-time curve within a dosing interval ($AUC_{0\text{-}tau}$), apparent terminal elimination half-life ($t_{1/2}$), terminal elimination rate constant (K_{el}), apparent oral clearance (CL/F) (SKI-O-592 only), apparent oral volume of distribution (V_z/F) (SKI-O-592 only), metabolite ratio (R_{met}), and accumulation ratio based on $AUC_{0\text{-}tau}$ (R_{AUC}), as applicable.
Pharmacodynamic Assessments	The PD variable will be the change from baseline in the percentage of activated gp53/CD63+ basophils in peripheral blood on Day 1 and at Week 12, including: maximum effect (E_{max}), time to achieve maximum effect (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 gp53/CD63+ basophils in peripheral blood on Day 1 and at Week 12.
Safety Assessments	**Secondary Endpoint** Safety and tolerability of SKI-O-703 compared to placebo including laboratory tests, infections, ECGs, vital signs, incidence of AEs, withdrawals due to AEs and serious adverse events (SAEs). Safety variables will include physical examination findings, vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral temperature [tympanic temperature for Korean subjects]), ECG tracings, clinical laboratory test results (hematology, coagulation, serum chemistry, urinalysis, and urine pregnancy test), weight, BMI, and reporting of adverse events. Safety monitoring will begin before dosing on Day 1 and continue through the end-of-study visit (Day 112).

Study Drug, Dosage, and Route of Administration	SKI-O-703 will be administered orally. Three dose levels of SKI-O-703 will be evaluated in separate cohorts: 100 mg BID, 200 mg BID, and 400 mg BID. Fourth cohort will be matching placebo.
Sample Size	At least 148 subjects will be enrolled in 4 cohorts (3 cohorts of SKI-O-703 and 1 cohort of placebo). Each cohort will consist of at least 37 subjects. The study is powered to detect a difference of 0.8 in mean change from baseline to Week 12 in DAS28-hsCRP score between one of the groups treated with SKI-O-703 and the group treated with placebo. At least 37 subjects on a course of SKI-O-703 treatment are required to complete the study to show a change from baseline to Week 12 of 0.80 and higher as statistically significant with a power of 0.80 at the significance level of 0.05, using a 1-way analysis of variance and assuming a standard deviation of 1.25, compared with in the placebo group. Sample size determinations were based on the 4-component DAS28 and are likely to be similar with the 3-component DAS28 with fewer variables. Given the 1:1:1:1 ratio of SKI-O-703 100 mg BID, 200 mg BID, 400 mg BID to placebo allocation, at least 37 subjects in each treatment group are required to complete the study, therefore at least 148 subjects need to be enrolled and randomized in the study. Assuming a drop-out rate of 10%, up to 20 additional subjects may be enrolled to achieve the target number of subjects required to complete the study.
Statistical Methods	Statistical analysis will be performed using SAS® software version 9.3 or later. The primary and secondary endpoints will be repeated for subgroups of the number of previous csDMARDs treatments (0~2 or ≥3), previous 1, 2 or more anti-TNFα biologic agents use (Yes or No), and specific geographic region (APAC, EMEA, and NA). The results for each efficacy endpoint will be summarized by visit and treatment for all subjects within the intention-to-treat (ITT), modified ITT (mITT), and per protocol (PP) set using descriptive statistical methods. Continuous variables will be summarized using the mean, SD, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. Data will be listed in data listings.
Version and Date of Protocol	Version 5.0, Amendment 4; 19 Oct 2020

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List of Abbreviations

Abbreviation	Definition
ACR	American College of Rheumatology
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC_{0-t}	area under the concentration-time curve from zero to the time of the last quantifiable concentration
AUC_{0-tau}	area under the concentration-time curve within a dosing interval
BID	twice daily
CD63	cluster of differentiation 63
CFR	Code of Federal Regulations
csDMARDs	conventional synthetic disease-modifying antirheumatic drugs
C_{max}	observed maximum plasma or serum concentration after administration
CL/F	apparent oral clearance
CV	coefficient of variation
CYP	cytochrome P
DAS	disease activity score
E_{max}	maximum effect
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end-of-study
EOT	end-of-treatment
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HAQ-DI	health assessment questionnaire-disability index
anti-HBc	anti-hepatitis B core
HBsAg	hepatitis B surface antigen

Abbreviation	Definition
HCV	hepatitis C virus
HIV	human immunodeficiency virus
hsCRP	high sensitivity C-reactive protein
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IgE	immunoglobulin E
IGRA	interferon-gamma release assay
IND	investigational new drug
IRB	institutional review board
ITT	intention-to-treat
IxRS	interactive voice or web response system
K_{el}	terminal elimination rate constant
LOCF	last observation carried forward
MCP	metacarpophalangeal
MTX	methotrexate
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention-to-treat
NOAEL	no observed adverse effect level
NRI	nonresponder imputation
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PIP	proximal interphalangeal
PK	pharmacokinetic(s)
PP	per protocol
PVG	pharmacovigilance
QD	once daily
QTc	QT interval correction for heart rate
QTcF	QT interval correction for heart rate (QTc) using Fridericia's correction formula
RA	rheumatoid arthritis
R_{met}	metabolite ratio

Abbreviation	Definition
R_{AUC}	accumulation ratio based on $AUC_{0\text{-}tau}$
SI	International System of Units
SAE	serious adverse event
SJC	swollen joint count
SUSARs	suspected unexpected serious adverse reactions
SYK	spleen tyrosine kinase
$t_{1/2}$	apparent terminal elimination half-life
TB	tuberculosis
TJC	tender joint count
TEAE	treatment-emergent adverse event
TE_{max}	time to achieve maximum effect
T_{max}	time to reach the observed maximum (peak) concentration
TNFα	tumor necrosis factor alpha
ULN	upper limit of normal
US	United States
VAS	visual analog scale
V_z/F	apparent oral volume of distribution

1 Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune polyarthritis that affects approximately 1% of the world's population (Lee and Weinblatt 2001), including 1.3 million people in the United States (Helmick et al 2008). Although RA is primarily a disease of the joints, it is a multisystem disease and other organ systems can be affected.

Treatment guidelines from the European League Against Rheumatism (EULAR) (Smolen et al 2014) and American College of Rheumatology (ACR) (Singh et al 2012) are similar: methotrexate (MTX), a nonbiologic disease-modifying antirheumatic drug, alone and in combinations with other agents, remains the mainstay of disease-modifying therapy for patients with RA. Biologic disease-modifying antirheumatic drugs, notably tumor necrosis factor alpha (TNFα) inhibitors due to their established efficacy and safety profiles, can reduce signs and symptoms of RA, induce a major clinical response, and provide protection against structural damage. A subset of patients has demonstrated an inadequate response to anti-TNF drugs, and some patients initially respond to anti-TNF therapy but experience a loss of efficacy over time. Despite recent advances, there is still a medical need for alternative RA treatments for patients with inadequate responses, who show intolerance to conventional nonbiologic therapies, such as MTX, or whose disease is refractory to treatment with biologic products, particularly widely used TNF inhibitors (Cohen et al 2006; Emery et al 2008; Smolen et al 2009).

Spleen tyrosine kinase (SYK) is a nonreceptor tyrosine kinase known to have a crucial role in immune receptor signaling. A number of studies have revealed that aberrant SYK activation is associated with diverse allergic disorders and antibody-mediated autoimmune diseases such as RA, asthma, and allergic rhinitis.

Spleen tyrosine kinase is broadly involved in regulating leukocyte immune function, principally by facilitating cellular activation in response to receptor engagement of an 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; Zarbock et al 2008). As such, specific inhibition of SYK has the potential to control B-cell antibody response to antigens as well as the downstream effector functions of mast cells, basophils, neutrophils, eosinophils, macrophages, dendritic cells, and platelets (Mócsai et al 2010). Targeting SYK therefore

represents a multifaceted approach to the modulation of immune function at several points of intervention, making it a potentially unique target for drug development (Coffey et al 2012).

The novel small-molecule SYK inhibitor SKI-O-592 (the free base of SKI-O-703) has demonstrated high selectivity and potency against SYK in a biochemical assay. For immunoreceptor activation linked to SYK, the effect of SKI-O-592 on the anti-inflammatory response consisting of TNFα, β-hexosaminidase, and cluster of differentiation (CD)69 expression was greater than the effects of first-generation SYK inhibitors (eg, R406) in several immune cell lines and in human primary cells. This anti-inflammatory activity was responsible for the selective inhibition of p-SYK (Y525/526), which led to the sequential inhibition of downstream effectors. More importantly, the inhibitory activity of SKI-O-592 was more potent than that of R406 in human CD14+ monocytes (38 and 106 nM in half-maximal inhibitory concentration [IC_{50}], respectively). SKI-O-592 also inhibited CD69 expression in Ramos with an IC_{50} value of 189 nM and was more potent than R406, which had an IC_{50} value of 978 nM. Hence, excellent SYK selectivity of SKI-O-592 led to no inhibition of SYK-independent signal pathways, indicating that SKI-O-592 shows more potent anti-inflammatory activity to allow continuous administration of SKI-O-703 compared with the first-generation SYK inhibitors.

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 study (OSCO-P1201) and a multiple ascending dose study (OSCO-P1202) in healthy subjects.

Safety

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 after receiving SKI-O-703 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- 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 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 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.

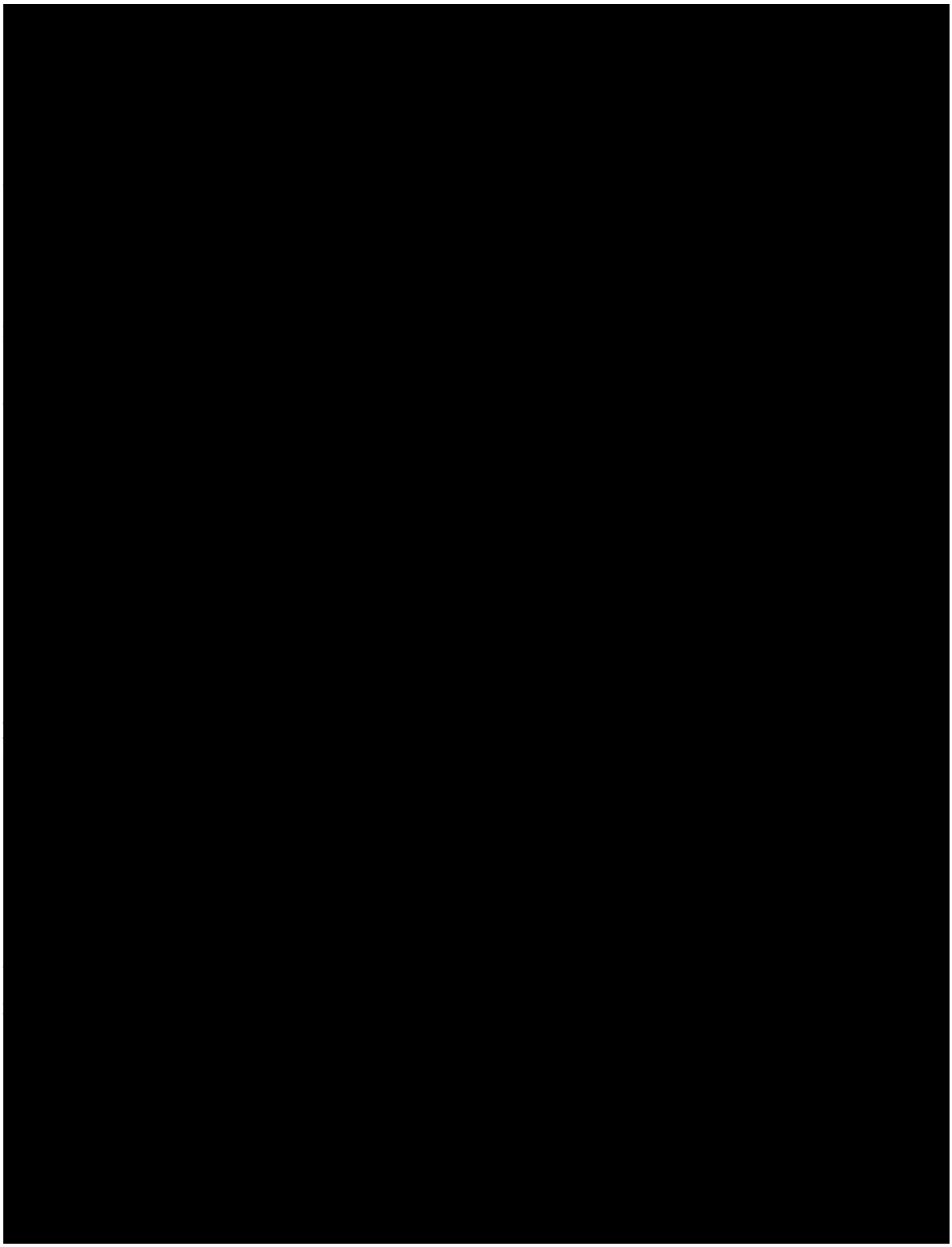
Pharmacokinetics

Pharmacodynamics

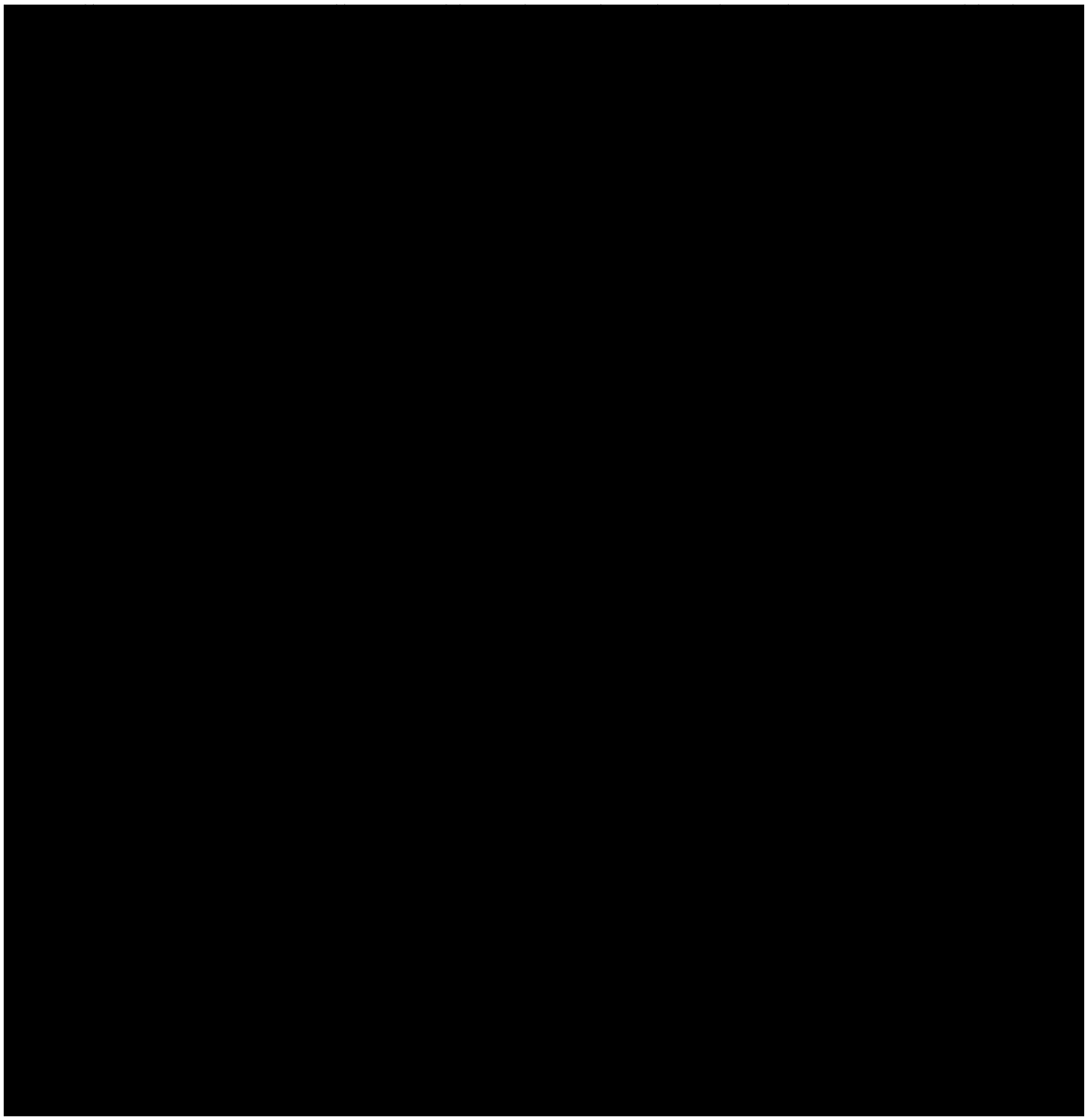
1.2 Nonclinical Studies

1.2.1 Pharmacology, Pharmacokinetics, and Toxicology Summary

Nonclinical Pharmacology



Nonclinical Pharmacokinetics and Toxicokinetics



Nonclinical Toxicology

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-hour period) following twice-daily dosing at 200 mg. As the maximum PD response was very similar across all 3 of these dosing regimens, a wider dose range (100 mg to 400 mg BID) has been selected in this Phase 2 study to fully explore changes in PD markers over a wider range, and, as the PD effect was sustained for longer after twice-daily dosing compared to once-daily dosing, twice-daily dosing 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 (R_{met}) 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 (100 mg BID, 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.

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-t} and AUC_{0-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 hour 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 (ie, high C_{max}) in SKI-O-592, M2 and M4.

1.4 Placebo Rationale

The proposed study is a placebo-controlled, double-blind study of oral SKI-O-703 coadministered with background therapies for RA. The double-blind, placebo-controlled, randomized clinical study design is considered the gold standard for the safety and efficacy assessment of a new therapy both by clinicians and regulatory authorities. In this study subjects will be allowed to receive background medications for RA, including MTX, and other oral DMARDs, therefore subjects are also allowed to receive permitted concomitant medications in line with current standard of care (SOC) practices for RA. Any subject who cannot adhere to the protocol or who discontinues treatment will have an end-of-treatment (EOT) 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 study (OSCO-P1201) and a multiple ascending dose 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 AEs were mild to moderate in intensity.

The identified potential risks associated with SKI-O-703 were formulated based on nonclinical data and the SKI-O-703 mechanism of action, and include immune system effects, gastrointestinal effects, liver enzyme changes, and cardiovascular effects. Based on the clinical information received from Study OSCO-P1201 and Study OSCO-P1202, the risk of gastrointestinal effects was updated and headache was included as an important potential risk.

The information is in line with the expected side effects of treatment with SKI-O-703. The proposed safety monitoring is deemed to be sufficient to monitor potential risks of SKI-O-703 administration.

Based upon 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

The primary objective of this study is to evaluate the efficacy of select (100 mg BID, 200 mg BID, and 400 mg BID) doses of SKI-O-703 compared with placebo in subjects with active RA who have had an inadequate response to conventional synthetic disease modifying antirheumatic drugs (csDMARDs) or previous 1, 2 or more anti-TNFα biologic agents.

2.2 Secondary Objectives

The secondary objectives of this study are as follows:

- To evaluate the efficacy on other clinical endpoints of select (100 mg BID, 200 mg BID, and 400 mg BID) doses of SKI-O-703 compared with placebo in subjects with active RA who have had an inadequate response to csDMARDs or previous 1, 2 or more anti-TNFα biologic agents.

- To evaluate the safety and tolerability of select (100 mg BID, 200 mg BID, and 400 mg BID) doses of SKI-O-703 compared with placebo in subjects with active RA who have had an inadequate response to csDMARDs or previous 1, 2 or more anti-TNFα biologic agents.

- To investigate the PK profile of SKI-O-592 (the free base of SKI-O-703) and its metabolites (M2 and M4) in subjects with active RA who have had an inadequate response to csDMARDs or previous 1, 2 or more anti-TNFα biologic agents.

- To evaluate the effects of SKI-O-703 on exploratory PD biomarkers (ie, the percentage of activated gp53/CD63+ basophils in peripheral blood) in subjects with active RA who have had an inadequate response to csDMARDs or previous 1, 2 or more anti-TNFα biologic agents.

2.3 Exploratory Objective

The exploratory objective of this study is as follows:

- To evaluate the PK/PD relationship between plasma concentrations of SKI-O-592, M2, and M4 and the percent change in activated gp53/CD63+ basophils in peripheral blood in subjects with active RA who have had an inadequate response to csDMARDs or previous 1, 2 or more anti-TNFα biologic agents.

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 (100 mg BID, 200 mg BID, and 400 mg BID) doses of SKI-O-703 in subjects with RA who have had an inadequate response to csDMARDs or anti-TNFα biologic agents. The proportion of subjects who have received previous biologics will be dependent on the enrollment metrics for the study since there are geographic factors that may influence this proportion. Ratio will be approximately 70% csDMARDs to 30% biological therapy.

Approximately 148 subjects are planned to participate in 4 cohorts (37 subjects each). Subjects will be randomly assigned using a 1:1:1:1 ratio to receive one of the three doses of SKI-O-703 (100 mg BID, 200 mg BID, or 400 mg BID) or placebo. Dosing will be twice daily for 12 weeks.

A schematic diagram of the overall study design is presented in Figure 3-1.

Figure 3-1 Study Design Schematic

<table>
<tr><td>Screening Period (up to 28 days)</td><td colspan="8">12-Week Treatment Period (Double-Blind) 1:1:1:1</td><td>Follow-up (EOT+14 days)</td><td>EOS (EOT+28 days)</td></tr>
<tr><td></td><td colspan="8">100 mg BID
200 mg BID
400 mg BID
Placebo BID</td><td></td><td></td></tr>
<tr><td>Week</td><td>0 [a]</td><td>2</td><td>4</td><td>6</td><td>8</td><td>10</td><td>12</td><td></td><td>14</td><td>16</td></tr>
<tr><td>Visit</td><td>1</td><td>2</td><td>3</td><td></td><td>4</td><td></td><td>5 (EOT)</td><td></td><td>6</td><td>7</td></tr>
</table>

Abbreviation: BID, twice daily; EOT, end-of-Treatment; EOS, end-of-Study
[a] randomization

Screening Period

The study will include screening period of up to 28 days. All potential subjects will sign and date the informed consent form (ICF) prior to any study assessments or procedures. Potential subjects will be assessed as per the eligibility criteria at screening. Medical history and concomitant medications will be recorded. After completing all screening assessments, subjects who meet all the inclusion and none of the exclusion criteria will proceed to the treatment period.

Randomization: Study Day 1

On Day 1, the subject should complete the Patient's Global Assessment of Disease Activity, the Patient's Assessment of Pain, and the Health assessment questionnaire before site personnel perform any clinical assessments. These should also be completed before any interaction with site personnel has occurred to avoid biasing the subject's response. After that subject's eligibility will be confirmed and baseline safety evaluations will be performed (12-lead ECG, physical examination, vital sign measurements, weight, urine pregnancy test, and safety laboratory assessment). Following predose study procedures, the subject will be randomly assigned to receive either SKI-O-703 or placebo. On Day 1, subject will be administered his/her first dose of study medication no later than 30 minutes after food with approximately 8 ounces (240 mL) of water by the site personnel. The study site personnel will check the subject's mouth to ensure the study drug and entire volume of water was swallowed.

A subset of subjects from each cohort who provide additional consent will be subjected to additional PK and PD assessments according to the Schedule of Events (Table 6-1). Due to PD assay limitations, PK and PD sampling will only be performed at selected sites that are deemed suitable to support PK/PD assessment (ie, which are within an acceptable shipping distance from a PD laboratory). Every effort will be made to achieve a minimum of 24 subjects (6 subjects per treatment group) in the PK/PD subgroup. It is important to note that there is no upper limit to the number of subjects that will be enrolled to the PK/PD subgroup in any region (as many subjects will be assigned to the PK/PD subgroup as is practical), and the number of subjects does not need to be identical between treatment groups; however, every effort will be made to ensure that the number of subjects enrolled to each treatment group is similar.

The second dose will be administered approximately 12 hours (±2 hours) after the first dose. The second dose and all subsequent doses will be self-administered by the subject. The subjects will be instructed to take study medication no later than 30 minutes after food.

12-week Treatment Period

Subjects will return to the clinic for routine safety and disease state review as outlined in the Schedule of Events (Table 6-1), with a ±3 days window for all visits after randomization. During the visits, the subject will undergo the following procedures at the timepoints specified in the Schedule of Events: vital sign measurements, urine pregnancy test (for WOCBP only), routine safety laboratory sampling, disease state analysis (hsCRP sampling, joint counts, and ACR assessments), IMP accountability and dispensation, 12-lead ECG, concomitant medication review, and AE review.

The subject should complete the Patient's Global Assessment of Disease Activity, the Patient's Assessment of Pain, and the Health assessment questionnaire before site personnel perform any clinical assessments. These should also be completed before any interaction with site personnel has occurred to avoid biasing the subject's response.

4-week Follow-up Period

After the EOT visit, subjects will complete a 4-week follow-up period. The subject will undergo following procedures at the timepoints specified in the Schedule of Events: vital sign and weight measurements, urine pregnancy test (for WOCBP only), routine safety laboratory sampling, disease state analysis (hsCRP sampling, joint counts, and ACR assessments), 12-lead ECG, concomitant medication review, and AE review.

The subject should complete the Patient's Global Assessment of Disease Activity, the Patient's Assessment of Pain, and the Health assessment questionnaire before site personnel perform any clinical assessments. These should also be completed before any interaction with site personnel has occurred to avoid biasing the subject's response.

The maximum duration of study participation for a subject will be 143 days (approximately 20 weeks), which consists of a screening period of up to 4 weeks (28 days), 12 weeks of dosing (84 days), and a 4-week follow-up period (28 days ± 3 days).

3.1.1 Dose Interruption and Reduction

Adverse Events:

It is recognized that some AEs may require dose adjustment or study drug discontinuation. Guidelines for dose reduction are outlined in Table 3-1.

Table 3-1 Guidelines for Dose Interruption and Reduction[a]

AE	Occurrence[b]	Action
ALT or AST elevations (range 3 to 5 × ULN) or ALP >3 × ULN and >2 × baseline	First	• If asymptomatic (no nausea, anorexia, vomiting), repeat test within 72 hours[c] 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 csDMARDs and study drug. Follow the subject weekly until symptoms abate and values return to baseline per confirmation from central laboratory, at which time csDMARDs may be restarted at the prior dose and study drug may be restarted at a reduced dose by skipping one of the doses. **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 <1500/mm^3 or <1.50 × 10^9/L	First	Study drug must be withheld. Repeat the test weekly until value return to baseline or ≥1500/mm^3 or ≥1.5 × 10^9/L, and then restart at a reduced dose by skipping one of the doses.
	Second	Discontinue study drug permanently if the intolerance reoccurs or persists.
Sustained increased systolic (>170 mm Hg) or sustained increased diastolic (>100 mm Hg) blood pressure in a previously normotensive subject	First	Study drug may be withheld and then restarted at a reduced dose by skipping one of the doses. **Irrespective of study drug dose adjustment, subjects who develop a sustained increased systolic (>140 mm Hg) or a sustained increased diastolic (>90 mm Hg) blood pressure should be started on antihypertensive medications (ie, diuretics, calcium channel blockers, ACE inhibitors, etc.) 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	First	Study drug may be withheld and then restarted at a reduced dose by skipping one of the doses.

AE	Occurrence[b]	Action
	Second	Discontinue study drug permanently if the intolerance reoccurs or persists.
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 PI 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; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; ECG, electrocardiogram; MOA, mechanism of action; PI, principal investigator; QTcF, QT interval correction for heart rate (QTc) using Fridericia's correction 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] First/second occurrence relates to AE; abnormalities at repeat tests during monitoring of an AE are considered to belong to the same event (AE).

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

Subject Error

If the subject does not take his/her study drug dose at regularly scheduled dosing time, he/she should take the dose as soon as possible but at least 8 hours before the next scheduled dose. If the next scheduled dose is within the 8 hours window, the dose is considered missed, and the subject should resume dosing with the subsequent dose on the original schedule.

If the subject experiences any drug interruption(s) he/she should notify their study site physician during the next scheduled study visit. 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.

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 subjects with RA who have had an inadequate response to csDMARDs or previous 1, 2 or more TNFα inhibitors. The results of this study will guide on further clinical evaluation of SKI-O-703 in adult subjects with moderately to severely active RA. The double-blind, placebo-controlled design has been selected to minimize bias in the evaluation of the safety, efficacy, PK, and PD.

Serial blood samples (5 mL) for PK assessment of SKI-O-592 and its metabolites (M2 and M4) from a subset of 6 subjects per cohort will be obtained from this study, which is common approach in Phase 2 studies for PK sampling. Full PK profile from subset of subjects in this study would help to define the underlying structure of the PK model, 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 2 most widely used sets of improvement criteria in clinical trials are the ACR improvement criteria using all 7 core set variables, and the EULAR response criteria based on the disease activity score (DAS), an index using only 3 or 4 core set variables. Studies in RA have interchangeably used these outcome measures as primary endpoints in clinical trials. Including more variables in a combined index such as the ACR does not increase the validity of these outcome measures (van Gestel et al 1999). The performance of the EULAR criteria and the ACR improvement criteria has been compared in different clinical trials (Prevoo et al 1995). It was shown that they behave similarly with less than 5% discrepancy in responder status.

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%) 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. Continuous variables are

significantly better suited to improving statistical power in small trials than dichotomous variables.

In this study, DAS28- high sensitivity C-reactive protein (hsCRP) is selected as the primary endpoint since it is a continuous variable whereas ACR20 is a dichotomous variable. Statistical implications of using a dichotomous variable requires more subjects of any study to show a difference, but for smaller studies such as a Phase 2 study, it would be better powered using a continuous endpoint minimizing the sample size to achieve a primary endpoint of DAS28-hsCRP.

4 Subject Selection and Withdrawal Criteria

4.1 Selection of Study Population

Approximately 148 subjects will be enrolled at multiple sites in the United States, Europe, and South Korea. Subjects will be assigned to study treatment 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 subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

If a subject fails one or more inclusion or exclusion criteria, one re-screening attempt is allowed per subject.

4.1.1 Inclusion Criteria

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

1. Subject is an adult male or female aged ≥18 years old at time of signing the informed consent (or per local customs for ≥19 years of age for Korean subjects).

2. Subject has Body Mass Index (BMI) of ≥18 and <40 kg/m^2 at screening.

3. Subject who has a diagnosis of RA according to the 1987 ACR criteria (Appendix 13.2) or the 2010 ACR/EULAR classification criteria (Appendix 13.3) for at least 6 months prior to Day 1.

4. Subject has active disease at screening and baseline following treatment of RA with inadequate response to csDMARDs or anti-TNFα biological agent(s) as per 2012 update of the 2008 ACR RA treatment recommendations (Singh JA 2012).
    a. Active disease is defined as:
        - presence of ≥5 swollen joints (of 28 assessed) and presence of ≥5 tender joints (of 28 assessed), and
        - serum hsCRP concentration ≥0.6 mg/dL (or ≥6.0 mg/L; 1 mg/L = 9.524 nmol/L) at screening (based on the upper limit of normal [ULN] of laboratory normal

range). Repeat may be allowed once during screening period (after an approval from medical monitor), if the result is considered unexplained/unexpected (eg, not corresponding with clinical disease activity or discordant with recent local result).

b. At least ONE of the following treatments for RA must have been received:

- anti-TNFα biological agent(s): Includes at least 1 of the following treatments, with completed washout period indicated prior to Day 1 dosing

adalimumab (Humira®)	60 days washout
etanercept (Enbrel®)	30 days washout
infliximab (Remicade®)	60 days washout
certolizumab pegol (Cinzia®)	60 days washout
golimumab (Simponi®)	60 days washout

- csDMARD therapy: Includes at least 1 of the following dosing regimen for at least 90 days of continuous use (prior to Day 1 dosing)*
  - MTX 15 to 25 mg/week. If the current MTX dose is <15 mg/week, the subject's intolerance to ≥7.5 mg dose must be documented in the subject's medical history
  - ≤3000 mg/day (3 g/day) sulfasalazine
  - ≤400 mg/day hydroxychloroquine
  - ≤200 mg/day minocycline
  - ≤20 mg/day leflunomide

    *Note: Combinations of up to 2 csDMARDs are allowed. However, combination of MTX and leflunomide is not allowed. Subjects are allowed to continue taking csDMARD therapy at stable doses (initiated ≥4 weeks prior to the first dose of study drug) throughout the study period.

    a) If subjects have to discontinue csDMARD therapy (except for leflunomide), the washout windows 30 days prior to Day 1 dosing must be observed.

b) If subjects have to discontinue leflunomide due to combination use with MTX before enrollment, the following washout windows must be observed: subjects who discontinued leflunomide and have had successful chelation with 8 g of cholestyramine (3 times daily) for 3 days must wait for 4 weeks prior Day 1 dosing. Subjects who discontinued leflunomide and did not have cholestyramine washout must wait 12 weeks after last dose of leflunomide prior to Day 1 dosing.

5. Subjects taking MTX while on study must be willing to take dietary supplement of oral folic acid (or equivalent, such as folinic acid) at a stable dose.

6. Subject who has adequate renal and hepatic function at screening as defined by the following clinical chemistry results:
    a. Serum creatinine <1.5 × ULN or an estimated creatinine clearance level ≤50 mL/min (by MDRD GFR equation)
    b. Serum alanine aminotransferase (ALT) <2.5 × ULN
    c. Serum aspartate aminotransferase (AST) <2.5 × ULN
    d. Serum total bilirubin <2 × ULN.

Repeat of clinical chemistry laboratory tests may be allowed once during screening period (after an approval from medical monitor), if the initial result is unexpected/unexplained (not due to a known underlying condition or concomitant medications or other known cause).

7. Subject who has the following hematology laboratory test results at screening:
    a. Hemoglobin ≥8.5 g/dL (International System of Units [SI]: ≥85 g/L or 5.28 mmol/L)
    b. White blood cell count ≥3.5 × 10^3 cells/μL (SI units: ≥3.5 × 10^9 cells/L)
    c. Neutrophil count ≥1.5 × 10^3 cells/μL (SI units: ≥1.5 × 10^9 cells/L)
    d. Platelet count ≥100 × 10^3 cells/μL (SI units: ≥100 × 10^9 cells/L).

Repeat of hematology laboratory tests may be allowed once during screening period (after an approval from medical monitor), if the initial result is unexpected/unexplained (not due to a known underlying condition or concomitant medications or other known cause).

8. Subject who can comprehend the full nature and purpose of the study, including possible risks and side effects, to cooperate with the investigator, to understand verbal and/or written instructions, and to comply with the requirements of the entire study.

9. Subject is informed of the full nature and purpose of the study, including possible risks and side effects, and given ample time and opportunity to read or understand this information, signed and dated the written informed consent before inclusion in the study.

10. A) For both male and female subjects (except subjects in Czech Republic and Republic of Korea), the subject and their partners of childbearing potential must agree to use one of the following medically acceptable methods of contraception during the study and for 6 months following discontinuation of study drug:

    a. Barrier contraceptives (male condom, female condom, or diaphragm with a spermicidal gel).

    b. Hormonal contraceptives (implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings).

    c. Intrauterine device.

    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 and their partners who have been surgically sterilized for less than 6 months prior to the date of informed consent must agree to use any medically acceptable methods of contraception.

    B) For subjects in Czech Republic and Republic of Korea, both male and female subjects must agree to take the following steps to reduce the potential for the 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.

   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

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

1. Subject is receiving or has previously received any treatment for RA other than the medications listed in the inclusion criteria for the treatment of RA. This includes but not limited to:
    a. Prior exposure to any biological agent other than TNFα inhibitor(s).
    b. Any prior use of SYK or Janus kinase (JAK) inhibitors.
    c. Alkylating agents used within 6 months prior to Day 1 dosing.
    d. Prior treatment with intra-articular, intramuscular, intravenous, trigger point or tender point, intra-bursa, or intra-tendon sheath corticosteroids in the proceeding 8 weeks prior to Day 1 dosing.
    e. Any surgical procedure, including bone or joint surgery or synovectomy (including joint fusion or replacement) within 12 weeks prior to Day 1 dosing.
2. Live or live-attenuated vaccine within 4 weeks prior to Day 1 dosing or expected need for live vaccination during study participation including at least 4 weeks after the last dose of study drug.
3. Subject has had treatment with any other investigational device or medical product within 4 weeks or 5 half-lives prior to Day 1 dosing, whichever is longer.
4. Subject who (based on the investigator's clinical assessment, makes the subject an unsuitable candidate for the study) has any active or recurrent or history of any of the following infections:

a. Hepatitis B virus (HBV): Serologic evidence of current/previous HBV infection based on the results of testing for hepatitis B surface antigen (HBsAg) and anti-hepatitis B core (anti-HBc) antibody as follows within 6 weeks of Day 1:

   - Subjects positive for HBsAg and/or positive for anti-HBc antibody (regardless of anti-HBs antibody status) are excluded.

b. Hepatitis C virus (HCV): Positive test for antibody confirmed on a subsequent blood sample by RNA-PCR assay within 6 weeks of Day 1.

   - Subjects who are positive for hepatitis C antibody and negative for hepatitis C RNA-PCR assay performed on a subsequent sample will be eligible to participate.
   - Subjects who are positive for hepatitis C antibody and have a positive result for hepatitis C RNA-PCR assay performed on the subsequent sample will not be eligible to participate.

c. Human immunodeficiency virus (HIV) 1 or 2: Positive test at screening.

d. Mycobacterium tuberculosis (TB):

   - For subjects with a history of TB, they may be enrolled if the following conditions met:
     - documented evidence of appropriate treatment, which must have been completed at least 4 weeks or 5 half-lives, whichever is longer, prior to Day 1 of dosing,
     - have no history of re-exposure since their treatment was completed,
     - have no clinical features of active TB, and
     - have a screening chest x-ray with no evidence of active TB.

   - For subjects with an indeterminate result for interferon-gamma release assay (IGRA) or latent TB (defined as a positive result of IGRA with a negative examination of chest x-ray) at screening, the following conditions must be met:
     - If the result of the IGRA is indeterminate at screening, retest can be performed once during the screening period.

- If the repeated IGRA result is indeterminate again or positive, the subject will be excluded from the study.
- If the repeated IGRA result is negative, the subject can be enrolled in the study.
- Note: QuantiFERON Gold will be tested in central laboratories for all subjects and will determine subject's eligibility with regards to TB.

- If subjects present with a history of latent TB, they may be enrolled if all of the following conditions are met:

  - have documented evidence of appropriate treatment (TB prophylaxis must have been completed at least 4 weeks or 5 half-lives, whichever is longer, prior to Day 1 of dosing),
  - have no history of re-exposure since their treatment was completed,
  - have no clinical features of active TB, and
  - have a screening chest x-ray with no evidence of active TB.

e. Interstitial pneumonia that is judged by the Investigator/subinvestigator to be inappropriate for the subject to participate in this study.

f. Granulomatous infections or other severe or chronic infection (such as sepsis, abscess or opportunistic infections, or invasive fungal infection such as histoplasmosis). A subject who has a past diagnosis with sufficient documentation of complete resolution >6 months prior to Day 1 can be enrolled.

g. Chronic or recurrent infection (including herpes zoster) within 6 weeks prior to Day 1.

h. Acute infection requiring oral antibiotics within 2 weeks or parenteral injection of antibiotics within 4 weeks prior to Day 1.

i. Other serious infection as assessed by the investigator within 6 months prior to Day 1 (such as sepsis, abscess or opportunistic infections, or invasive fungal infection such as histoplasmosis).

5. Subject who has any condition that could confound the evaluation of the data or the effect of the study drug, such as:

a. Any other inflammatory or rheumatic diseases, including but not limited to psoriatic arthritis, ankylosing spondylitis, spondyloarthritis, systemic lupus erythematosus, Lyme disease, or uncontrolled fibromyalgia. Subjects with inactive or well-controlled fibromyalgia will be allowed to be enrolled in this study if the disease does not impact the study assessments, as per the investigator's judgement. Subjects with Sjogren's disease secondary to RA are eligible.

b. Any conditions significantly affecting the nervous system (ie, neuropathic conditions or nervous system damage) if it may interfere with the investigator's assessment on DAS including joint counts.

c. Severe physical incapacitation (unable to perform routine self-care, has RA ACR functional status class 4 [Arnett et al 1988], or who cannot benefit from medication).

d. Any other serious acute or chronic medical or psychiatric condition that may increase the risk associated with study participation or study drug administration or that may interfere with the interpretation of study.

6. Subject who currently has one or more of the following medical conditions which in the opinion of the investigator would put the subject at risk by participating in the protocol:

   a. Uncontrolled diabetes mellitus, even after insulin treatment.

   b. Uncontrolled hypertension (as defined by systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg on >1 occurrence or as judged by the investigator).

   c. Clinically significant finding meeting any protocol exclusion criteria on chest x-ray. Chest x-ray must be obtained during the screening period, unless a radiograph lung imaging (ultrasound not acceptable) was obtained within 12 weeks prior to the screening visit.

   d. Evidence of cardiac conditions as defined by the following:

      - New York Heart Association (NYHA) class III or IV heart failure, severe uncontrolled cardiac disease (unstable angina), or myocardial infarction within the 6 months prior to Day 1.

- Clinically relevant or significant ECG abnormalities, including ECG and QT interval correction for heart rate (QTc) using Fridericia's correction formula (QTcF). Subject with prolonged QT interval (using QTcF) defined as QTc >450 ms for male and >470 ms for female at retest will be excluded at screening.

e. Any uncontrolled, clinically significant respiratory disease (in the opinion of the investigator), including but not limited to chronic obstructive pulmonary disease, asthma, bronchiectasis, or pleural effusion.

7. Subject who has a history of any of the following medical conditions:

   a. Any malignancy within the 5 years prior to Day 1, except completely excised and cured squamous cell carcinoma, carcinoma of the cervix in situ, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma.

   b. Lymphoma or lymphoproliferative disease or bone marrow hyperplasia.

   c. Organ transplantation, including corneal graft/transplantation.

   d. Previous diagnosis or symptoms suggestive of demyelinating disorders, including multiple sclerosis and Guillain-Barré syndrome.

8. Subject who has planned to receive any of the following prohibited medications or treatment(s) from the time of informed consent through any additional time periods indicated below:

   a. Live or live-attenuated vaccination.
   b. Any surgical procedure, including bone or joint surgery or synovectomy (including joint fusion or replacement) within 6 months after Day 1.
   c. High potency opiates including (but not limited to): oxycodone, oxymorphone, fentanyl, levorphanol, buprenorphine, methadone, hydromorphone, morphine, and meperidine. Subject should discontinue at least 4 weeks prior to Day 1.

9. Subject who has clinically significant (per investigator's judgment) history of drug or alcohol abuse within the last 6 months.

10. Female subject who is currently pregnant, breastfeeding, or planning to become pregnant or breastfeed during the study or within 6 months after the last dose of study drug.

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

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.

    - 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.

2. Pregnancy.

    - If a female subject becomes pregnant, she must discontinue study drug immediately.

3. A serious or intolerable adverse event(s) (AE[s]) that in the Investigator's opinion requires withdrawal from the study.

    - Upon occurrence of a serious or intolerable AE that in the investigator's opinion requires withdrawal from the study, 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.

4. Laboratory safety assessments that reveal clinically significant hematological or biochemical changes from the baseline values.

5. Symptoms or an intercurrent condition not consistent with the protocol requirements or that justifies withdrawal (eg, development of contraindications of use of study drug).

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. Death of the subject.

8. Early termination of the study by the sponsor.

9. The subject withdraws consent.

4.2.2 Handling of Withdrawals

Subjects who discontinue study treatment or active participation in the study will no longer receive study drug. When a subject withdraws from the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the eCRF. Whenever possible, all subjects who discontinue study drug or withdraw from the study prematurely will undergo all end-of-study assessments.

Subject who choose to discontinue study drug treatment but continue to participate in the study should complete end of treatment visit as soon possible, preferably within 2 weeks. Afterwards, subjects should follow the regular visit schedule and adhere to all study procedures except for dispensing study drug and blood sample collection for optional exploratory research and validation studies.

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 serious AE (SAE). In every case, efforts must be made to undertake protocol-specified, safety, follow-up procedures.

4.2.3 Replacements

The subjects who are randomized but not dosed will be replaced; replacement will be accomplished by randomizing one more subject in a sequential order. Subjects who are randomized and received at least 1 dose of study drug will not be replaced.

5 Study Treatments

Three dose levels of SKI-O-703 will be evaluated in separate cohorts: 100 mg BID, 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 and magnesium stearate to match in color and weight.

5.1 Method of Assigning Subjects to Treatment Groups

Subjects will be randomly assigned in a 1:1:1:1 ratio to receive SKI-O-703 100 mg BID, 200 mg BID, 400 mg BID, or matching placebo. An interactive voice or web response system (IxRS) will be used to administer the randomization schedule. The randomization schedule will be generated using SAS software version 9.3 or later (SAS Institute Inc., Cary, North Carolina) for IxRS, which will link sequential subject randomization numbers to treatment codes. The randomization schedule will be stratified by prior anti-TNFα biologic agents use (Yes or No), the number of previous csDMARDs treatments (0~2 or ≥3), specific geographic region (APAC, EMEA, and NA), and PK/PD sampling (Yes or No). 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 (PI) at the study site. The study drugs will be similar in number and appearance for each cohort to maintain the study blind. The following dosing scheme will be performed:

Cohort	Treatment Arm	Treatment per Dosing Timepoint	
		Placebo Capsule	SKI-O-703 100 mg Capsule
1	Placebo	4	-
2	SKI-O-703 100 mg	3	1
3	SKI-O-703 200 mg	2	2
4	SKI-O-703 400 mg	-	4

SKI-O-703 100 mg BID, 200 mg BID, 400 mg BID, and placebo will be administered orally. The study medication will be taken no later than 30 minutes after food.

Day 1 Dosing:

On Day 1, subject will be administered his/her first dose of study medication no later than 30 minutes after food with approximately 8 ounces (240 mL) of water by the study site personnel. The study site personnel will check the subject's mouth to ensure the study drug and entire volume of water was swallowed.

The second dose will be administered approximately 12 hours (±2 hours) after the first dose. The second dose and subsequent doses will be self-administered by the subject. The subjects will be instructed to take study medication no later than 30 minutes after food.

Study Visit Day Dosing:

On study visit days, subjects will take the first dose of study drug no later than 30 minutes after food in the office under the guidance of study site personnel after all specified study tests and procedures have been completed, and new bottles of medication have been issued. However, if the visit cannot be scheduled within the regular dosing schedule for the first daily dose of a new cycle, the subject will be instructed to take the first dose at the regular schedule on that visit day from the bottle of the preceding cycle.

5.3 Identity of Investigational Product

SKI-O-703 capsule is a Swedish orange capsule and will contain the active ingredient SKI-O-703 (100 mg). Placebo capsules will be identical in appearance and weight to the SKI-O-703 capsule and contain microcrystalline cellulose and magnesium stearate.

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

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 ProFill® capsule filler, packaged 70 count each into high density polyethylene bottles, and shipped to the study site. Study drug will be packaged and labeled according to applicable local and regulatory requirements.

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

5.4.2 Test Article Accountability

The investigator or pharmacy designee will maintain accurate records of receipt of all test articles, including dates of receipt from sponsor, assignment and dispensation to the subject(s), return from subject(s), and destruction of returned IMP (and/or return to the depot for destruction). This is denoted as pharmacy IMP accountability.

In addition, accurate records will be kept by the responsible site personnel regarding when and how much test article is dispensed to, used by, and returned from each subject in the study. At each study visit requiring dispensation (Visit 1, 3, and 4), a new set of 4 bottles of IMP will be dispensed to the subject to cover that study visit period and the previous set of 4 bottles will be collected. Subject dosing will be recorded on a subject dosing diary. 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 and reasons for departure from the expected dispensing regimen in study source documents. This is denoted as subject IMP accountability.

At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drugs will be reconciled and retained or destroyed according to applicable regulations.

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. Overdoses without signs or symptoms do not need to be recorded as AEs; in case of any AEs associated with the overdose, these should be reported on relevant AE/SAE sections in the eCRF.

Overdoses (including those without signs or symptoms) and medication errors should be documented in the PIP system 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.

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. In the event that the blind needs to be broken because of a medical emergency, the investigator can unblind an individual subject's treatment allocation. The treatment assignment will be unblinded through IxRS.

As soon as possible, the investigator should first contact the medical monitor to discuss the medical emergency and the rationale for revealing the actual treatment received by that subject. 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

All doses must be taken in accordance with the original dosing schedule outlined at subject's Day 1 visit with the first dose. All doses must be taken approximately 12 hours (±2 hours) after the previous dose in a consistent BID dosing pattern.

All IMP consumed must be documented clearly on the subject's dosing diary for accountability purposes. Each subject's dosing diary should be closely monitored by the site personnel at each study visit to ensure compliance with the original dosing schedule, beginning with the first dose of study drug has been maintained.

Missed Dose(s)

If the subject does not take their study drug dose at their regularly scheduled dosing time, they should take the dose as soon as possible but at least 8 hours before the next scheduled dose. If the next scheduled dose is within an 8 hours window, the dose is considered missed, and the subject should resume dosing with the subsequent dose on the original schedule.

If the subject experiences any drug interruption(s) they should notify their study site physician during the next scheduled study visit. Missed doses should be reported as a protocol deviation (or violations depending on the number of doses missed) 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.

5.8 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 drug name and the dates of administration (including start and end dates), dosage information including dose, route and frequency, and reason for drug use are to be recorded in the eCRF. This will include all prescription drugs, herbal products, vitamins, minerals, vaccines, over the counter medications (including folic acid or equivalent), and food products listed in Appendix 13.1 and in prohibited medications (Section 5.8.2). Any changes in concomitant medications also will be recorded in the subject's eCRF.

5.8.1 Permitted Concomitant Medications

Any concomitant medication, except the prohibited medications (Section 5.8.2), 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 are allowed to continue taking csDMARDs therapy with stable doses (eg, no escalations or additions, initiated ≥4 weeks prior to the first dose of study drug) and no change in route of administration for the previous 4 weeks prior to Day 1 dosing. Furthermore, dose(s) must have been stable during any screening, or treatment periods, unless dictated by tolerability requirements, as indicated in inclusion criteria 4 (Section 4.1.1).

Subjects may choose to washout csDMARDs 30 days prior to Day 1 dosing except for leflunomide. Subjects who discontinued leflunomide and have had successful chelation with 8 g of cholestyramine (3 times daily) for 3 days must wait 4 weeks prior to the first administration of the study drug (Day 1). Subjects who discontinued leflunomide and did not have cholestyramine washout must wait 12 weeks after last dose of leflunomide prior to Day 1 dosing (Section 4.1.1).

Subjects are permitted to receive either oral or parenteral glucocorticoids (≤10 mg daily of prednisone/prednisolone or equivalent) and nonsteroidal anti-inflammatory drug, if they have received a stable dose for at least 28 days prior to Day 1 dosing and must not be changed (eg, no escalations or additions) during any washout, screening, or treatment periods, unless dictated by tolerability requirements. In addition, subjects are permitted to receive low-potency topical, otic, and ophthalmic glucocorticoid preparations provided the preparations are administered per the instructions on the product label.

Subjects taking MTX must also be receiving a folic acid (or equivalent, such as folinic acid) supplementation at a stable dose for at least 4 weeks prior to Day 1 dosing. Subjects should continue with their stable doses of folic acid throughout the study.

5.8.2 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 other than TNFα inhibitor(s)
- Any csDMARDs other than those listed in the inclusion criteria
- Alkylating agents within 6 months prior to Day 1 dosing
- Prior treatment with intra-articular, intramuscular, intravenous, trigger point or tender point, intra-bursa, or intra-tendon sheath corticosteroids in the proceeding 8 weeks prior to Day 1 dosing

- Live or live-attenuated vaccine within 4 weeks prior to Day 1 dosing or expected need for live vaccination during study participation including at least 4 weeks after the last dose of study drug

- Combinations between MTX and leflunomide

- Known CYP1A2 and UGT1A1 inhibitors and inducers (see Appendix 13.1 for a list of suggested named CYP1A2 and UGT1A1 inhibitors and inducers) at least 4 weeks or 5 half-lives, whichever is longer, prior to Day 1 dosing

- High potency opiates including (but not limited to): oxycodone, oxymorphone, fentanyl, levorphanol, buprenorphine, methadone, hydromorphone, morphine, and meperidine at least 4 weeks prior to Day 1 dosing

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 schedule of events is summarized in Table 6-1.

Table 6-1 Schedule of Events

Procedure[a]	**Screening**	**Baseline**	**Treatment Period**			**EOT**	**Follow-up**	**EOS[b]**
Visit[c]		**1**	**2**	**3**	**4**	**5**	**6**	**7**
Study Day	**Day-28 to -1**	**Day 1[d]**	**Day 14 (±3 days)**	**Day 28 (±3 days)**	**Day 56 (±3 days)**	**Day 84 (±3 days)**	**Day 98 EOT+14 days (±3 days)**	**Day 112 EOT+28 days (±3 days)**
Study Week		**0**	**2**	**4**	**8**	**12**	**14**	**16**
GENERAL ASSESSMENTS								
Informed consent	X							
Inclusion/exclusion criteria	X	X						
Demographics	X							
Medical/surgical history	X							
Alcohol and nicotine use	X							
Height	X							
Weight	X	X				X		X
Physical examination[e]	X	X				X		X
Vital sign measurements[f]	X	X	X	X	X	X	X	X
Adverse event monitoring	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X
Prior medications	X							
RA ASSESSMENTS								
Tender/painful and swollen joint counts (TJC28/SJC28)	X	X	X	X	X	X	X	X
Physician/patient's global assessments of disease activity[g]		X	X	X	X	X	X	X
Patient assessment of general health[g]		X	X	X	X	X	X	X
Patient assessments of arthritis pain[g]		X	X	X	X	X	X	X

Procedure[a]	**Screening**	**Baseline**	**Treatment Period**			**EOT**	**Follow-up**	**EOS[b]**
Visit[c]		**1**	**2**	**3**	**4**	**5**	**6**	**7**
Study Day	**Day-28 to -1**	**Day 1[d]**	**Day 14 (±3 days)**	**Day 28 (±3 days)**	**Day 56 (±3 days)**	**Day 84 (±3 days)**	**Day 98 EOT+14 days (±3 days)**	**Day 112 EOT+28 days (±3 days)**
Study Week		**0**	**2**	**4**	**8**	**12**	**14**	**16**
HAQ-DI[g]		X	X	X	X	X	X	X
Randomization/drug assignment		X						
INVESTIGATIONAL PRODUCT ADMINISTRATION								
Dispense study drug and subject dosing diary		X		X	X			
Study drug administration		X	X	X	X	X		
Review and copy subject dosing diary and perform drug reconciliation			X	X	X	X		
CENTRAL LABORATORY EXAMINATIONS								
HBsAg, HBcAb, HCV, and HIV tests	X							
QuantiFERON Gold - tuberculosis test[h]	X							
Serum pregnancy test[i]	X							
FSH level[i]	X	X						
Urine pregnancy test[i]		X	X	X	X	X	X	X
Hematology[j]	X	X	X	X	X	X	X	X
Coagulation	X	X	X	X	X	X	X	X
Chemistry[j]	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X
hsCRP[k]	X	X	X	X	X	X	X	X
IMAGING								
Chest x-ray[l]	X							
12-lead electrocardiogram[m]	X	X	X	X	X	X	X	X
SUBSTUDY								

Procedure[a]	**Screening**	**Baseline**	**Treatment Period**			**EOT**	**Follow-up**	**EOS**[b]
Visit[c]		**1**	**2**	**3**	**4**	**5**	**6**	**7**
Study Day	**Day-28 to -1**	**Day 1**[d]	**Day 14 (±3 days)**	**Day 28 (±3 days)**	**Day 56 (±3 days)**	**Day 84 (±3 days)**	**Day 98 EOT+14 days (±3 days)**	**Day 112 EOT+28 days (±3 days)**
Study Week		**0**	**2**	**4**	**8**	**12**	**14**	**16**
Blood sampling for PK[n]		X	X	X	X	X		
Blood sampling for PD (CD63 + basophils)[n]		X	X	X	X	X		

Abbreviations: ACR, American College of Rheumatology; CD63, cluster of differentiation 63; DAS, disease activity score; EDTA, ethylenediaminetetraacetic acid; EOS, end-of-study; EOT, end of treatment; FSH, follicle-stimulating hormone; HBsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus; HAQ-DI, Health assessment questionnaire disability index; HBcAb, hepatitis B core antibody; HCV, hepatitis C virus; hsCRP, high sensitivity C-reactive protein; PD, pharmacodynamic; PK, pharmacokinetic; PPD, purified protein derivative; RA, rheumatoid arthritis; TB, tuberculosis; WOCBP, women of child bearing potential.

[a] When procedures overlap at the same timepoints, the vital parameters assessment will be performed first followed by laboratory parameters and other procedures (Section 6.4.2).

[b] Subject who choose to discontinue study treatment, but continue to participate in the study should complete EOT visit as soon possible, preferably within 2 weeks. Afterwards, subjects should follow the regular visit schedule and adhere to all study procedures except for dispensing study drug, and blood sample collection for optional exploratory research and validation studies.

[c] Any of the procedures may be performed at an unscheduled visit at the discretion of the investigator.

[d] All study procedures on Day 1 must be completed prior to randomization in order to save time for IMP dispensation and postdose PK/PD sampling.

[e] A complete physical examination should be performed at the time points specified. Interim physical examinations can be performed at the discretion of the investigator, if deemed necessary to evaluate AEs or clinical laboratory abnormalities (Section 6.4.1).

[f] Vital sign measurements include systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral temperature (tympanic temperature for Korean subjects). The subject must be seated for 5 minutes before all measurements are taken (Section 6.4.2).

[g] Patient questionnaires and scales should be performed prior to any procedures and assessments. The HAQ-DI should be scored for all 8 categories (Section 6.3.3).

[h] TB testing will be performed for all subjects within 28 days of Day 1. Positive diagnostic TB test, which is defined as positive QuantiFERON Gold test will be tested in central laboratories for all subjects and will determine subject's eligibility with regards to TB.

[i] For women of child bearing potential (WOCBP), serum pregnancy test performed with screening safety laboratory tests and sent to the central laboratory for processing. To confirm pregnancy, urine pregnancy test will be performed locally on Day 1 prior to randomization and prior to study drug administration on each subsequent visit. If urine pregnancy test is negative, dosing will be started; if urine pregnancy test is positive then withhold dosing and perform a serum pregnancy test. For post-menopausal female subjects, FSH levels will be assessed at screening and baseline to confirm post-menopausal status.

[j] Repeat of clinical chemistry and hematology laboratory tests may be allowed once during screening period (after an approval from medical monitor), if the initial result is unexpected/unexplained (not due to a known underlying condition or concomitant medications or other known cause).

[k] Repeat of hsCRP test may be allowed once during screening period (after an approval from medical monitor), if the result is considered unexplained/unexpected (eg, not corresponding with clinical disease activity or discordant with recent local result).

[l] Chest x-ray must be obtained during the screening period, unless a radiograph was obtained within 12 weeks prior to screening visit.

[m] Single 12-lead ECGs will be obtained, after the subject has been in the supine position for at least 5 minutes, prior to randomization at Visit 1 (Section 6.4.3).

[n] PK/PD Subset Only: Samples to be collected at the following time points:

Day 1: 0 hour (predose), 15 minutes (PK only +5 minutes), 30 minutes (±5 minutes), 1 hour, 2, 4, 8, and 12 hours (±10 minutes) postdose (12 hours sample should be collected prior to the evening dose).

Day 14 (Weeks 2), Day 28 (Week 4), and Day 56 (Week 8): predose samples will be collected prior to the morning dose only.

Day 84 (Week 12): 0 hour (predose), 15 minutes (PK only +5 minutes), and 30 minutes (±5 minutes), 1 hour, 2, 4, 8, and 12 hours (±10 minutes) after administration of the morning dose.

PK and PD whole blood samples must be collected using heparin as the anticoagulant. EDTA and citric acid should not be used as anti-coagulants for the collection of these samples. 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. (Section 6.5.1)

6.2 Demographic and Medical History

Demographic data consisting of age, sex, race, body weight, height, and BMI will be collected at the time points specified in the schedule of events (Table 6-1). A complete medical history (including prior and concomitant medical conditions and procedures; drug, alcohol, and tobacco use) and current/recent medications taken (including use of herbal remedies and vitamin supplements) will be collected at the time points specified in the schedule of events (Table 6-1).

6.3 Efficacy Assessments

Efficacy will be assessed by the evaluation of the mean decrease from baseline in disease activity score in 28 joints (DAS28; individual components, DAS28 [hsCRP]), ACR criteria (individual components; ACR20; ACR50; ACR70), count of tender/painful and swollen joints, global assessment of disease activity (assessed using the visual analog scale [VAS] by physician and subject), subjects assessment of arthritis pain, and health assessment questionnaire-disability index (HAQ-DI) at the time points specified in the schedule of events (Table 6-1).

6.3.1 Disease Activity Score Using 28 Joint Counts

Disease activity score using 28 joint counts (hsCRP) will be evaluated prior to randomization at Visit 1 and at each subsequent visit.

The core set of variables for DAS28 for this study include:

- Number of tender and swollen joints with a total of 28 joints assessed for tenderness and 28 for swelling (Appendix 13.5)
- Subject's global assessment of disease activity (VAS) (Appendix 13.8)
- hsCRP

Note: During the Protocol Amendment 2 dated 08 Feb 2019, the subject's global assessment of disease activity VAS scale was reversed from the standard way they are presented in clinical trials. Scoring of this VAS scale was found to be variable across the sites, since some sites used the reverse scales, while others used the original anchors. Given this inherent

variability, the primary endpoint will now include only the 3 component DAS28-hsCRP, excluding the global assessment of disease activity VAS.

DAS28 based on CRP (DAS28-CRP) may be calculated using 3 or 4 variables. DAS28-CRP(4) is computed using 4 variables: swollen and tender joint count, CRP, and subject's global assessment of disease activity. DAS28-CRP(3) only includes swollen and tender joint count and CRP as subject global assessment has been excluded. DAS28-CRP(3) may seem more feasible than DAS28-CRP(4) as it does not include subject global assessment, therefore it may be less influenced by subject's mood, etc., and may be considered a more reliable measure of disease activity. Baseline and 4 months disease activity data from 239 rheumatoid arthritis patients treated with a biological agent were extracted from the Danish registry for biological treatment in rheumatology (DANBIO). DAS28-CRP(4) at baseline was 4.8 ± 1.2 versus 4.6 ± 1.1 for DAS28-CRP(3). After 4 months of biological treatment, the scores for DAS28-CRP(4) and DAS28-CRP(3) had improved by −1.39 ± 1.34 ($p<0.0001$) and −1.18 ± 1.22 ($p<0.0001$), respectively. It was concluded that the thresholds for low and high disease activity and for improvements were the same for the 2 scores. While DAS28-CRP(3) yielded lower scores, categorized less patients as having high disease activity level, and scores may differ in individual subjects, and was less sensitive to change than DAS28-CRP, the 2 DAS-scores were highly correlated at both baseline ($r =0.96$, $p<0.0001$) and at 4 months ($r =0.97$, $p<0.0001$). Hence, DAS28-CRP(3) and DAS28-CRP(4) agree well on group level that are relevant for analysis of group-level data in a clinical trial setting (Madsen 2011).

A sensitivity analysis will also be performed using the 4 components DAS28-hsCRP on these subjects. The clinical team will determine on a subject by subject basis how the subject's global assessment of disease activity VAS in the DAS28-hsCRP from each subject was scored, and identify subjects who consistently completed the subject's global assessment of disease activity reverse VAS scale to include in this analysis. Only subjects who completed this VAS scale in a consistent manner throughout the study will be included in this analysis; other subjects will be excluded. For subjects who will be included in this analysis using the reversed scale, the values collected will be changed using 100 minus the original value to determine the final score to be used in the analysis. The details of the subjects who will be included for this sensitivity analysis will be provided in a separate document.

The joint counts will be completed by an Independent Joint Assessor who is not responsible for the primary care of the subjects. The Independent Joint Assessor should be a qualified medical professional (eg, nurse, physician's assistant, physician). Any other joint assessor must be trained (eg, GRAPPA training) and competent in performing such assessments. It is the responsibility of the Investigator to ensure that all assessors are qualified and trained to perform joint assessment. Independent Joint Assessors should be listed in the Delegation of Authority.

6.3.2 American College of Rheumatology Criteria and Individual Components

The ACR criteria are a series of individual assessments used for the calculation of ACR20, ACR50, and ACR70. The ACR criteria will be evaluated from Visit 2 onwards till EOS. The ACR core set of variables (individual components) for this study include:

- Number of tender and swollen joints with a total of 68 joints assessed for tenderness and 66 for swelling
- Subject's assessment of pain using visual analog scale (VAS) (Appendix 13.7)
- Subject's and physician's global assessment of disease activity (VAS) (Appendix 13.8)
- HAQ-DI estimate of physical ability (Appendix 13.10)
- hsCRP

The joint counts will be completed by an Independent Joint Assessor who is not responsible for the primary care of the subjects. The Independent Joint Assessor should be a qualified medical professional (eg, nurse, physician's assistant, physician). Any other joint assessor must be trained (eg, GRAPPA training) and competent in performing such assessments. It is the responsibility of the Investigator to ensure that all assessors are qualified and trained to perform joint assessment. Independent Joint Assessors should be listed in the Delegation of Authority.

6.3.3 Health Assessment Questionnaire-Disability Index

The HAQ-DI will be completed by the subject prior to randomization at Visit 1 and at each subsequent visit as specified in the schedule of events (Table 6-1).

There are 8 categories in HAQ-DI: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities. Scoring for each category is from 0 (without any difficulty) to 3 (unable to do). The highest score reported by the subject for any component question of the 8 categories determines the score for the category. If an aid/device or help is required from another individual, then the minimum score for that category will be 2. If the section score is already 2 or more, then no modification will be made.

If an item does not apply to subject (eg, they don't shampoo their hair, take tub baths, or reach for a heavy object above their heads), they should leave the item(s) blank since the purpose is to obtain data about what they can do.

If a component question is left blank or the response is too ambiguous to assign score, then the score for the category will be determined by the remaining completed question(s).

If all component questions are blank or if more than one answer is given, then the subject should be followed up.

If subject's mark is between the response columns, then score will be moved with the closest one. If subject's mark is directly between two response columns, score will be moved with the higher one.

Each of the disability items on the HAQ has a companion aids/devices variable that is used to record what types of assistance, if any, the subject uses for performing usual activities. If no aids, devices, or help is used, subject will leave those questions blank.

The aids and devices are assigned to the specific HAQ sections as follows:

- Dressing and Grooming: devices used for dressing (button hook, zipper pull, shoehorn, etc.)
- Arising: special or built up chair
- Eating: built up or special utensils
- Walking: cane, walker, crutches, wheelchair
- Hygiene: bathtub bar, long-handled appliances in bathroom, raised toilet seat
- Reach: long-handled appliances for reach

- Grip: jar opener for previously opened

These variables are scored as:

- 0 = no assistance
- 1 = special device is used by subject for usual activities
- 2 = subject needs help from another person
- 3 = subject usually needs both a device and help from another person

For more detailed guideline and examples refer to Appendix 13.10.

6.4 Safety Assessments

Safety variables will include physical examination findings, vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral temperature [tympanic temperature for Korean subjects]), ECG tracings, clinical laboratory test results (hematology, coagulation, serum chemistry, urinalysis, and urine pregnancy test), weight, body mass index, and reporting of AEs.

Safety assessments will be conducted as shown in the schedule of events (Table 6-1).

6.4.1 Physical Examination

A complete physical examination will be performed at screening, Day 1, EOT (Visit 5), and EOS (Visit 7) as indicated in the schedule of events (Table 6-1).

A complete physical examination will include assessments of general appearance; head, ears, eyes, nose, and throat (HEENT); chest and lungs; cardiovascular; abdomen (gastrointestinal); skin (including nails and hair); lymph nodes; psychiatric/emotional; neurological; and musculoskeletal.

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 oral temperature (tympanic temperature for Korean subjects). The subject must be seated for at least 5 minutes before all measurements are taken.

Vital signs will be measured at screening and other visits as indicated in the schedule of events (Table 6-1).

Height will be measured at screening only. Weight will be measured at screening, Day 1 (Visit 1), and EOS (Visit 7).

When procedures overlap at the same timepoints, the vital parameters assessment will be performed first followed by laboratory parameters and other procedures.

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 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 value has reached either the reference range, the value at screening, or until the Investigator determines that follow-up is no longer medically necessary.

6.4.3 Electrocardiograms

Single 12-lead ECGs will be obtained, after the subject has been in the supine position for at least 5 minutes, prior to randomization at Visit 1 and at subsequent visit as indicated in the schedule of events (Table 6-1). Electrocardiogram assessments will include comments on the rhythm; presence of arrhythmia or conduction defects; morphology; or ST segment, T wave, and U wave abnormalities; whether the tracings are normal or abnormal and whether 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 corrected QT interval from Fridericia's formula (QTcF).

The Investigator will determine whether any of the 12-lead 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.

If ECG tracings are printed on a thermal paper, a certified copy must be made, attached to the original, and filed in the subject's records to ensure results remain clear and legible over time.

6.4.4 Clinical Laboratory Tests

Clinical laboratory tests required for the study will be performed by PPD's central laboratory (except for the urine pregnancy test performed locally from Visits 1 to 7). For adverse event assessment and support, local laboratory results may be used.

Blood (hematology, coagulation, chemistry, hsCRP) and urine (urinalysis and urine pregnancy test) samples will be collected at screening, prior to randomization at Visit 1, and at each subsequent visit as indicated in the schedule of events (Table 6-1). Repeat of hsCRP may be allowed once during screening period (after an approval from medical monitor), if the result is considered unexplained/unexpected (eg, not corresponding with clinical disease activity or discordant with recent local result). Repeat of clinical chemistry and hematology laboratory tests may be allowed once during screening period (after an approval from medical monitor), if the initial result is unexpected/unexplained (not due to a known underlying condition or concomitant medications or other known cause).

The following assessments will be performed at screening only to determine eligibility:

- HBsAg, HBcAb, HCV, and HIV tests
- For WOCBP, serum pregnancy test performed with baseline safety laboratory tests and sent to the central laboratory for processing.

For WOCBP, to confirm pregnancy, urine pregnancy test will be performed locally on Day 1 prior to randomization and prior to study drug administration on each subsequent visit as indicated in the schedule of events (Table 6-1). If urine pregnancy test is negative, dosing will be started; if urine pregnancy test is positive then site staff must withhold dosing and perform a confirmatory serum pregnancy test.

For post-menopausal female subjects, FSH levels will be assessed at screening and on Day 1 (baseline) prior to randomization to confirm post-menopausal status.

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

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
Serum Chemistry:	ALT, albumin, alkaline phosphatase (ALP), amylase, anion gap, AST, bicarbonate, bilirubin (total and direct), blood urea nitrogen, calcium, chloride, cholesterol (total, high-density lipoprotein, and calculated low-density lipoprotein), creatine phosphokinase, creatinine, gamma-glutamyltransferase, globulin, glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total protein, triglycerides, troponin I, uric acid, and C-reactive 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 (for urine macroscopy), pH, protein, specific gravity, and urobilinogen
Pregnancy:	Urine dipstick pregnancy test except at screening

In cases of abnormal urinalysis results, urine microscopy will be performed.

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, even if asymptomatic. 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 US Food and Drug Administration (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.

All laboratory specimen (clinical and bioanalysis) analysis, details in storage and shipment will be followed according to the laboratory manual.

6.4.5 Adverse Events

6.4.5.1 Definitions of Adverse Events

An AE is any adverse change from the subject's baseline conditions, ie, any unfavorable and unintended sign, including an abnormal laboratory findings, symptoms or disease, that occurs during the course of the study, whether or not considered related to the study drug.

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 from study drug initiation until after the last dose of study drug whether or not considered related to the study drug. 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 elective surgery/procedure scheduled to occur during the study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry.

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, or 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 require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include an allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, 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 (ANC) $<1500/mm^3$ or $<1.5 \times 10^9/L$ 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 mm Hg, or diastolic blood pressure >100 mm Hg, 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 and reported from the time the subject takes the first dose of IMP until and including the EOS visit (Visit 7).

All SAEs occurring after signing the ICF must be reported (whether considered associated or not associated to study design or study-mandated procedures).

If the Investigator becomes aware of an SAE that occurs after the EOS 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. 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.

All AEs will be followed to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

6.4.5.5 Reporting Serious Adverse Events

Any AE that meets SAE criteria (Section 6.4.5.2) must be reported to PPD Pharmacovigilance (PVG) immediately (ie, within 24 hours) after site personnel are aware of the event. This must be done via the eCRFs on the AE page. The entry will automatically be

sent to the PPD PVG team for review. If the eCRF system is unavailable, a manual SAE form may be used and faxed to the numbers outlined below.

The nonserious adverse event of special interest (AESI) defined in Section 6.4.5.6 should be recorded in the eCRF using the same process as for reporting SAEs.

The following contact information is to be used for PPD PVG:

PVG Hotline: +44 1223 374 240/+1 800 201 8725

PVG Fax line:+44 1223 374 102/+1 888 488 9697 or +1 919 654 3849

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 eCRF using the same process as for reporting SAEs.

- **Neutropenia** with fever defined as ANC <1500/mm^3 or <1.5 × 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 AEs of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators, institutional review board (IRBs)/independent ethics committee (IECs), 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. Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by Oscotec Inc. as needed.

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.

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 following criteria:

Grade 1 No interference with activity
Grade 2 Some interference with activity not requiring medical intervention
Grade 3 Prevents daily activity and requires medical intervention
Grade 4 Emergency room visit or hospitalization
Grade 5 Fatal

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 until a satisfactory resolution, until the Investigator deems the event to be chronic or not clinically significant, or until the subject's condition is considered to be stable.

6.5 Pharmacokinetic Assessments

6.5.1 Pharmacokinetic Blood Samples

Timepoints for Sample Collection

Serial blood samples for PK assessment of SKI-O592 and its metabolites (M2 and M4) will be collected in a subset of subjects at the following time points (Table 6-2):

- Day 1: 0 hour (predose), at 15 (+5 minutes) and 30 minutes (±5 minutes), 1 hour, 2, 4, 8, and 12 hours (±10 minutes) postdose (12 hour sample should be collected prior to the evening dose).
- Trough: predose samples will be collected pre-morning on Day 14 (Weeks 2), Day 28 (Week 4), and Day 56 (Week 8).
- Day 84 (Week 12): 0 hour (predose), at 15 (+5 minutes) and 30 minutes (±5 minutes), 1 hour, 2, 4, 8, and 12 hours (±10 minutes) after administration of the morning dose.

Clinical staff is encouraged to take the blood samples for PK analysis at the scheduled time points listed above. The exact time and date of the blood draw must be recorded using an unambiguous format such as DD MON YYYY and HH:MM using a 24-hour clock.

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.

Processing of Blood Samples

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.

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 site until the study is completed, unless shipment to another facility is requested by Oscotec Inc. Instructions regarding the disposition of the B samples will be provided by Oscotec Inc. Plasma samples will be stored at approximately –70°C in an upright position.

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 metabolites M2 and M4 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.

6.6 Pharmacodynamic Assessments

6.6.1 Pharmacodynamic Blood Samples

Timepoints for Sample Collection

Serial blood samples for assessment of the percentage of activated gp53/CD63+ basophils in peripheral blood will be collected in the same subset of subjects for whom PK sample will be collected (Table 6-2):

- Day 1: 0 hour (predose), at 30 minutes (±5 minutes), 1 hour, 2, 4, 8 and 12 hours (±10 minutes) postdose (12 hour sample should be collected prior to the evening dose)
- Trough: predose samples will be collected pre-morning on Day 14 (Week 2), Day 28 (Week 4), and Day 56 (Week 8)
- Day 84 (Week 12): 0 hour (predose), at 30 minutes, 1 hour, 2, 4, 8, and 12 hours (±10 minutes) after administration of the morning dose

Clinical staff is encouraged to take the blood samples for PD analysis at the scheduled time points listed above. The exact time and date of the blood draw must be recorded using an unambiguous format such as DD MON YYYY and HH:MM using a 24-hour clock.

Processing of Samples

The samples must be dispatched to the processing laboratory as quickly as possible to ensure transport, cataloging, and processing is complete within the required timeframe for the selected assay.

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

6.6.2 Pharmacodynamic Variables

The primary PD endpoint will be the change in the percentage of activated gp53/CD63+ basophils in peripheral blood. 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.

Table 6-2 Pharmacokinetic and Pharmacodynamic Schema

	Dose Reference Timing*	Predose (0 hour)	15 min (+5 min)**	30 min	1 h (±10 min)	2 h (±10 min)	4 h (±10 min)	8 h (±10 min)	12 h (±10 min)
Visit 1: Day 1									
PK Sample Volume	AM	X	X	X	X	X	X	X	X
PD Sample Volume	AM	X		X	X	X	X	X	X
Visit 2: Day 14									
PK Sample Volume	AM	X							
PD Sample Volume	AM	X							
Visit 3: Day 28									
PK Sample Volume	AM	X							
PD Sample Volume	AM	X							
Visit 4: Day 56									
PK Sample Volume	AM	X							
PD Sample Volume	AM	X							
Visit 5: Day 84									
PK Sample Volume	AM	X	X	X	X	X	X	X	X
PD Sample Volume	AM	X		X	X	X	X	X	X

Abbreviations: PD, pharmacodynamic; PK, pharmacokinetic.

* Sampling should be performed after AM (morning) dose only.

** Applicable for PK samples only.

6.7 Safety Monitoring Committee

No formal safety monitoring committee will be established for the study.

6.8 Pregnancy

Subjects must be counseled during the informed consent process to inform the investigator of any pregnancy that occurs during study participation and for 6 months after the last dose of study drug. In the event of an unexpected pregnancy during study participation or for 6 months after the last dose of study drug, it must be reported via fax or email to PPD within 24 hours of the study site knowledge of the pregnancy via manual Initial Pregnancy Report Form.

For a female subject, the study drug must be discontinued immediately and the subject should inform the Investigator as soon as possible (see Section 4.2). Although study drug will be discontinued, the subject may choose to remain in study and will continue to be monitored for safety while following their regular visit schedule. If the partner of a male subject becomes pregnant, the male subject is not required to discontinue study drug and may remain on the study. The male subject is responsible for informing his partner(s) of the risk of becoming pregnant and for reporting any pregnancy to the Investigator.

The pregnancy must be followed up 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, and should be reported to PPD via fax or email on the manual follow-up pregnancy form.

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.

6.9 Laboratory Analyses

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, radiological scans, 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.

6.10 Sample Collections

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

7 Statistical and Analytical Plan

7.1 Primary Endpoint

- Mean change from baseline in DAS28-hsCRP score (based on 3 individual components including TJC, SJC, and hsCRP) at Week 12

7.2 Secondary Endpoints

Secondary endpoints will be evaluated at Weeks 2, 4, 8 and 12 unless otherwise stated.

- Percentage of subjects who would achieve ACR20, ACR50 and ACR70 response over time
- Change from baseline in DAS28-hsCRP score (based on 3 individual components including TJC, SJC, and hsCRP)
- Change from baseline in the tender/painful and swollen joint count (28)
- Change from baseline in the physician global assessment of disease activity by VAS
- Change from baseline in the subject global assessment of disease activity by VAS
- Change from baseline in the subject's assessment of arthritis pain by VAS
- Change from baseline in the HAQ-DI
- Change from baseline in median hsCRP values at each visit
- Safety and tolerability of SKI-O-703 compared to placebo including laboratory tests, infections, ECGs, vital signs, incidence of AEs, withdrawals due to AEs and serious adverse events (SAEs).
- PK parameters of SKI-O-592 and its metabolites (M2 and M4) from a subset of subjects per cohort on Day 1 and at Week 12, including: Cmax, Tmax, AUC0-tau, t1/2, Kel, CL/F (SKI-O-592 only), Vz/F (SKI-O-592 only), Rmet, and RAUC, as applicable
- PD parameters for the change from baseline in the percentage of activated gp53/CD63+ basophils in peripheral blood on Day 1 and at Week 12, including: Emax, TEmax, AUEC0-tau, as applicable

7.3 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 gp53/CD63+ basophils in peripheral blood on Day 1 and at Week 12

7.4 Sample Size Calculations

Approximately 148 subjects will be enrolled in 4 cohorts (3 cohorts of SKI-O-703 and 1 cohort of placebo). Each cohort will consist of at least 37 subjects.

The study is powered to detect a difference of 0.80 in mean change from baseline to Week 12 in DAS28-hsCRP score between one of the groups treated with SKI-O-703 and the group treated with placebo. At least 37 subjects on a course of SKI-O-703 treatment are required to complete the study to show a change from baseline to Week 12 of 0.80 and higher as statistically significant with a power of 0.80 at the significance level of 0.05, using a 1-way analysis of variance and assuming a standard deviation of 1.25, compared with in the placebo group. Sample size determinations were based on the 4-component DAS28 and are likely to be similar with the 3-component DAS28 with fewer variables (Breedveld et al 2016).

Given the 1:1:1:1 ratio of SKI-O-703 100 mg BID, 200 mg BID, 400 mg BID to placebo allocation, at least 37 subjects in each treatment group are required to complete the study, therefore at least 148 subjects need to be enrolled and randomized in the study. Assuming a drop-out rate of 10%, up to 20 additional subjects may be enrolled to achieve the target number of subjects required to complete the study.

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 study treatment they receive. This population will be used for summaries of safety data.

Intention-to-Treat (ITT) set: The ITT set will consist of all subjects who receive at least 1 dose of study drug (SKI-O-703 or placebo). Subject will be analyzed according to the

treatment group to which they were randomized. This population will be used for summaries of demographic data and efficacy summaries.

Modified Intention-to-Treat (mITT) set: The mITT 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 postbaseline assessment. This population will be used for efficacy summaries and will include imputed data for subjects who withdraw from the study prior to the Week 12 visit.

Per-protocol (PP) set: The PP set will consist of all subjects from the ITT set without important protocol deviations.

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 population. This population 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 population. This population will be used for summaries of PD data.

Pharmacokinetic (PK)/pharmacodynamic (PD) set: The PK/PD set will consist of all subjects included in both the PK and PD populations. This population will be used for the PK/PD analyses.

7.6 Description of Subgroups to be Analyzed

The primary and secondary endpoints described in Section 7.1 and Section 7.2 will be repeated for the following subgroups:

- The number of previous csDMARDs treatments (0~2 or ≥3)
- Previous 1, 2 or more anti-TNFα biologic agents use (Yes or No)
- Specific geographic region (APAC, EMEA, and NA)

7.7 Statistical Analysis Methodology

Statistical analysis will be performed using SAS® software Version 9.3 or later. The results for each efficacy endpoint will be summarized by visit and treatment for all subjects within the ITT, mITT, and PP sets using descriptive statistical methods. Continuous variables will be summarized using the mean, SD, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. Data will be listed in data listings.

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

All statistical tests will be 2-sided and performed using a 5% significance level, leading to 95% CIs (2-sided). There will be no adjustments for multiplicity.

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, sex, race, body weight, height, BMI, and medical history will be summarized by treatment group using descriptive statistics.

7.7.3 Analysis of Primary Endpoint

The primary endpoint is the mean change from baseline in DAS28-hsCRP at Week 12 which is based on 3 individual components including TJC, SJC and hsCRP (see calculation in Appendix 13.6).

The mean change from baseline in DAS28-hsCRP at Week 12 between each of the active treatment groups and the placebo arm will be analyzed using an analysis of covariance (ANCOVA). The difference in mean change from baseline between each active treatment and the placebo will be estimated and the corresponding 95% CI and p-value will be calculated.

The primary endpoint will be analyzed using the ITT, mITT, and PP analysis sets. For the mITT set, results for subjects that are missing at Week 12 will be imputed using the last observation carried forward (LOCF) method.

A sensitivity analysis based on the 4-component DAS28-hsCRP (consisting of 4 individual components including TJC, SJC, hsCRP, and subject's global assessment of disease activity [VAS]; see calculation in Appendix 13.6) will be performed on the ITT set restricted to subjects who consistently completed the subject's global assessment of disease activity reverse VAS scale.

7.7.4 Analysis of Secondary Endpoints

For secondary endpoints, change from baseline will be analyzed at Weeks 2, 4, 8, and 12 using a mixed model repeated measures (MMRM) analysis. The Chi-square tests will be used to compare the ACR20, ACR50, and ACR70 rates between the active treatment and placebo groups at Weeks 2, 4, 8, and 12. The median hsCRP will be summarized descriptively.

The DAS28-related secondary endpoint is based on 3 individual components including TJC, SJC and hsCRP (see calculation in Appendix 13.6). Sensitivity analyses based on the 4-component DAS28-hsCRP (consisting of 4 individual components including TJC, SJC, hsCRP, and subject's global assessment of disease activity [VAS]; see calculation in Appendix 13.6) will be performed using the ITT set restricted to subjects who consistently completed the subject's global assessment of disease activity reverse VAS scale.

All secondary endpoints will be analyzed using the ITT and PP analysis sets. The ACR20, ACR50, and ACR70 will be also analyzed using the mITT set, where results for subjects that are missing at the relevant visit will be imputed using nonresponder imputation (NRI).

For analyses on ACR responses (ACR20, ACR50 and ACR70) described above, the analysis will be performed on the subjects assessment of arthritis pain and physician global assessment of disease activity VAS scales, using the same approach as the sensitivity analysis on 4-compoent DAS28-hsCRP to identify the subjects to be included in this analysis set.

For the analyses on the other VAS-related secondary endpoints (ie, the individual assessments using VAS), using the same approach as the sensitivity analysis on 4-component DAS28-hsCRP, only subjects who completed the corresponding individual VAS assessment consistently will be included.

7.7.5 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 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 safety data will be listed.

7.7.6 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.

7.7.7 Pharmacodynamic Analyses

Absolute and percentage change from baseline in the percentage of activated gp53/CD63+ basophils in peripheral blood will be listed and summarized separately for each treatment and day at each nominal time point using descriptive statistics (n, mean, SD, CV, minimum, median, and maximum). Individual and mean absolute and percentage change from baseline in the percentage of activated gp53/CD63+ basophils will be plotted versus time for each treatment and day.

PD parameters for the percentage of activated gp53/CD63+ basophils will be calculated using noncompartmental 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.

7.7.8 Exploratory PK/PD Analysis

Individual and mean plasma concentrations of SKI-O-592, M2 and M4 will be plotted versus change from baseline in the percentage of activated gp53/CD63+ basophils in peripheral blood on Day 1 and at Week 12.

Exploratory PK/PD modeling may also be performed; full details will be provided in the statistical analysis plan.

7.7.9 Interim Analyses

There is no interim analysis planned for this study.

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 diary cards, laboratory reports, and ECG strips.

Study site personnel will enter subject data into Medidata Rave. 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 Medidata Rave 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, 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 study 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 subject to change 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
- 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 study drug. 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

No external data monitoring committee is planned for the study.

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. A risk-based approach to data monitoring in line with ICH E6(R2) will be utilized for this study.

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, enrollment of the subject without prior sponsor approval, 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 identified during a monitoring visit. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal investigator is responsible for notifying IRB/IEC/regulatory authorities (as applicable), as well as their site monitor.

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.

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, Oscotec Inc. will ensure that the clinical study reports are prepared and provided to the regulatory agencies as required by the applicable regulatory requirements. Oscotec Inc. will also ensure that the clinical study reports in marketing applications meet the standards of the ICH harmonized 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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