Title:	A Phase II, randomized, multi-center, placebo-controlled, double-blind study investigate the safety of GS-248, and efficacy on Raynaud's phenomenon (RP) peripheral vascular blood flow, in subjects with systemic sclerosis (SSc)
Protocol:	Version 5.0, dated 10 December 2021
SAP:	Version 2.0, dared 19 July 2022
NCT:	04744207

CLINICAL TRIAL PROTOCOL

A Phase II, randomized, multi-center, placebo-controlled, double-blind study to investigate the safety of GS-248, and efficacy on Raynaud's phenomenon (RP) and peripheral vascular blood flow, in subjects with systemic sclerosis (SSc)

Protocol Number:	GS-2001
Investigational Medicinal Product:	GS-248
Indication:	Raynaud's phenomenon (RP)
Phase:	II
Sponsor:	Gesynta Pharma AB Wallingatan 24 SE-111 24 Stockholm, Sweden
Coordinating Investigator	Professor Ariane Herrick Centre for Musculoskeletal Research University of Manchester Oxford Road Manchester M13 9PT, United Kingdom
EudraCT Number:	2020-002081-13
Protocol Version and Date:	Final v5.0, 10 December 2021
Replaces Protocol Version and Date:	Final v4.0, 25 March 2021
Replaces Protocol Version and Date:	Final v3.0, 01 September 2020
Replaces Protocol Version and Date:	Final v2.0, 15 July 2020
Replaces Protocol Version and Date:	Final v1.0, 12 June 2020

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

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Principal Investigator Agreement

I, _____, (Investigator's Name) have read this protocol and agree that it contains all necessary details for carrying out this trial. I will conduct the trial as outlined herein and will complete the trial within the time designated.

The information contained in this protocol is provided to me in confidence, for review only by myself, the ethics committee authorised to review and approve the trial at this trial site, and designated trial staff participating in this clinical trial.

I agree to the conditions as set out in this protocol and fully accept that any change requires prior approval by the trial sponsor.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this trial. I will discuss this material with them to ensure they are fully informed regarding the IMP (investigational medicinal product) and the conduct of the trial.

I will use only the informed consent form approved by the sponsor or its representative and will fulfil all responsibilities for submitting pertinent information to the Independent Ethics Committee (IEC) responsible for this trial.

I agree to carry out all terms of this protocol in accordance with the ICH GCP (Good Clinical Practice) Guidelines, the Declaration of Helsinki and local regulations. I will ensure that the IMP is used only as described in the protocol or any subsequent amendment.

I understand that the information/technology contained in this protocol is proprietary and may not be disclosed to any other party, in any form, without prior authorization from the trial sponsor except to the extent necessary to obtain informed consent from potential trial subjects.

_____ _____

Investigator's Signature Date

_____

Clinical Trial Site Name

PROTOCOL SYNOPSIS

<table>
<tr><td>Title:</td><td>A Phase II, randomized, multi-center, placebo-controlled, double-blind study to investigate the safety of GS-248, and efficacy on Raynaud's phenomenon (RP) and peripheral vascular blood flow in subjects with systemic sclerosis (SSc).</td></tr>
<tr><td>Protocol Number:</td><td>GS-2001</td></tr>
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<tr><td>Sponsor:</td><td>Gesynta Pharma AB</td></tr>
<tr><td>Coordinating Investigator:</td><td>Professor Ariane Herrick, University of Manchester</td></tr>
<tr><td>Objectives and Endpoints:</td><td>
<table>
<tr><td>Objectives

<u>Primary:</u>
To determine the safety and efficacy of GS-248 versus placebo on RP in subjects with SSc.</td><td>Endpoints

<u>EFFICACY</u>
<u>Primary Efficacy:</u>
Mean change from baseline to week 4 in the number of Raynaud's Phenomenon attacks per week.

Key secondary efficacy:
• Mean change from baseline to week 4 in the Raynaud's Condition Score (RCS).
• Mean change from baseline to week 4 in the cumulative duration of Raynaud's Phenomenon attacks.
• Mean change from baseline to week 4 in pain experienced during RP attacks.

<u>SAFETY</u>
<u>Safety Endpoints:</u>
• Incidence of Adverse events.
• Incidence of Serious Adverse Events.
• Clinical laboratory and vital signs.

Exploratory efficacy:
• Patient Global Impression of Change at week 4.
• Physician Global Impression of Change at week 4.</td></tr>
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		• Mean change in ASRAP Questionnaire score from baseline to week 4.
	Secondary: To determine the efficacy of GS-248 on peripheral vascular blood flow in subjects with SSc and RP.	***Secondary:*** • Mean change from baseline to week 4 in peripheral blood flow prior to cold challenge and IMP administration. • Mean change in peripheral blood flow from pre-IMP, to post-IMP administration at Visit 2. • Mean change in recovery of peripheral blood flow after cold challenge from pre-IMP to post-IMP administration at Visit 2. • Mean change from baseline to week 4 in recovery of peripheral blood flow after cold challenge.
	Exploratory: • To explore the pharmacokinetics (PK) of GS-248. • To explore the efficacy of GS-248 on PGE_2 formation in whole blood *ex vivo*. • To explore the efficacy of GS-248 on formation of arachidonic acid metabolites. • To explore the efficacy of GS-248 on inflammation and endothelial dysfunction. • To explore the efficacy of GS-248 on platelet activation. • To explore the efficacy of GS-248	***Exploratory:*** • GS-248 levels in plasma. • Change in PGE_2 level in whole blood *ex vivo* from baseline to week 4. • Change in levels of PGEM, PGIM and TXM in urine from baseline to week 4. • Change in levels of biomarkers in blood/plasma from baseline to week 4. • Expression of platelet surface markers. • Change in microvascular volume from baseline to week 4.

	on microvascular volume. • To collect blood and urine for potential future analysis of inflammatory biomarkers and endothelial dysfunction (results will be reported at a later date).
Design:	This is a randomised, double-blind, placebo-controlled study conducted in multiple sites in 3-4 countries in Europe. Approximately 80 subjects will be randomised in a 1:1 allocation to receive either GS-248 (120 mg) or placebo once daily, stratified for use of background vasodilatory treatment (Ca-blockers, PDE-5 inhibitors, or no background vasodilatory treatment) with approximately 40 subjects in each treatment group. The study will comprise an enrolment period, a treatment period, and a follow-up period, with a total of 5 study visits. Some study assessments will only be conducted at pre-selected sites. **Run-in/Enrolment Period** At Visit 1 (Screening Visit) confirmation of informed consent has been gained from each subject and eligibility for the study will be established. Eligibility screening will be conducted, including demographic data, subject medical history, a physical examination, and other procedures. In addition, blood and urine samples will be collected. Subjects will be issued with an eDiary to record information on a daily basis, including the number of Raynaud attacks and RCS. **Treatment Period** On Day 1 (Visit 2, Baseline Visit) eligible subjects will be randomised and receive their first dose of IMP under medical supervision at the study site. Study assessments including PK sampling and safety will be performed throughout this visit. In total, this visit will last for approximately 4 or 6 hours dependent on whether the subject is enrolled in the cold challenge assessment. Subjects will be permitted to leave the study clinic for short periods of time between assessments as feasible but will be asked to remain on site. At the end of the visit, subjects will be dispensed sufficient amount of medication to last until the next study visit, scheduled for 14 (±2) days later. Subjects will continue to fill in their eDiary throughout the Treatment Period. On Day 15 (±2 days) subjects will return to the study site for Visit 3. Safety assessments, PK sampling and safety monitoring will be performed. Treatment compliance will be checked, used bottle of IMP collected, and sufficient IMP for the remainder of the Treatment Period will be distributed. The visit will last approximately 1,5 hours. Visit 4, End of Treatment Visit, will occur on Day 28 (-2/+1 days), which will be the day subjects take their final dose of IMP, to be administered at the study site.

	This visit will last for up to 5 hours, and for subjects undergoing rich PK sampling, this visit will last for up to 9 hours. Additional safety monitoring assessments will be performed. The eDiary will be checked, and all IMP will be collected. An ASRAP questionnaire will be completed by subjects, along with a Global Impression of Change, which is also completed by physicians. **Follow-Up Period** The follow-up visit (Visit 5, Day 42-49) should occur 2-3 weeks after the last dose of IMP. Safety assessments will be performed. Subjects will complete the final entry in their eDiary, and these will be collected. The visit will last approximately 1,5 hours.
Study Population:	Adults aged 18-75 years with a confirmed diagnosis of SSc and subject-reported Raynaud attacks typically ≥7 times per week during the 4 weeks prior to screening.
Inclusion Criteria:	1. Subjects must provide signed and dated written informed consent before the conduct of any study-specific procedures. 2. Male and female subjects aged 18-75 years inclusive. 3. SSc diagnosed according to European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) criteria (van den Hoogen F et al. 2013). *Subjects with signs of other autoimmune diseases (e.g. Sjögren's syndrome, myositis, rheumatoid arthritis) could be included if SSc is the dominating phenotype.* 4. Raynaud attacks typically ≥7 times per week during the last 4 weeks prior to screening despite background medication (only allowed vasodilatory therapy is calcium channel blockers *or* PDE-5 inhibitors). 5. Women of childbearing potential (WOCBP) must be using a highly effective method of contraception to avoid pregnancy throughout the study and for 4 weeks after the last dose of IMP in such manner that the risk of pregnancy is minimised Clinical Trials Facilitation Group, 2014). 6. Women must not be pregnant or breastfeeding. 7. Male subjects to agree to use condom in combination with use of contraceptive methods with a failure rate of <1% to prevent pregnancy and drug exposure of a partner and refrain from donating sperm from the first date of dosing until 3 months after last dosing of the IMP. 8. Ability of subjects to participate fully in all aspects of this clinical trial.
Exclusion Criteria:	1. SSc disease duration of greater than 120 months from first non-Raynaud manifestation 2. Current smokers or stopped smoking or used nicotine in any form <3 months prior to Visit 1. 3. Dose-change or initiation of vasodilating substances (calcium blockers *or* PDE-5 inhibitors) within 4 weeks prior to Visit 1. Subjects are not allowed to use a combination of calcium blockers and PDE-5 inhibitors from 4 weeks prior to Visit 1 and throughout the study. 4. Use of iloprost or other intravenous (iv) or per os (po) prostacyclin receptor agonist within 4 weeks prior to Visit 1. 5. Ongoing treatment with immunosuppressive therapies (other than mycophenolate) including, but not restricted to;

	cyclophosphamide, azathioprine, methotrexate, or cyclosporine, or use of those medications within 4 weeks prior to Visit 1. *Note: Subjects could be included if they have been treated with a stable dose of mycophenolic acid during 4 weeks prior to study entry.* 6. Use of systemic corticosteroids within 4 weeks prior to Visit 1 and during the course of the study. 7. Use of moderate or strong CYP3A4 inhibitors within 5 terminal half-lives or one week, whichever is longer, prior to Visit 2. Examples of a moderate or strong CYP3A4 inhibitors are diltiazem, verapamil and grapefruit juice. 8. Concurrent serious medical condition, with special attention to cardiovascular conditions, which in the opinion of the Investigator makes the subject not suitable for this study. 9. Prolonged corrected QT interval by Fridericia (QTcF) defined as a mean QTcF >450 msec at Visit 1, or at Visit 2 (prior randomization). 10. Creatinine clearance <50 mL/min (determined by Cockcroft-Gault equation) at Screening (Visit 1). 11. Active digital ulcer (DU) within 4 weeks prior to Visit 1. 12. Have known allergies to any components of the GS-248 formulation. 13. Clinically meaningful laboratory abnormalities at Screening (Visit 1), as determined and documented by the Investigator. 14. Positive test results for HBsAg, HCVAb or HIV-1 and/or -2 antibodies at Screening (Visit 1). 15. Subjects known or suspected of not being able to comply with this trial protocol (e.g. due to alcoholism, drug dependency or psychological disorder). 16. Subject is mentally or legally incapacitated at the time of screening or has a history of clinically significant psychiatric disorders that would impact the subject's ability to participate in the study according to the Investigator. 17. Malignancy within the past 5 years except for in situ removal of basal cell carcinoma and cervical intraepithelial neoplasia grade I. 18. Planned major surgery within the duration of the study. 19. Blood donation (or corresponding blood loss) within 12 weeks prior to Visit 1. 20. Participation in another interventional clinical study involving IMP within 4 weeks or given an experimental drug within 5 half-lives, whichever longest, prior to Visit 1.
Exclusion Criterion for Cold Challenge	At Visit 2: Finger temperature below 27°C after acclimatising at an ambient temperature of 23°C (±2°C) for a period of 20 minutes.
Randomization Criteria:	In addition to fulfilling all inclusion and exclusion criteria, subjects must fulfil the following criteria to be randomised: 1. ≥7 RP attacks during the last week of the run-in period as captured in the eDiary, with no more than 2 days without RP attacks. 2. Compliance with the eDiary during the 7 most recent days prior to baseline (Visit 2), excluding the visit day itself, defined as having submitted ≥5 days of eDiary records (out of a possible 7 days) for RCS and RP during that period.

Number of Subjects:	Approximately 80 subjects.
Countries/Number of Sites:	Approximately 15 sites in 4 countries in Europe.
Investigational Medicinal Product:	GS-248, supplied as 40 mg capsules. Each single dose consists of 3 capsules constituting a total of 120 mg GS-248 per IMP administration. Placebo supplied as capsules identical to GS-248. Each single dose consists of 3 capsules.
Duration of Participation:	Between 56 and 70 days, depending on the length of the run-in period.
Laboratory Assessments:	For all subjects • Standard haematological, clinical chemistry and urine analyses. • Spot urine for analysis of urinary excretion of arachidonic acid metabolites. • Blood samples for analysis of GS-248 concentration in plasma. • Blood samples for pre-defined exploratory biomarker analyses. • Blood samples for potential future analyses of exploratory biomarker (to be stored in Biobank). At a few pre-selected sites • Repeated blood samples for analysis of GS-248. • Analysis of PGE_2 levels in whole blood *ex vivo*. • Analysis of platelet activation (surface markers by fluorescence-activated cell sorting [FACS] analysis).
Permitted, Restricted and Prohibited Medications and Restricted Procedures:	• Sun protection required from dose administration to follow-up in line with CDC recommendations (https://www.cdc.gov/cancer/skin/basic_info/sun-safety.htm) • Avoidance of artificial sunlight (e.g. sunbeds) from dose administration to follow up. • Patients taking permitted (i.e. not prohibited) medication should continue the dosing of it, unchanged, during the study. • Use of non-steroidal anti-inflammatory drugs (NSAIDs), Cox-inhibitors, Aspirin, Nitrates, Nitric oxide donors, ERAs, Alpha-blockers and Anti-thrombotic agents is not allowed from Visit 1 to Visit 5. • Subjects are not allowed to use a combination of calcium blockers *and* PDE-5 inhibitors from Visit 1 to Visit 5. • Subjects are not allowed to use immunosuppressive therapies including, but not restricted to; cyclophosphamide, azathioprine, methotrexate, or cyclosporine from Visit 1 to Visit 5. *Note: Subjects who have been treated with a stable dose of mycophenolic acid during 1 month prior to Visit 1 could continue that dose during the study.* • Use of systemic corticosteroids is not allowed from Visit 1 to Visit 5. *Note: Use of topical or inhaled corticosteroids is allowed throughout the study.* • Use of the selective serotonin reuptake inhibitor (SSRI) fluoxetine, angiotensin receptor blockades (ARBs), and bosentan, are not allowed from Visit 1 to Visit 5. • Subjects are not allowed to use any moderate or strong CYP3A4 inhibitors, e.g. diltiazem, verapamil or grapefruit

	juice, 1 week or 5 terminal half-lives, whichever is longest, prior to Visit 2 and until the day after Visit 4. • Use of herbal remedies, supplements and drugs taken without prescription, with the exception of paracetamol, may only be permitted with prior consent from the Investigator. • Subjects should report use of all vitamin (especially vitamin PP [niacin]), vitamin supplements and food supplements prior to and during the study. • Subjects should not use nicotine -containing products including patches or chewing gum. • For WOCBP, use of highly effective contraceptive method, that includes an additional barrier method in case a hormonal contraceptive method is used, until 4 weeks post last dose. • Male subjects with partners who are WOCBP must use a condom in combination with the use of contraceptive methods with a failure rate of <1% to prevent pregnancy and drug exposure of a partner, and refrain from donating sperm from the first date of dosing until 3 months after last dosing of the IMP.
Statistical Methods:	Descriptive statistics (sampling statistics for quasi-continuous parameters and frequency tables for categorical parameters) will be presented for all endpoints separately for each treatment group. To compare the treatment effect of GS-248 with placebo after 4 weeks of treatment, two-sided hypothesis tests on the specified efficacy endpoints (primary and secondary) will be performed at the 0.05 level of significance.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACR	American College of Rheumatology
ADR	Adverse Drug Reaction
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ARB	Angiotensin receptor blockade
ASRAP	Assessment of Scleroderma-associated Raynaud's Phenomenon
AST	Aspartate aminotransferase
BDRM	Blinded data review meeting
CHMP	Committee for Medicinal Products for Human use
CPMP	Committee for Proprietary Medicinal Products
DDP	Data display plan
DMP	Data Management Plan
D-OCT	Dynamic Optical Coherence Tomography
DRM	Data Review Meeting
DU	Digital ulcer
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ERAs	Endothelin receptor antagonists
FACS	Fluorescence-activated cell sorting
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	First-in-human
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface antigen
HCVAb	Hepatitis C antibody
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus

Abbreviation	Definition
HPMC	Hydroxypropyl methylcellulose
IEC	Independent Ethics Committee
ICH	International Council for Harmonization
IMP	Investigational Medicinal Product
iv	intravenous
ISF	Investigator Site File
ITT	Intent-to-treat
IWRS	Interactive Web Response System
LOCF	Last observation carried forward
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
Min	Minute
mL	Milliliter
mPGES-1	Microsomal prostaglandin E synthase-1
NRS	Numeric rating scale
NSAID	Non-steroidal anti-inflammatory drug
qd	Once daily
PDE-5	Phosphodiesterase type 5 inhibitor
PGE_2	Prostaglandin E_2
PGEM	11-alfa-hydroxy-9,15-dioxo-13,14-dihydro-2,3,4,5, tetranor-prostan-1,20-dioic acid
PGIM	2, 3-dinor-6-ketoprostaglandin F1α
PK	Pharmacokinetic
PKAS	Pharmacokinetic Analysis Set
po	Per os
pMI	placebo Multiple Imputation Method
PPS	Per Protocol Set
PRO	Patient-reported outcome
QoL	Quality of Life
QT	Uncorrected QT interval
QTcF	Corrected QT interval by Fridericia
RCS	Raynaud's Condition Score
RP	Raynaud's phenomenon

Abbreviation	Definition
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SCR	Set of Screening Failures
SoA	Schedule of Assessments
SSc	Systemic sclerosis
SSRI	Selective serotonin reuptake inhibitor
TXM	11-dehydro-thromboxane B2
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

1 INTRODUCTION

1.1 Background

1.1.1 Indication

Raynaud's phenomenon (RP) is recurrent episodic painful ischemic events affecting primarily fingers and toes in response to cold exposure or to emotional stress. Approximately 95% of patients with SSc, an orphan autoimmune disease, report RP (Elhai et al, 2016). The mean age at onset of RP, which usually is the first symptom of SSc, is around 40 years and preceded symptoms from other organ manifestations within on average 4 years (Meier et al, 2012). In an international survey of patients with RP, most subjects (78%) reported making at least one life adjustment due to RP, and QoL was significantly reduced (Hughes et al, 2015). Of those with current or previous use of medications for RP, only 16% reported at least one medication being effective (Hughes et al, 2015).

Microvascular injury and endothelial cell activation that results in vascular damage are considered to be the earliest, and possibly primary, events in SSc (Allanore et al, 2015). Changes in capillary morphology as investigated with nailfold video capillaroscopy demonstrate a distinct and typical pattern (Ruaro et al, 2017), but also small and medium size arteries are involved (Aïssou et al, 2016).

Peripheral blood flow after cold challenge can reliably be assessed also in multi-center clinical studies with thermography (Wilkinson et al, 2018). RCS, a patient-reported outcome (PRO), is a validated method to assess and document disease activity and functional status in subjects during clinical trials (Merkel et al, 2002).

1.2 Rationale

GS-248 is a selective and potent inhibitor of the microsomal prostaglandin E synthase-1 (mPGES-1), which is an inducible enzyme that catalyses the second step in the PGE_2 formation from arachidonic acid and is also an anticipated target to treat inflammation. The aim with this study is to reduce the pro-inflammatory PGE_2 levels and, in parallel, utilise the substrate shunting effect of mPGES-1 inhibition to increase the endogenous production of prostacyclin (PGI_2), which is a potent mediator of vasodilation and platelet inhibition.

Therefore, this study is intended to investigate the efficacy of GS-248 on RP, peripheral vascular blood flow, and vascular inflammation in subjects with SSc. The study will collect information about safety, efficacy and PK, following 28 (-2/+1) consecutive days of once daily treatment with GS-248 at a dose of 120 mg in capsule form.

1.3 Risk-Benefit Assessment

The Sponsor has performed 28-day Good Laboratory Practice (GLP) repeated dose toxicology studies in rats and dogs with results supporting the initiation of the clinical program.

In the first-in-human (FIH) study (GS-1001), the target enzyme, mPGES-1, was fully inhibited at low doses and a dose dependent increased excretion of prostacyclin metabolites was observed in the urine. Thus, the subjects assigned to the GS-248 treatment group in this study may have potential medical benefit on RP from their participation.

In the GS-1001 study GS-248 was administered as an oral solution in single ascending doses (1 mg to 300 mg) and in multiple ascending doses (MAD) (20 mg to 180 mg once daily for 10 days) to healthy volunteers was safe and well tolerated. There was no obvious trend in terms of adverse event (AE) reporting frequency with increasing dose of GS-248 and there was no difference in reporting frequency between subjects who received active treatment and those who received placebo except with regards to gastrointestinal disorders, which were more frequently reported by subjects receiving GS-248 in the MAD part of the study. However, there was no consistent pattern and no apparent dose dependency of gastrointestinal disorders, and a majority of the events were of mild intensity and no event was reported as severe.

The second study in healthy volunteers (GS-1002) evaluated the pharmacokinetic (PK) properties of GS-248 120 mg in single doses using a lipid-based and a dry powder-based formulation in capsule, including food interaction, in healthy volunteers. The number of AEs were low, and GS-248 was considered safe and well tolerated. The lipid-based formulation was selected for this study.

In the GS-1002 study a modest increase in mean QTcF (12.0 – 16.1 msec) was observed at time of peak concentrations, but there were no clinically significant patterns in ECG and no individual ECG was assessed as clinically significant abnormal. The QTcF findings are uncertain due to several factors including high variability, ECGs were collected only as single measurements, and no placebo groups were included. In the GS-1001 study there were no drug-related changes in QTcF. In addition, GS-248 did not demonstrate any cardiac repolarization risk in non-clinical studies including *in vitro* assay and *in vivo* studies in dogs (cardiovascular and 28 days toxicology studies) at plasma exposures exceeding those in the clinical studies. For further details please see current Investigator's Brochure.

A third study in healthy volunteers (GS-1003) was conducted during October and November 2021. This was a drug-drug-interaction study where 90 mg GS-248 was administered concomitantly with and without erythromycin, a moderate CYP3A4 inhibitor, at an oral dose of 500 mg three times daily. The pharmacokinetic results for GS-248 showed that the concurrent use of erythromycin caused an about eight-fold increase of the area under the plasma concentration curve and little less than three-fold increase of peak plasma concentrations. There is a sizable margin between the systemic exposures in the GS-1003 study and the maximum exposure limits established in toxicity studies at the so called No Observed Adverse Effect Level (NOAEL).

The current study concerns 28 (-2/+1) consecutive days of once-daily dosing with placebo or GS-248 (120 mg taken as 3 x 40 mg capsules in a lipid-based formulation), is predicted to yield a systemic exposure lower than, or close to, that observed following 10 days of repeated dosing with an oral solution formulation at 180 mg/day in the GS-1001 study. To secure the safety of the subjects in the study the following measures have been implemented:

- Subjects will receive their initial dose of study treatment in the study site, under medical supervision and they will be closely monitored.
- Subjects with a mean QTcF interval exceeding 450 msec are not eligible for randomization and will be excluded. Enrolled subjects with a mean QTcF exceeding 480 msec after the first dose will be withdrawn from further treatment as well as subjects with a mean QTcF interval exceeding 500 msec after 2 weeks treatment. This will minimize the potential for arrythmia which is considered to be increased at QTcF intervals >500 msec.

- Subjects are not allowed to use moderate or strong CYP3A4 inhibitors within 5 terminal half-lives or one week, whichever is longer, prior to Visit 2 and throughout the treatment period i.e. day after Visit 4.
- IMP compliance will be recorded by subjects in an eDiary and this information will be collected on a daily basis. In addition, a scheduled visit is planned 2 weeks after the first dose of IMP: AEs will be recorded, and safety assessments performed at this visit.
- Subjects will have access to the clinic, either in person, or by telephone or email, at all times throughout the duration of the study.

Besides any potential risks related to the IMP, there may also be risks related to the medical devices used in the study. However, these are devices used in routine medical care and while they may cause transient discomfort, the associated risk is considered low and ethically justifiable.

Overall, the combined safety data from the pre-clinical studies and the studies in healthy volunteers have not revealed any safety concerns that would outweigh the expected benefits of the study. It is therefore concluded that the potential benefits from the study will outweigh the potential risks for the treated subjects.

More detailed information about the known and expected benefits and risks and reasonably expected adverse drug reactions (ADRs) of GS-248 is found in the current version of the Investigator's Brochure (IB).

The Sponsor is conscious that in the current environment, hospitals should preferentially treat subjects with COVID-19 and give priority to trials for the prevention or treatment of COVID-19 infection. This trial will therefore only be initiated at a time when it is ethically and operationally feasible for each of the selected study sites to do so (see Section 7.1.6). There is currently no known increased risk of contracting COVID-19 as a result of taking the IMP. In addition, study visits will be conducted in such a manner as to ensure subject safety is paramount and to eliminate potential risks of COVID-19 transmission.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objective and Endpoints

Table 2.1: Study Objectives and Endpoints

Objectives	Endpoints
Primary: To determine the safety and efficacy of GS-248 versus placebo on RP in subjects with SSc.	**EFFICACY** ***Primary Efficacy:*** Mean change from baseline to week 4 in the number of Raynaud's Phenomenon attacks per week. ***Key secondary efficacy:*** • Mean change from baseline to week 4 in the Raynaud's Condition Score (RCS). • Mean change from baseline to week 4 in the cumulative duration of Raynaud's Phenomenon attacks. • Mean change from baseline to week 4 in pain experienced during RP attacks. ***Exploratory efficacy:*** • Patient Global Impression of Change at week 4. • Physician Global Impression of Change at week 4. • Mean change in ASRAP Questionnaire score from baseline to week 4. **SAFETY** ***Safety Endpoints:*** • Incidence of Adverse events. • Incidence of Serious Adverse Events. • Clinical laboratory and vital signs.
Secondary: To determine the efficacy of GS-248 on peripheral vascular blood flow in subjects with SSc and RP.	***Secondary:*** • Mean change from baseline to week 4 in peripheral blood flow prior to cold challenge and IMP administration. • Mean change in peripheral blood flow from pre-IMP to post-IMP administration at Visit 2.

Objectives	Endpoints
	• Mean change in recovery of peripheral blood flow after cold challenge from pre-IMP to post-IMP administration at Visit 2. • Mean change from baseline to week 4 in recovery of peripheral blood flow after cold challenge.
Exploratory: • To explore the PK of GS-248. • To explore the efficacy of GS-248 on PGE_2 formation in whole blood *ex vivo*. • To explore the efficacy of GS-248 on formation of arachidonic acid metabolites. • To explore the efficacy of GS-248 on inflammation and endothelial dysfunction. • To explore the efficacy of GS-248 on platelet activation. • To explore the efficacy of GS-248 on microvascular volume. • To collect blood and urine for potential future analysis of inflammatory biomarkers and endothelial dysfunction (results will be reported at a later date).	***Exploratory:*** • GS-248 levels in plasma. • Change in PGE_2 level in whole blood *ex vivo* from baseline to week 4. • Change in levels of PGEM, PGIM and TXM in urine from baseline to week 4. • Change in levels of biomarkers in blood/plasma from baseline to week 4. • Expression of platelet surface markers. • Change in microvascular volume from baseline to week 4.

3 OVERALL DESIGN AND PLAN OF THE STUDY

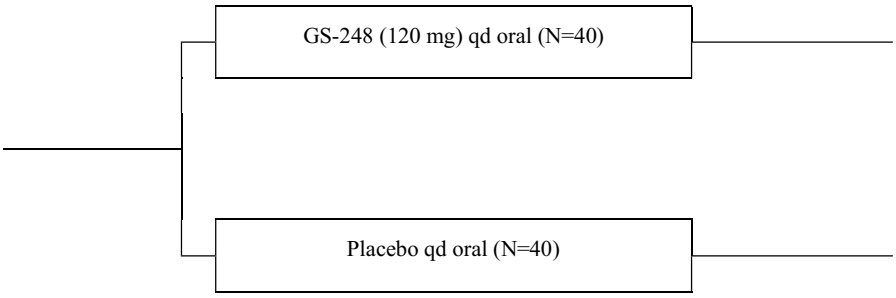
3.1 Overview

This is a randomised, double-blind, placebo-controlled study conducted in multiple sites in 4 countries in Europe. Approximately 80 subjects will be randomised in a 1:1 allocation to receive either GS-248 (120 mg) or placebo once daily, stratified to any of the 3 strata of background vasodilatory treatment (Ca-blockers, PDE-5 inhibitors, or no background vasodilatory treatment), with approximately 40 subjects in each treatment group.

The study will comprise a run-in/enrolment period, a treatment period, and a follow-up period, with a total of 5 study visits (see Overall Schedule of Assessments, APPENDIX 2).

Study assessments of thermography and pharmacodynamics will be conducted at pre-selected sites based on availability of technology (see Overall Schedule of Assessments, APPENDIX 2).

Figure *1*: Study Design



Day	-21 to -14	1	15(±2)	28 (-2/±1)	42-49
Visit	1 Screening/ Run-in	2 Randomization/ Start Treatment	3 Treatment/analyses	4 End of Treatment	5 Follow-up/ Final Visit

qd: once daily

Run-in/Enrolment Period

Informed consent will be confirmed at Visit 1 (Screening Visit) from each subject and eligibility for the study will be established. Eligibility screenings will be conducted, including demographic data, subject medical history, a physical examination, and other procedures. In addition, blood and urine samples will be collected. Subjects will be issued with an eDiary to record information on a daily basis, including the number of Raynaud attacks and RCS (see Overall Schedule of Assessments, APPENDIX 2).

Treatment Period

On Day 1 (Visit 2, Baseline Visit) subjects will be reviewed for eligibility and subsequently randomised and receive their first dose of IMP under medical supervision at the study site. Study assessments, including PK sampling and safety, will be performed throughout this visit. In total, this visit will last for approximately 4 or 6 hours depending on whether the subject is enrolled in the cold challenge assessment or not. Subjects will be permitted to leave the study clinic for short time

periods between assessments as feasible but will be asked to remain on site. At the end of the visit, subjects will be dispensed sufficient amount of medication to last until the next study visit, scheduled for 14 (±2) days later.

Subjects will continue to fill in their eDiary throughout the Treatment Period.

On Day 15 (±2 days) subjects will return to the study site for Visit 3. Safety assessments, PK sampling and safety monitoring will be performed (see Overall Schedule of Assessments, APPENDIX 2). Treatment compliance will be checked, used bottle of IMP collected, and sufficient IMP for the remainder of the Treatment Period will be distributed. The visit will last approximately 1,5 hours.

Visit 4, End of Treatment Visit, will occur on Day 28 (-2/+1 days), which will be the day subjects take their final dose of IMP, to be administered at the study site.

This visit will last for up to 5 hours, and for subjects undergoing rich PK sampling, this visit will last for up to approximately 9 hours. Additional safety and monitoring assessments will be performed (see Appendix 4).

The eDiary will be checked, and all IMP will be collected.

An ASRAP questionnaire will be completed by subjects, along with a Global Impression of Change, which is also completed by physicians.

Follow-Up Period

The follow-up visit (Visit 5, Day 42-49) should occur 2-3 weeks after the last dose of IMP. Safety assessments will be performed (see Overall Schedule of Assessments, APPENDIX 2). Subjects will complete the final entry in their eDiary, and these will be collected. The visit will last approximately 1,5 hours.

3.2 Discussion of Study Design

This is a randomised, double-blind, placebo-controlled, multi-center study. The aim of this study is to collect safety and efficacy data of GS-248 at a dose of 120 mg. To meet the objectives, a control group treated with placebo in a parallel group design will be applied. Power calculations have been performed to ensure the number of subjects needed is limited to a reasonable number. To maintain the integrity of the study data, a double-blind design has been selected. The safety and tolerability of GS-248 has already been studied in two Phase I studies that included healthy male and female subjects (age range 18-75 years) dosed up to 300 mg single dose and up to 180 mg for 10 days. In the present study, subjects with SSc and RP will be included to explore the possible treatment efficacy on RP and potential safety concerns of the IMP in a relevant population. The duration of the treatment period is considered long enough to be able to evaluate a significant effect on the primary endpoints based on previous experience in this patient population.

3.3 Dose justification

The dose in the present study (120 mg once daily) is chosen to achieve a PK profile that completely blocks mPGES-1 generated PGE_2 production and results in an increased PGI_2 production, to secure a reliable read-out of the clinical efficacy of GS-248 in the selected study population.
GS-248 administered orally as single doses (40 mg to 300 mg) resulted in complete mPGES-1-mediated inhibition of PGE_2 synthesis. Furthermore, GS-248 administered orally as multiple doses (60 mg and 180 mg) for 10 days resulted in an increase in the

vasodilatory and platelet-inhibitory prostacyclin, PGI_2, as measured by the increased urinary excretion of the prostacyclin metabolite PGIM. The data also suggest a dose-dependent effect on the PGIM excretion from 20 mg to 180 mg.

The selected dosing regimen of repeated once daily doses of 120 mg GS-248 with the chosen lipid-based formulation in capsules is predicted to yield a systemic exposure lower than, or close to, that observed following 10 days of repeated dosing with an oral solution formulation at 180 mg/day.

In previous Phase I studies it was demonstrated that GS-248 was safe and well tolerated at single doses of 300 mg and at multiple doses of 180 mg daily for 10 days see current version of the Investigator's Brochure.

3.4 End of Study Definition

A subject is considered to have completed the study if he/she has completed all phases of the study including the Follow-up visit.

The end of the study is defined as the date of the last visit of the last subject in the study.

4 STUDY POPULATION

4.1 Inclusion Criteria

Individuals who meet all of the following criteria are eligible to participate in the study.

1. Subjects must provide signed and dated written informed consent before the conduct of any study-specific procedures.
2. Male and female subjects aged 18-75 years inclusive.
3. Systemic Sclerosis diagnosed according to European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) criteria (van den Hoogen F et al. 2013).
   Subjects with signs of other autoimmune diseases (e.g. Sjögren's syndrome, myositis, rheumatoid arthritis) could be included if SSc is the dominating phenotype.
4. Raynaud attacks typically ≥7 times per week during the last 4 weeks prior to screening despite background medication (only allowed vasodilatory therapy is calcium channel blockers or PDE-5 inhibitors).
5. Women of childbearing potential (WOCBP) must be using a highly effective method of contraception to avoid pregnancy throughout the study and for 4 weeks after the last dose of IMP in such manner that the risk of pregnancy is minimised (see APPENDIX 12).
6. Women must not be pregnant or breastfeeding.
7. Male subjects to agree to use condom in combination with use of contraceptive methods with a failure rate of <1% to prevent pregnancy and drug exposure of a partner, and refrain from donating sperm from the first date of dosing until 3 months after last dosing of the IMP.
8. Ability of subjects to participate fully in all aspects of this clinical trial.

   In addition to fulfilling all eligibility criteria, subjects must fulfil the following criteria to be randomised:
   - ≥7 RP attacks during the last week of the run-in period as captured in the eDiary, with no more than 2 days without RP attacks.
   - Compliance with the eDiary during the 7 most recent days prior to baseline (Visit 2), excluding the visit day itself, defined as having submitted ≥5 days of eDiary records (out of a possible 7 days) for RCS and RP during that period.

4.2 Exclusion Criteria

Individuals who meet any of the following criteria are not eligible to participate in the study.

1. SSc disease duration of greater than 120 months from first non-Raynaud manifestation
2. Current smokers or stopped smoking or used nicotine in any form <3 months prior to Visit 1.
3. Dose-change or initiation of vasodilating substances (calcium blockers *or* PDE-5 inhibitors) within 4 weeks prior to Visit 1. Subjects are not allowed to use a combination of calcium blockers and PDE-5 inhibitors from 4 weeks prior to Visit 1 and throughout the study.
   .

4. Use of iloprost or other intravenous (iv) or po prostacyclin receptor agonist within 4 weeks prior to Visit 1.
5. Ongoing treatment with immunosuppressive therapies (other than mycophenolate) including, but not restricted to; cyclophosphamide, azathioprine, methotrexate, or cyclosporine, or use of those medications within 4 weeks of trial entry.
   Note: Subjects could be included if they have been treated with a stable dose of mycophenolic acid during 4 weeks prior to Visit 1.
6. Use of systemic corticosteroids during 4 weeks prior to Visit 1 and during the course of the study.
7. Use of moderate or strong CYP3A4 inhibitors within 5 terminal half-lives or one week, whichever is longer, prior to Visit 2. Examples of a moderate or strong CYP3A4 inhibitors are diltiazem, verapamil and grapefruit juice. See Appendix 13 for more examples.
8. Concurrent serious medical condition, with special attention to cardiovascular conditions, which in the opinion of the Investigator makes the subject not suitable for this study.
9. Prolonged QTcF interval defined as a mean QTcF >450 msec at Visit 1, or at Visit 2 (prior randomisation).
10. Creatinine clearance <50 mL/min (determined by Cockcroft-Gault equation) at Screening (Visit 1).
11. Active digital ulcer (DU) within 4 weeks prior to Visit 1.
12. Have known allergies to any components of the GS-248 formulation.
13. Clinically meaningful laboratory abnormalities at Screening (Visit 1), as determined and documented by the Investigator.
14. Positive test results for HbsAg, HCVAb or HIV-1 and/or -2 antibodies at Screening (Visit 1)
15. Subjects known or suspected of not being able to comply with this trial protocol (e.g. due to alcoholism, drug dependency or psychological disorder).
16. Subject is mentally or legally incapacitated at the time of screening or has a history of clinically significant psychiatric disorders that would impact the subject's ability to participate in the study according to the Investigator.
17. Malignancy within the past 5 years except for in situ removal of basal cell carcinoma and cervical intraepithelial neoplasia grade I.
18. Planned major surgery within the duration of the study.
19. Blood donation (or corresponding blood loss) within 12 weeks prior to Visit 1.
20. Participation in another interventional clinical study within 4 weeks or given an experimental drug within 5 half-lives, whichever longest, prior to Visit 1.

Exclusion criterion for cold challenge:

- At Visit 2: Finger temperature below 27°C after acclimatising at an ambient temperature of 23°C (±2°C) for a period of 20 minutes.

4.3 Screening Failures

Screening failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screening failure information is required to ensure transparent reporting of screening failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities.

Minimal information includes demography, screening failure details, eligibility criteria, and any serious adverse event (SAE).

If due to COVID-19 restrictions, Visit 2 cannot be conducted within 2 to 3 weeks of the Screening Visit re-screening is permitted. SSc Related Autoantibody tests do not need to be repeated: the initial Screening Visit result will be used. Re-screened subjects will be given a new subject number.

4.4 Subject Identification and Randomization

Each participating investigative study site will be assigned a 3-digit investigative study site number: the first digit will denote the country and the second and third digits will denote the site (e.g., 101, 102, 103, and up). Each subject will receive a3-digit Screening number in sequential order at the Screening Visit after the consent form is signed (e.g., 001, 002, 003), regardless of the investigative study site at which the subject is enrolled. Each subject will then have a unique 6-digit study number comprising of the 3-digit Investigative study site number and 3-digit Screening number (e.g., 101-001, 101-002, 101-003), Enrolled subjects who fail Screening or discontinue study participation early, regardless of whether treatment was received or not, will retain their subject number and a new number will be assigned to the next enrolled subject.
Subjects will be randomised in a 1:1 allocation and stratified into 3 strata for use of background vasodilatory treatment Ca-blockers, background vasodilatory treatment PDE-5 inhibitors, or no background vasodilatory treatment, to receive either GS-248 (120 mg) or placebo.
Randomization will be performed by central randomization using the electronic Case Report Form (eCRF).

4.5 Subject Withdrawal and Replacement

As a result of treatment discontinuation, all subjects must complete an Early Termination visit (Visit 5) within 2-3 weeks after their last IMP dose.

There will be no replacement of withdrawn subjects.

The study participation of an individual subject must be discontinued, and no additional IMP doses given if the mean QTcF interval is above 480 msec post IMP administration at Visit 2, or above 500 msec at Visit 3.

The study participation of an individual subject may be discontinued prematurely for reasons such as:

- Adverse Event: Clinical or laboratory events that in the judgment of the investigator or the Sponsor and in the best interest of the subject constitute grounds for discontinuation. This includes serious and non-serious AE regardless of relation to IMP.
- Withdrawal of written informed consent: If a subject withdraws consent for disclosure of future information at the discontinuation of the study or after completion of the study, no further evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use data collected before the subject withdrew his/her consent. The reason for withdrawal of consent is only applicable if the subject denies any further contact with the site and no further data collection.

- Required treatment with any prohibited medication known or suspected to interfere with the pharmacological effect of IMP (see Section 5.7) as assessed by the Medical Monitor.
- Lack of study compliance: The subject´s findings, or conduct, fails to meet protocol entry criteria or fails to adhere to the protocol requirements.
- Treatment unblinding.
- Any other condition which in the opinion of the Investigator no longer permits safe participation in the study.

A subject may discontinue participation in the clinical study at his/her own request at any time without stating a reason.

The Investigator can stop a subject's participation in the study at any time if continuation could lead to disadvantages for the subject which cannot be justified by the Investigator.

The reason for withdrawal of the subject must be documented by the Investigator together with all data collected until the day of premature study discontinuation including laboratory results and assessment of AEs.

4.6 Lost to Follow-up

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

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

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel them on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.
- For all randomised subjects, including those who did not receive any IMP, site personnel will attempt to collect the vital status of the subject within legal and ethical boundaries. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the subject will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

5 INVESTIGATIONAL MEDICINAL PRODUCT AND CONCOMITANT MEDICATION

5.1 Identity

GS-248 is a selective inhibitor of mPGES-1.

For this clinical trial, GS-248 will be provided in a capsule formulation. Each capsule contains 40 mg of GS-248.

Each single treatment dose is to be administered once daily, orally, and consists of 3 capsules, constituting a total of 120 mg GS-248 per IMP administration.

The capsules are orange HPMC capsules size 1. The active capsules contain GS-248 hydrogen sulphate salt and Macrogol-32 stearate.

Placebo will be supplied as identical orange HPMC capsules size 1. The placebo contains the same excipients as the active capsules, but no GS-248.

5.2 Administration

The initial dose of IMP will be taken at the study site at Visit 2 under supervision of the Investigator or their staff. Subsequent doses of IMP will be self-administered by the subject, taken orally, once daily, with the exception of the final dose of IMP, which will be taken at the study site (Visit 4). The IMP will be administered with water, in the morning with food.

5.2.1 Continued Access to Study Intervention After the End of the Study

Treatment with the investigational drug GS-248 cannot continue for individual subjects when study participation ends. At present, only pre-clinical safety coverage for up to 1 month of treatment in humans is available. GS-248 is in early clinical development and patients should be monitored carefully in clinical studies until safety and efficacy have been demonstrated. Other licensed treatments are available to alleviate the symptoms of RP.

5.3 Packaging, Labelling and Storage

IMP will be packaged by the Sponsor according to all local legal requirements. IMP will be labelled in accordance with applicable regulatory requirements.

All IMP supplies must be stored in accordance with the manufacturer's instructions (i.e. packed in plastic (HDPE) bottles and stored at 15-25°C. Until dispensed to the subjects, IMP will be stored in a securely locked area, accessible to authorised personnel only.

Each bottle will be given a unique code, clearly visible on the label. All bottle codes will be included in a master list, which neither the Investigators nor study staff will be able to access (see Section 5.4). To ensure the second bottle received by a subject contains the same IMP as the first (i.e. either both contain active drug or placebo), and to maintain the double-blind, codes will be automatically generated electronically from the master list.

Packaging and labelling of IMP will comply with Good Manufacturing Practice (GMP), GCP rules, Annex 13, and country specific regulatory requirements; this information will be available in the local language.

5.4 Blinding and Breaking the Blind

The study will be performed double-blind to treatments. IMP and placebo will be supplied in identical plastic (HDPE) bottles and will be similar in colour, smell, taste, and appearance, thereby enabling double-blind conditions.

The study blind should not be broken except in a medical emergency (where knowledge of the IMP received would be required in order to provide appropriate medical treatment for the subject) or regulatory requirement. The blind can be broken by the Investigator, following an assessment, if they deem it to be in the interest of the subject; the Investigator **must** inform the Medical Monitor within 24 hours after breaking the blind.

If an Investigator, site personnel performing assessments, or subject is unblinded, the subject must be withdrawn from the study and procedures accompanying withdrawal (e.g. follow-up) are to be performed.

In the event that unblinding is necessary, this will be done through the eCRF and the Medical Monitor/Sponsor must be notified within 24 hours of unblinding. The eCRF will also record the time and date of the blind break, together with details of the person breaking the blind.

The overall randomization code will be broken only for study reporting purposes. This will occur once all final clinical data have been entered onto the database and all data queries have been resolved.

5.5 Drug Accountability

The Investigator is ultimately responsible for maintaining accurate IMP accountability records throughout the study, although this may be delegated to an appropriate sub-Investigator or department, such as the Pharmacy.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for maintaining up to date inventory and accountability logs. Each dispensing of IMP will be documented in the medical records and/or inventory/accountability logs.

The Investigator is responsible for destroying all unused IMP locally and must verify that all unused IMP supplies have been returned by the subject, and that no remaining supplies are in the subject's or Investigator's possession.

5.6 Compliance with IMP

Subjects will receive their first and last dose of IMP at the study site under supervision. At visit 2 they will be discharged from the study site and dispensed with sufficient IMP to enable daily dosing until the next study visit. All subjects will record the time they take each dose of IMP into the eDiary: each subject's eDiary will be reviewed at each study visit.

5.7 Concomitant Medications

Any medication the subject takes other than the IMP is considered a concomitant medication. All concomitant medications must be recorded in the eCRF. The following information must be recorded in the eCRF for each concomitant medication: generic name, route of administration, start date, stop date, dosage, and indication. Any changes

in the dosage or regimen of a concomitant medication must be recorded in the eCRF. A COVID-19 vaccination is considered a permitted concomitant medication and is therefore not contraindicated for use with GS-248.

At each subsequent study visit, subjects will be asked what concomitant medications they are currently taking.

Table 5.1: Prohibited Concomitant Medications and Restricted Procedures

Permitted or restricted	Not Permitted
	Subjects are not allowed to use any moderate or strong CYP3A4 inhibitors, e.g. diltiazem, verapamil or grapefruit juice, 1 week or 5 terminal half-lives, whichever is longest, prior to Visit 2 and until the day after Visit 4. (See Appendix 13 for additional examples of moderate and strong CYP3A4 inhibitors.)
Sun protection required from dose administration to follow-up in line with CDC recommendations (https://www.cdc.gov/cancer/skin/basic_info/sun-safety.htm) Avoidance of artificial sunlight (e.g. sunbeds) from dose administration to follow up.	Use of non-steroidal anti-inflammatory drugs (NSAIDs), Cox-inhibitors, Aspirin, Nitrates, Nitric oxide donors, endothelin receptor antagonists (ERAs), Alpha-blockers and Anti-thrombotic agents is not allowed from Visit 1 to Visit 5.
	Any treatment (oral or topical) for RP other than Calcium channel blockers or PDE5 inhibitors from Visit 1 to Visit 5. Subjects are not allowed to use a combination of calcium blockers and PDE-5 inhibitors from Visit 1 to Visit 5.
Subjects who have been treated with a stable dose of mycophenolic acid during 1 month prior to visit 1 could continue that dose during the study.	Subjects are not allowed to use immunosuppressive therapies including, but not restricted to; cyclophosphamide, azathioprine, methotrexate, or cyclosporine from Visit 1 to Visit 5.
Use of inhaled and topical corticosteroids is allowed throughout the study.	Use of systemic corticosteroids is not allowed from Visit 1 to Visit 5
Use of herbal remedies, supplements and drugs taken without prescription, with the exception of paracetamol, may only be permitted with prior consent from the Investigator due to potential interaction. Subjects should report use of all vitamins (especially vitamin PP [niacin]), vitamin supplements and food supplements during the study.	Use of the SSRI fluoxetine, ARBs, and bosentan are not allowed from Visit 1 to Visit 5.
For WOCBP, use of highly effective contraceptive methods that includes an additional barrier method (in case a hormonal contraceptive method is used), until 4 weeks post last dose. Male subjects with partners who are WOCBP must use a condom in combination with the use of contraceptive methods with a failure rate of <1% to prevent pregnancy and drug exposure of a partner, and refrain from donating sperm from the first date of dosing until 3 months after last dosing of the IMP.	Subjects should not use nicotine-containing products including patches or chewing gum.

5.8 Treatment of Overdose

No experience with overdose of GS-248 in humans exists. In case of an overdose of IMP, treatment should be suspended, and the subjects should receive appropriate medical treatment according to the clinical condition. At present there is no known antidote for use in the case of overdose with GS-248.

6 ENDPOINTS AND METHODS OF ASSESSMENT

All subjects will be issued with an eDiary which will be used on a daily basis throughout the study. All eDiary assessments and reminders to the subjects are presented in the appendices (see APPENDIX 10).

6.1 Efficacy Endpoints

6.1.1 Primary Efficacy Endpoint

The mean change in number of weekly RP attacks from baseline (from the 7 most recent days prior to Visit 2) to week 4 (from the 7 most recent days prior to Visit 4) will be collected prior to each visit using data entered by subjects in the eDiary.

6.1.2 Key Secondary Efficacy Endpoints

- The mean change in RCS from baseline (from the 7 most recent days prior to Visit 2) to week 4 (from the 7 most recent days prior to Visit 4) will be collected prior to each visit using data entered by subjects in the eDiary.
- The mean change in cumulative duration of RP attacks from baseline (from the 7 most recent days prior to Visit 2) to week 4 (from the 7 most recent days prior to Visit 4) will be collected prior to each visit using data entered by subjects in the eDiary.
- Data for numeric rating scale (NRS) pain will be assessed using eDiaries, and the mean change in pain experienced during RP attacks from baseline (from the 7 most recent days prior to Visit 2) to week 4 (from the 7 most recent days prior to Visit 4) will be collected prior to each visit using data entered by subjects in the eDiary.

6.1.3 Secondary Efficacy Endpoints

- Mean change from baseline to week 4 in peripheral blood flow prior to cold challenge and IMP administration.
- Mean change in peripheral blood flow from pre-IMP to post-IMP administration at Visit 2.
- Mean change in recovery of peripheral blood flow after cold challenge from pre-IMP to post-IMP administration at Visit 2
- Mean change from baseline to week 4 in recovery of peripheral blood flow after cold challenge (see APPENDIX 5).

Peripheral vascular blood flow will be assessed by thermography. Methods for thermography and cold challenge are described in APPENDIX 5.

6.1.4 Exploratory Efficacy Endpoints

- Patient Global Impression of Change will be completed at Visit 4 to gain subjects' impression of change in their RP.
- Physician Global Impression of Change will be completed at Visit 4 to gain their impression of change in the subject's RP.
- ASRAP questionnaires will be completed by subjects to determine mean change in ASRAP score from baseline (Visit 2) to week 4 (Visit 4).

6.2 Safety Assessments

6.2.1 Adverse Events

6.2.1.1 Definitions

Per ICH, an AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. The AE may be any of the following:

- A new illness
- An exacerbation of a sign or symptom of the underlying condition or of a concomitant illness
- Unrelated to participation in the clinical study or an effect of the study medication or comparator drug
- A combination of 1 or more of the above factors

No causal relationship with the study medication is implied by the use of the term adverse event.

Planned or elective surgical or invasive procedures for pre-existing conditions that have not worsened are not AEs. However, any complication that occurs during a planned or elective surgery is an AE. Conditions leading to unplanned surgical procedures may be AEs.

When an AE occurs after written consent has been obtained but before the first dose of IMP, the AE will be considered a non-treatment emergent AE. An AE that occurs from the time the subject receives his/her first dose of IMP until his/her last study visit will be considered a treatment-emergent AE regardless of the assessed relationship to the administration of the IMP.

For the recording of pregnancy and relevant laboratory data see Section 6.2.1.2.

Immediately Reportable Information

Immediately reportable information that must be reported to the Sponsor within 24 hours of the study site being informed (reporting requirements are detailed in Section 6.2.1.2).

Immediately reportable information includes:

- All SAEs
- Overdose (with or without AEs)
- Pregnancy (with or without AEs)

Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence or effect that at any dose:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity

- Is a congenital anomaly or birth defect
- Is another medically important condition

An important medical event that is not immediately life threatening or will result in death or hospitalization, but which may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above, should be reported as "serious" as well.

"Occurring at any dose" does not imply that the subject is receiving IMP at the time of the event.

Severity of Adverse Event:

Refers to the extent to which an AE affects the subject's daily activities. Severity will be categorised according to the following criteria:

Mild:	The AE does not interfere with the subject's routine activities.
Moderate:	The AE interferes with the subject's daily routine, but usual routine activities can still be carried out.
Severe:	The AE results in the inability to perform routine activities.

The term "severity" is used to describe the intensity of an event. This is not the same as "serious". Seriousness, not severity, serves as the guide for defining regulatory reporting obligations. The highest severity grade attained should be reported, for AEs with divergent severities.

Causality of Adverse Event:

The Investigator must assess the causal relationship between an AE and the IMP using the definitions below and record it the AE Log of the eCRF. An AE is considered causally related to the use of the IMP when the causality assessment is probable or possible.

Probable:	The event has a strong temporal relationship to the IMP or recurs on re-challenge, and another aetiology is unlikely or significantly less likely.
Possible:	The event has a suggestive temporal relationship to the IMP, and an alternative aetiology is equally or less likely.
Unlikely:	The event has no temporal relationship to the IMP or is due to underlying/concurrent illness or effect of another drug (that is, there is no causal relationship between the IMP and the event).

6.2.1.2 Recording Adverse Events

All SAEs will be collected from the signing of the informed consent form (ICF) until the follow-up visit at the time points specified in the Overall Schedule of Assessments (SoA) (see APPENDIX 2).

All AE will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA.

Period: Subject Enrolment to the First Administration of IMP: Non-treatment emergent AEs will be recorded from the time when the subject is enrolled into the study (date of signature of the informed consent) until first administration of IMP.

Period: First Administration of IMP to Subject's last study visit: Thereafter all AEs are treatment-emergent AEs (TEAEs, see Definitions, Section 6.2.1.1) and will be recorded until the final follow-up visit has been performed.

Period after last study visit: Any SAE occurring after the subject's last study visit but considered by the investigator to be related to the IMP will be recorded.

If an AE (serious or not) started during the study but did not end before the final follow-up visit, the investigator should make a reasonable effort to establish the outcome and the end date. If this is not possible, the outcome recorded at the final follow-up visit will be assumed to be the final outcome.

If an event stops and later restarts, all the occurrences must be reported. AEs assessed as related to study medication by the investigator and all SAEs must be followed up until resolution.

Signs/symptoms should be documented if a definite diagnosis cannot be established. The investigator should attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms. If a diagnosis is accompanied by unusual symptoms, the diagnosis itself and the symptoms must be reported separately.

In addition to the definition as given, the following special types of events should be recorded:

a) **Pregnancy –** Although not an AE per se, occurrence of pregnancy in a subject during a clinical study must be recorded.
b) **Laboratory values that are outside the normal range** and if, in the opinion of the investigator, these values represent a clinically relevant change versus pre-treatment values are also defined as AEs.

If abnormal laboratory values are signs of an AE (e.g., an infection) that has already been recorded, the respective abnormal laboratory value does not constitute a separate AE.

Wherever reasonable the reporting investigator will use the clinical term rather than the laboratory term (e.g., anaemia versus low haemoglobin value).

6.2.1.3 Responsibilities of the Investigator

AE data should be obtained through observation of the subject, from any information volunteered by the subject, or through subject questioning. The general type of question asked could be similar to: "Do you have any health problems?" or "Have you had any health problems since your last clinic visit?"

AEs are to be documented/recorded accurately and completely in the subject's medical records and subsequently reported on the AE pages of the respective eCRF.

All non-treatment and treatment-emergent AEs will be recorded.

This is true even if the IMP was not administered according to the study protocol.

For conditions leading to unplanned surgical procedures the underlying condition, should be documented as an AE, but not the procedure.

Reporting of Immediately Reportable Information:

For AEs that are "serious" (SAEs) additional separate documentation is required using the electronic SAE Forms.

The following variables will be recorded on the SAE Form and on the eCRFs provided in accordance with the eCRF completion guidelines:

- Description of the event, including its duration (date of onset and resolution),
- Whether the event constitutes a SAE or not (if yes, see event seriousness criteria in Section 6.2.1.1)
- Any action taken *(e.g., changes to study treatment, other treatment given and follow up tests*
- Outcome of the event
- Investigator's assessment of causality *(the relationship to the study treatment[s] and study procedures)*
- Severity.

For all SAEs where important or relevant information is missing, active follow-up should be undertaken by the pharmacovigilance department.

The assumption of a causal relationship between the study medication/study conduct and the AE is irrelevant to the obligation to record AEs and notifying Immediately reportable AEs (IRAEs) to the Sponsor.

For withdrawals due to AEs the eCRF page "Study completion / Study termination Form" and a copy of the eCRF AE page needs to be completed and forwarded to the pharmacovigilance department.

Pregnancy Reporting: Each pregnancy that starts during the study must be reported by the investigator to the pharmacovigilance department within 24 hours of the investigator's knowledge of the pregnancy by using the Pregnancy Form. The investigator should make any reasonable effort to follow any pregnancy until birth of the child.

Overdose needs to be reported to the pharmacovigilance department following the criteria for SAE reporting, regardless of whether AE is observed due to overdose.

If additional information is required by the pharmacovigilance department, then as a representative of the Sponsor/PrimeVigilance must be granted access to the medical records.

After subject's last study visit:

The investigator records and forwards to the Sponsor all SAEs that she or he becomes aware of and she or he considers related to the IMP.

6.2.1.4 Responsibilities of the Sponsor

For purposes of safety analyses all AEs will be recorded in the clinical database. To ensure expedited and periodic notification of authorities, SAEs will also be recorded in the drug safety database.

6.2.2 Evaluation of Adverse Events

6.2.2.1 Responsibilities of the Investigator

The investigator will assess the seriousness, severity, and causality of each AE in accordance with the definitions in Section 6.2.1.1. Notification of immediately reportable information must follow the procedure described in Section 6.2.1.3.

Causality of AE:

For all AEs a causality assessment **must** be provided and documented on the respective form (eCRF AE page for all AEs, SAE form for SAEs and eCRF page "Study completion / termination form" for withdrawals due to AEs) even if it is preliminary information.

6.2.2.2 Responsibilities of the Sponsor

The Sponsor will not downgrade the causality assessment provided by the investigator. If the Sponsor disagrees with the investigator's causality assessment, both the opinion of the investigator and the Sponsor will be recorded.

6.2.3 Outcome of Events

This is the outcome of the SAE. This may differ on initial and follow-up reports of an SAE. The Investigator will indicate the outcome on the initial report (for example unresolved) and update as appropriate on follow-up SAE Forms.

1. Resolved – no sequelae. The condition has resolved completely with no lasting side effects.
2. Resolved – with sequelae. The condition has resolved but a medical condition remains as a consequence of the event (e.g. the subject experiences a stroke the sequelae may be numbness in right/left arm and leg).
3. Unresolved. The condition is still present at the time of the report. Follow-up information should be provided on resolution.
4. Death. Condition prompting SAE resulted in the subject's death.

If "Resolved – with sequelae" is chosen, the nature of the sequelae must be specified, and a resolution date should be provided. If "Unresolved" is chosen, the resolution date should be left blank. Subjects should be followed up until the event is resolved and a follow-up SAE Form should be provided at this time. Hence, it is anticipated that on the conclusion of an event an outcome other than "Unresolved" would be chosen and a resolution date would be provided. The only exception to this would be:

1. If the event described is classified as a congenital abnormality/birth defect. In this circumstance this should be clearly indicated on the form.
2. If "Death" is chosen, the resolution date will be the date of death. An autopsy report should be provided if available.

6.2.4 Notifying of Adverse Events

6.2.4.1 Responsibilities of the Investigator

For immediately reportable information (SAEs, overdose, and pregnancy) the investigator must inform the pharmacovigilance department via e-mail or fax using the SAE report within 24 hours of the study site being informed of such event.

Adverse Event Reporting Contact:

For this study, the pharmacovigilance department will be the PrimeVigilance Safety Department.

Fax: +44 (0) 800 471 5289
E-mail: GesyntaPV@primevigilance.com

For any questions regarding safety reporting, the Investigator should reach out to the PrimeVigilance Safety Department using the contact details above. In case of any

urgent queries related to the safety of the subjects involved in the trial, the site should phone the Medical Monitor.

Investigators or other site personnel should inform PrimeVigilance's Safety department of any follow-up information that becomes available for a previously reported SAE immediately but no later than 24 hours of becoming aware of the information. Follow-up reports (as many as required) should be completed and faxed or e-mailed following the same procedure above. Any requested supporting documentation (e.g., electrocardiogram [ECG], laboratory results, autopsy report) should be sent to PrimeVigilance's Safety department.

Prior to forwarding any copies of medical records as supporting documentation for safety reporting, these documents need to be coded in a way that keeps the subject's identity confidential (e.g., by using the subject's identification code, randomization number, etc. and subject personal data blinded – further instructions will be provided by your responsible Monitor).

For fatal and life-threatening SAEs, PrimeVigilance's Safety department will work with the investigator to ensure that any additional information is provided by the investigator within 1 business day. The investigator will ensure that all the necessary information for all other SAEs will be provided within the timelines stipulated by the Sponsor when the request for information is made.

If required, the investigator is responsible for informing local IECs of safety reports in compliance with applicable regulatory requirements. Copies of all correspondence relating to reporting of any safety reports to the IEC should be maintained in the Investigator Site File (ISF).

Subject Enrolment to the First Administration of IMP:

Only serious procedure-related AEs will be reported to the Sponsor using the reporting process (SAE report form) as described above.

After subject's last study visit:

The investigator will notify PrimeVigilance's Safety Department of any SAE that she or he becomes aware of and considers related to the IMP.

Following-up AEs / SAEs:

At the subject's last study visit (including the Early Termination Visit), a Safety Follow-up Visit should be scheduled up to 2 weeks after the final examination only for those subjects who experienced not resolved related AEs or laboratory parameters showing not normalised clinically relevant changes or SAEs. The assessments measured will be determined by the investigator. All data must be documented in the eCRF.

6.2.4.2 Responsibilities of the Sponsor

PrimeVigilance's safety department is responsible for fulfilling all obligations regarding notification of Regulatory Authorities and IECs according to applicable regulatory requirements (expedited and periodic reporting, e.g., serious unexpected suspected adverse reactions, Development Safety Update Report). In addition, the Sponsor will provide safety information to investigators according to the current regulations.

6.2.5 Laboratory Parameters

During the study, the following estimated total amounts of blood for both safety and PD assessments will be taken.

- All subjects –approximately 130 ml
- Subset analyses:
    - PK sampling rich – an additional 28 ml
    - PGE_2 levels in whole blood – an additional 8 ml
    - Platelet activation (FACS) – an additional 12 ml

Laboratory assessments will be performed centrally at the central laboratory by means of their established methods. Before starting the study, the central laboratory will supply PrimeVigilance/the Sponsor with a list of the normal ranges and units of measurement.

Safety laboratory assessments (Table 6.1) will be conducted on samples collected and analysed by standard laboratory procedures at the time points designated in the Overall Schedule of Assessments (see APPENDIX 2). Tests that are not done must be reported as such on the eCRFs.

Table 6.1: Safety Laboratory Assessments

Clinical chemistry	Haematology
P/S-Albumin	B-Haemoglobin (B-Hb)
P/S-Sodium	B-Erythrocyte count (B-EPC)
P/S-Potassium	B-Ery-Mean Corpuscular Volume (B-MCV)
P/S-Calcium, total	B-Haematocrit (Erythrocyte volume fraction B-EVF)
P/S-Glucose	B-Platelet count (B-Thrombocyte particle concentration B-TPC)
P/S-C-reactive protein (P-CRP)	B-Leukocyte count (B-LPC)
P/S-Bilirubin, total	B-Leukocyte differential, absolute count (lymphocytes, monocytes, neutrophil-, eosinophil- and basophil-granulocytes)
P/S Bilirubin – conjugated	
P/S-Uric acid	
P/S-ASAT	HBV
P/S-ALAT	HCV
P/S-Cholesterol	HIV
P/S-Cystatin C	**Urinalysis – dipstick semi-quantitatively**
P/S-Creatinine	In event of abnormal findings reanalysis or urine to be sent for further lab analysis if considered clinically relevant by the investigator
eGFR	
P/S-Osmolality	
P/S-Urea or BUN	
U – Creatinine	
P/S-ALP	U – pH
P/S-GT	U – Glucose
P/S-LDH	U – Ketone
S-Electrophoresis	U – Bilirubin
pro-BNP	U – Blood
Hormone analysis (enrolment only)	**FSH test** (at enrolment, postmenopausal females only)
P/S-free T3	P/S-FSH
P/S-total T4	
P/S-free T4	**Drug screen***
P/S-Thyroid Stimulating Hormone (TSH)	Standard practice at site (minimally to include alcohol† and cocaine)
	Pregnancy test (WOCBP)
	Urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG)

* To minimally include screening for alcohol and cocaine, but preferably also THC, opioids, barbiturates, and benzodiazepines.

† Subjects are not permitted to consume alcohol from midnight prior to a visit involving cold challenge until the end of that study visit.

6.2.6 Vital Signs

Vital signs will be measured and recorded at the time points designated on the Overall Schedule of Assessments (see APPENDIX 2). The following measurements must be performed: systolic/diastolic blood pressure and pulse. Vital signs will be measured after the subject has been in the supine position for at least 5 minutes. All measurements will be recorded on the vital signs eCRF. Abnormal test results may be repeated at the discretion of the investigator and must be reported on the corresponding eCRF. When vital signs, ECGs, and/or blood sample collection occur at the same time, vital signs should be performed before ECGs and/or blood sample collection.

6.2.7 Electrocardiograms

During the study, 12-lead ECGs will be performed at the time points designated on the Overall Schedule of Assessments (see APPENDIX 2).

The subject must be in a supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position possible. All ECGs should be performed in a standardised method, in triplicate, and approximately 30 seconds apart, prior to blood draws or other invasive procedures. Each ECG must include the following automatically derived measurements: QRS, uncorrected QT interval (QT), corrected QT, RR, and PR intervals.

The Principal Investigator or designated site physician will review and sign all ECGs. Results must be summarised in writing and classified as normal; abnormal, clinically relevant; or abnormal, not clinically relevant. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the Sponsor, a copy of the original ECG will be made available.

6.2.8 Physical Examinations

The investigator or qualified designee will perform a complete physical examination (genitourinary examination not required) at Screening (Visit 1) and Follow-up (Visit 5) and then abbreviated physical examinations at the time points designated on the Overall Schedule of Assessments (see APPENDIX 2). Pre-dose abnormal findings will be reported on the medical history eCRF. Any adverse change from the baseline physical examination (day 1 examination) will be documented on the AE eCRF. Height will be measured at Screening (Visit 1) only.

A full physical examination will include weight, inspection of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, extremities, musculoskeletal system, nervous system and presence or absence of DUs.

6.3 Other Exploratory Endpoints

6.3.1 Pharmacokinetics

Sparse PK sampling for determination of GS-248 levels in plasma will be performed on all subjects at Visit 2, Visit 3 and Visit 4.

One PK blood sample will be drawn at Visit 2 shortly after the ECG assessment is conducted post IMP administration and one PK blood sample will be drawn at Visit 3 any time during the visit.

At Visit 4 the IMP dose is administered at the study site. Two PK blood samples will be drawn from subjects in the sparse PK group. One sample is drawn immediately before IMP administration and the second sample is drawn either at 120 minutes after IMP administration or, if the subject is enrolled to cold challenge assessments, at 175 minutes after IMP administration.
In approximately 30 subjects, rich PK sampling will be performed at Visit 4, with an additional 6-7 PK samples to be drawn (see APPENDIX 4). Time points for all rich PK sampling at Visit 4 will be pre-dose, 30-, 60-, 90-, 120-, 175-, 240- and 360-min post dose. If feasible, one additional sample should also be drawn at 480 min or as late as possible post dose.

Exact times of IMP administration and time for sampling will be captured in the eDiary and eCRF.

Blood samples will be centrifuged, and separated plasma will be shipped to a bioanalytical laboratory.

The combined data from sparse and rich PK sampling will be incorporated into model-based population PK analyses, the results of which are to be reported separately.

6.3.2 Pharmacodynamics

- PGE_2 levels in whole blood: In up to 30 subjects blood samples will be drawn at Visit 2 and Visit 4 pre-IMP administration to assess change in PGE_2 level in whole blood *ex vivo* from baseline to week 4.
- Levels of PGEM, PGIM and TXM in urine: Spot morning urine samples will be collected by subjects at home and brought to the study site at Visit 2 and Visit 4 for assessment to determine change in levels of PGEM, PGIM, and TXM in urine from baseline to week 4.
- Biomarkers for inflammation and endothelium dysfunction: Blood samples will be collected from all subjects at Visit 2 and Visit 4 pre-IMP administration for analysis of hsCRP, Endothelin-1, sE-selectin, ICAM1, TNF, IL-1b, IL-4, IL-6, IL-10, s-PECAM1 CXCL-4, CD40L and von Willebrand factor to determine change in levels of biomarkers in blood/plasma from baseline to week 4.
- Expression of platelet surface markers: In up to 20 subjects blood samples will be drawn at Visit 2 and Visit 4 pre-IMP administration for analysis of surface markers of platelet activation by FACS analysis to determine change from baseline to week 4.
- Microvascular volume in skin/nailfold: At one pre-defined site, microvascular volume in skin/nailfold (see APPENDIX 6 and APPENDIX 7) will be performed on consenting subjects twice at Visit 2 and Visit 4 (pre-IMP administration and at expected C_{max} by D-OCT), and once at Visit 3 and Visit 5, to determine change in microvascular volume from baseline to week 4.
- Collection of blood and urine samples for Biobank storage: One urine sample each from Visit 2 and Visit 4and four plasma samples, two from Visit 2 and Visit 4 will be stored in a Biobank for up to 3 years after study end for potential future analysis of inflammatory biomarkers and biomarkers for endothelial dysfunction.

7 STUDY CONDUCT

7.1 Observations by Visit

Visits should occur as specified in the Overall Schedule of Assessments (see APPENDIX 2). All times should be recorded using the 24-hour clock (e.g., 23:20, not 11:20 pm).

7.1.1 Screening (Visit 1)

The following procedures and assessments are to be completed at the Screening Visit (Day -21 to -14) at time points designated in the Overall Schedule of Assessments (see APPENDIX 2).

- Confirm ICF signature was obtained before any study related assessments are conducted.
- Record demographic data including sex, age and race
- Record medical/surgical history (including any risk factors)
- Record previous and current medications as well as history of vaccinations
- Complete full physical examination (including weight and height)
- Perform nailfold capillaroscopy (see APPENDIX 7)
- Measure and record vital signs (heart rate and blood pressure)
- Perform 12-lead ECG
- Draw blood for clinical chemistry, haematology and thyroid hormone tests (see Table 6.1)
- Urinalysis dipstick test (see Table 6.1)
- SSc-related autoantibody status test, including antinuclear antibodies (ANA), Sci-70 antibody (anti-topoisomerase I), and anti-centromere antibodies (ACA) (this test does not need to be repeated for subjects who are re-screened)
- Urine pregnancy test in WOCBP, FSH assessment for women not of childbearing potential
- Verify eligibility (inclusion/exclusion criteria)
- Blood draw for hepatitis B, C, and HIV test
- Drug screen (for presence of alcohol or prohibited substances, e.g. cocaine)
- Issue of and training on use of the eDiary
- Perform and record the following assessments:
    - AEs

7.1.2 Baseline Visit (Visit 2)

The following procedures and assessments are to be completed during the Baseline Visit (Visit 2, Day 1) at time points designated in the Overall Schedule of Assessments (see APPENDIX 2) and refer to Schedule of Assessments by Time – Visit 2 (see Appendix 3).

- Record current concomitant medications
- Perform abbreviated physical examination (statement regarding DUs)
- Measure and record vital signs (heart rate and blood pressure)

- Perform 12-lead ECGs pre- and post-IMP administration
- Draw blood for clinical chemistry and haematology tests (see Table 6.1)
- Urinalysis dipstick test (see Table 6.1)
- Urine pregnancy test in WOCBP,
- Verify eligibility (inclusion/exclusion criteria)
- Drug screen (for presence of alcohol or prohibited substances, e.g. cocaine)
- Review of eDiary to check for compliance (eligibility criterion) prior to study enrolment and randomization
- Collect blood and urine samples for storage at the Biobank
- Perform and record the following assessments:
    - Randomisation
    - ASRAP questionnaire (see APPENDIX 11)
    - AEs
    - Initial IMP administration, to be taken with food
    - IMP distribution (a single bottle with sufficient doses until next visit)
    - Urinalysis: AA metabolites and U-creatinine (on the morning sample brought from home by subject)
    - PK sampling (sparse)
    - Blood biomarker sampling
- In addition, but only for subjects at pre-selected sites:
    - For subjects evaluated for enrolment to cold challenge: Measure finger temperature
    - Cold challenge and thermography (see APPENDIX 5)
    - PGE_2 levels in whole blood
    - Platelet activation (FACS)
    - Microvascular volume (see APPENDIX 6)

7.1.3 Visit 3

The following procedures and assessments are to be completed during Visit 3 (Day 15±2 days) at time points designated in the Overall Schedule of Assessments (see APPENDIX 2).

- Record current concomitant medications
- Perform abbreviated physical examination (statement regarding DUs)
- Measure and record vital signs (heart rate and blood pressure)
- Perform 12-lead ECG
- Draw blood for clinical chemistry and haematology tests (see Table 6.1)
- Urinalysis dipstick test (see Table 6.1)
- Review of eDiary
- Perform and record the following assessments:
    - ASRAP questionnaire (see APPENDIX 11)
    - AEs

  - IMP collection and compliance
  - IMP distribution (a single bottle with sufficient doses until next visit)
  - PK sampling (sparse)
- In addition, but only for subjects at pre-selected sites
  - Microvascular volume (see APPENDIX 6)

7.1.4 End of Treatment, Week 4 (Visit 4)

The following procedures and assessments are to be completed during the Treatment Visit, Visit 4 (Day 28-2/+1 days) at time points designated in the Overall Schedule of Assessments (see APPENDIX 2) and refer to Schedule of Assessments by Time – Visit 4 (see APPENDIX 4).

- Record current concomitant medications
- Perform abbreviated physical examination (statement regarding DUs)
- Measure and record vital signs (heart rate and blood pressure)
- Draw blood for clinical chemistry and haematology tests (see Table 6.1)
- Urinalysis dipstick test (see Table 6.1)
- Urine pregnancy test in WOCBP,
- Drug screen (for presence of alcohol or prohibited substances, e.g. cocaine)
- Review of eDiary
- Collect blood and urine samples for storage at the Biobank
- Perform and record the following assessments:
  - ASRAP questionnaire (see APPENDIX 11)
  - Global Impression of Change (Patient and Physician)
  - AEs
  - IMP administration at study site, to be taken with food
  - IMP collection and compliance
  - Urinalysis: AA metabolites and U-creatinine (on the morning sample brought from home by subject)
  - Blood biomarker sampling
  - PK sampling (sparse)
- In addition, but only for subjects at preselected sites:
  - Cold challenge and thermography (see APPENDIX 5)
  - PGE_2 levels in whole blood
  - Platelet activation (FACS)
  - Microvascular volume (see APPENDIX 6)
  - PK sampling (rich)

7.1.5 Follow-up (and/or Early Termination) Visit (Visit 5)

The following procedures are to be completed during the Follow-up Visit (Day 42 to 49) at time points designated on the Overall Schedule of Assessments (see APPENDIX 2). In addition, any subject who withdraws or is withdrawn early from the study during

the Treatment Period, must complete this Follow-up Visit 2-3 weeks after their last dose of IMP.

- Record current concomitant medications
- Perform full physical examination (including weight)
- Measure and record vital signs (heart rate and blood pressure)
- Perform 12-lead ECG
- Draw blood for clinical chemistry and haematology tests (see Table 6.1)
- Urinalysis dipstick test (see Table 6.1)
- WOCBP given home pregnancy test to be used 35-40 days after their last dose of IMP (Visit 4).
- Review and collection of eDiary
- Perform and record the following assessments:
    - ASRAP questionnaire (see APPENDIX 11)
    - AEs
- In addition, but only for subjects at preselected sites:
    - Microvascular volume (see APPENDIX 6)

7.1.6 Study Conduct During a COVID-19 Outbreak

The Sponsor acknowledges that hospitals should preferentially treat subjects with COVID-19 and prioritise trials for the prevention or treatment of COVID-19 infection. Therefore, this trial will only be initiated when it is ethically and operationally feasible for the selected study sites to do so.
In the event of a further COVID-19 outbreak or further restrictions, the Sponsor will review the situation and initiate prepared plans based on the extent of the situation and local conditions. To mitigate for a future impact of the pandemic, the study will be conducted at multiple sites in 4 countries in Europe to increase the possibility of including subjects in sites/countries not (or minimally) affected by COVID-19. The Sponsor will adhere to national and local regulations due to the pandemic, and the study or specific sites or countries will halt recruitment and stop treatment of enrolled subjects as needed. In any event, the subjects' safety will be paramount and all endeavours will be made to judge whether before a subject is enrolled into the study there is a possibility of all safety assessments being conducted during the subject's entire study period.
If the study were to continue, the Sponsor will consider initiating a range of options including, but not limited to:

- Provision of private transport and protective equipment (at least a mask, gloves and hand sanitiser) to facilitate subject visits to the study site.
- A review of study procedures and assessments to ascertain whether it is appropriate for certain study activities to be undertaken remotely. The following plans are in place;
    - If Visit 2 cannot be performed according to the schedule the subject will be a screen failure but can be rescreened at a later time point.
    - If Visit 3 cannot be performed according to the study schedule, study medication should be stopped on the day of Visit 3. Visit 3 and 5 should be scheduled according to SoA but conducted over the

telephone and an onsite Early Termination visit scheduled as close as possible to protocol schedule to conduct laboratory tests and ECG.
    - If Visit 4 cannot be performed according to the schedule, study medication should be stopped at the day of Visit 4. Visit 4 and 5 should be scheduled according to SoA but conducted over the telephone and an onsite Early Termination visit scheduled as close as possible to protocol schedule to conduct laboratory tests and ECG.
    - If Visit 5 cannot be performed, it should be scheduled according to SoA but conducted over the telephone and an onsite Early Termination visit scheduled as close as possible to protocol schedule to conduct laboratory tests and ECG.
- Feasibility of gaining remote (telephone or email) informed consent from subjects in countries where this is permitted, following the current EMA guidance for management of clinical trials during COVID-19 pandemic.
- Initiation and on-going central monitoring of data if study Monitors are not permitted access to study sites.

Whilst general plans can be prepared in advance, the implementation of each activity will be dependent on local (country, site, subject) circumstances at the time, and the extent of the COVID-19 situation.
In the event that a subject is diagnosed with active COVID-19, the intention is for the subject to continue in the study, and to receive regular phone calls from study staff to monitor safety and ensure compliance. The subject should not visit a study site until they have received medical clearance.
All Protocol Deviations as a result of COVID-19 will be noted as such for future analysis and reporting.
In this study, the primary endpoint is based on PRO via the eDiary, and this can be completed remotely. Therefore, the primary endpoint should not be influenced by the inability of subjects to attend study visits on site.

8 STATISTICAL METHODS

8.1 Statistical Analysis Plan

The principal features of the statistical analysis of the data are described in this section. A more technical and detailed elaboration of the principal features will be written in a separate Statistical Analysis Plan (SAP). A data display plan (DDP) will also be prepared and included in the SAP. The DDP will describe the layout of the tables and listings to be produced.

8.1.1 Disposition of Subjects

A subject will be considered enrolled into the study after giving written informed consent. Those subjects not completing the study until the End of Study visit will be considered early withdrawals. In addition, there will be the Set of Screening Failures (SCR), consisting of all subjects that were enrolled, but not randomised and received no dose of IMP.

8.1.2 Protocol Deviations

Deviations from the procedures set forth in this study protocol will be recorded and classified into ‘major’ and ‘minor’. Additionally, a list of protocol deviations that are considered important, i.e. influencing the interpretability of the analysis results, will be given in the Statistical Analysis Plan (SAP).

8.1.3 Analysis Populations

The following analysis populations will be considered:

- The Full Analysis Set (FAS) consists of all subjects that were randomised and received at least one dose of IMP.
- The Per Protocol Set (PPS) encompassing all subjects of the FAS who sufficiently complied with the study protocol and had no major protocol deviations.
- The Safety Analysis Set (SAS) consists of all subjects who administered the IMP at least once.
- The PK Analysis Set (PKAS) consists of all subjects who received at least one dose of GS-248 within 30 hours before a blood sample for GS-248 bioanalysis was taken.

The decision on the membership of subjects in the analysis populations will be made during a blinded Data Review Meeting (DRM) before final lock of the clinical database and disclosure of the treatment assignment. A subject data listing and a table with protocol deviations will be presented.

8.2 General Considerations

In general, descriptive statistics, sampling statistics for quasi-continuous measurements and frequency tables for discrete and ordinal measurements, will be presented separated by treatment group. Also, figures (histograms or plots of means vs. time) for selected efficacy measures will be presented separated by treatment group.

Whenever statistical hypothesis tests are performed these will be two-sided. The type I error will be set at alpha = 0.05. Details on the planned statistical methods will be

given in a Statistical Analysis Plan (SAP) which will be finalised before treatment unblinding.

8.3 Demographics, Baseline Characteristics and Concomitant Medications

Subject characteristics obtained at screening and baseline visit, such as gender, body weight and height, medical history findings, the results of the nailfold capillaroscopy, and relevant prior medications will be presented in a purely descriptive manner by treatment group and in total.

All continuous variables will be described using standard statistical measures, i.e., number of observations, mean and median value, standard deviation, minimum and maximum value. All categorical variables will be summarised in frequency tables.

8.4 Treatment Compliance

All subjects will record the time they take each dose of IMP into their eDiary, and each subject's eDiary will be reviewed at all study visits. Compliance with the treatment regimen will be calculated using data recorded in the eDiary.

8.5 Efficacy Analyses

A complete description of the derivation rules for the endpoints will be described in the SAP.

All available data will be summarised by descriptive statistics separated by treatment group for each visit. Where possible, differences in measurements between week 4 and baseline will be computed and descriptively presented.

The primary analysis population for the assessment of efficacy will be the FAS.

8.5.1 Primary Efficacy Endpoint Analysis

The analysis of the primary endpoint is conducted on the FAS (the primary analysis population) and the PPS.

For the derivation of the endpoint, the 7 most recent days prior to the date of each visit will be used. Missing data will be replaced using the mean value of the observed days. The primary analysis of the primary endpoint is mean change from baseline to week 4 in the number of RP attacks per week, and will be performed using the analysis of covariance, ANCOVA test, including the stratification factor and treatment as fixed factors and baseline levels as a covariate in the model.

The null hypothesis is that there is no difference between treatments.

The primary objective will be met if there is a p-value <0.05 with a numerical superior efficacy of the IMP versus placebo with regard to the primary endpoint, i.e. the mean change in RP attacks. There will be no adjustment for multiplicity for the primary endpoint.

Data for the primary endpoint will be presented using observed data. The primary statistical analysis of the primary endpoint will be done using the placebo multiple imputation method, pMI, and as a sensitivity analysis, the last-observation-carried-forward (LOCF).

8.5.2 Key Secondary Efficacy Endpoints Analysis

The same analysis approach used for the primary efficacy endpoints will be applied to the key secondary endpoints mean change in the RCS from baseline (Visit 2) to week 4 (visit 4), mean change in cumulative duration of RP attacks from baseline (Visit 2) to week 4 (Visit 4), and mean change from baseline (Visit 2) to week 4 (Visit 4) in pain experienced during RP attacks.

The null hypothesis is that there is no difference between treatments.

Adjustment for multiplicity will be done and its procedures will be described in detail in the SAP.

8.5.3 Exploratory and Secondary Efficacy Endpoints Analysis

The same analysis approach used for the primary efficacy and key secondary endpoints will be applied to the exploratory efficacy variables referred to as a mean change analysis.

Categorical endpoints such as "proportion of subjects" will be evaluated using the Cochran Mantel-Haenzel method, adjusting for the stratification factor in the analyses.

The following exploratory endpoints will be analysed

- Patient Global Impression of Change at Visit 4
- Physician Global Impression of Change at Visit 4
- Mean change in ASRAP Questionnaire score from Visit 2 to Visit 4.
- Mean change from baseline (Visit 2) to week 4 (Visit 4)
  in peripheral blood flow prior to local cold challenge determined by thermography
- Mean change from baseline (Visit 2) to week 4 (Visit 4) in rewarming profile after local cold challenge determined by thermography

No multiplicity adjustments will be made for the exploratory endpoints. The reported p-values are nominal.

The null hypothesis is that there is no difference between treatments.

For the analysis of exploratory endpoints, missing endpoint data will not be imputed. Hence the observed cases approach will be used in the exploratory presentations.

8.6 Safety Analyses

For all subjects the analysis of the safety will be based on the SAS and be primarily descriptive. Frequency tables will be presented for the occurrence of any AEs and subtypes (e.g. serious, related, fatal AEs). Sampling statistics will be provided for physical examinations, vital signs, ECG and safety laboratory measurements.

8.7 Pharmacokinetic Analyses

For subjects in the active treatment group with sparse PK sampling, statistics on the levels of GS-248 will be presented for all scheduled sampling timepoints. This will be supplemented by plots (e.g. scatter plots for Visit 3) on the time courses of the concentrations.

For the subgroup of subjects with rich PK sampling, separate statistics on the levels of GS-248 will be presented for all scheduled sampling timepoints and PK parameters (e.g. AUC, C_{max}, $t_{½}$) will be derived from the concentration versus time profiles using

non-compartmental calculation methods. Descriptive statistics (including geometric means and standard deviations) will be presented for all derived PK parameters and supplemented by plots (e.g. line plots for Visit 4) on the time course of the concentrations. Pharmacokinetic calculations will be further detailed in the SAP.

8.8 Pharmacodynamic Analyses

The following variables will be evaluated:

- Effect of GS-248 on PGE_2 formation in whole blood *ex vivo.*
- Effect of GS-248 on formation of the arachidonic acid metabolites PGEM, PGIM and TXM.
- Effect of GS-248 on inflammation and endothelial dysfunction.
- Effect of GS-248 on platelet activation.
- Effect of GS-248 on microvascular volume.

All data will be evaluated for the observed cases. Each variable will be estimated for the absolute and percent change from baseline (Visit 2) to week 4 (Visit 4). The changes will be presented using summary statistics and bar graphs. The difference between treatment groups will be analysed using statistical test which will be presented in the SAP.

8.9 Interim Analyses

Not applicable.

8.10 Determination of Sample Size

Power calculation for the primary efficacy endpoint is based on a two-sided t-test for independent samples with a type-I error rate of 0.05. Calculations assumed a mean change from baseline to week 4 of 12.0 for the active treatment arm versus 4.0 for the placebo arm, and a common standard deviation of 10.0, with a power goal of 80%.

Power calculations reveal that 26 subjects per group are needed to meet the power goal. To allow for a dropout rate of 10%, and some margin for uncertainty in the assumption of variation in the power calculation assumed, approximately 80 subjects will be enrolled and randomised into this study.

An estimated 50 subjects will be assessed for the secondary endpoint of mean change in peripheral blood flow using thermography and cold challenge.

8.10.1 Handling of Dropouts and Missing Data

For the analyses of primary and secondary efficacy endpoints listed above, missing data will be replaced using the model based multiple imputation method, based on 10 repeated imputation runs. Additional methods for handling missing data, such as the placebo-imputation approach, may be used for additional sensitivity analyses and will be described in the SAP. In any case, additional analysis results based only on the non-missing data will be presented for the primary and secondary endpoints.

8.10.2 Rules for Excluding Subjects from Analysis

Subjects will not be excluded from any analyses unless they fall outside a specific definition of the populations described earlier. Protocol deviations will be described in the monitoring plan for the purposes of defining the Per Protocol Set prior to database lock.

9 DATA MANAGEMENT

9.1 Data Collection

The trained investigator site staff will enter the data required by the protocol into the eCRFs either from source documents (e.g., medical records and study-specific data capture tools as needed) or directly into the eCRFs. All information in the eCRFs must be traceable to these source documents or other sources.

A validated, electronic data capture (EDC) system will be used to capture data from sites. An audit trail of all changes to this database, including the date, reason for the data change and who made the change, will be maintained within the same database. The audit trail will be part of the archived data at the end of the study.
The complete data management process (data capture, data entry, data validation, checks on plausibility, query handling, data editing after entry, coding, data base closure, etc.) will be defined in advance within a Data Management Plan (DMP) together with a description of the personnel responsible for data entry.

All subjects will be issued with an eDiary for them to complete on a daily basis throughout the entire study. Data for the primary endpoint i.e. number of RP attacks, will be recorded in the eDiary by the subjects. In addition, the duration of each RP attack, maximum pain during each RP attack, daily RCS, timepoint for the daily IMP administration and a Patient Global Impression of Change at Visit 4 will be recorded by the subjects.

Data recorded in the eDiary will be transmitted electronically to a secure site and monitored for compliance on a regular basis. All eDiary assessments and reminders to the subjects are presented in APPENDIX 10.

9.2 Data Correction

The responsible Study Monitor will review eCRFs entered by investigational staff for completeness and accuracy. If any errors or discrepancies in the eCRFs are found during data entry or review, discrepancies will be generated programmatically within the EDC system, and manual queries will be generated by either a study monitor or Data Management. Discrepancies and queries can only be corrected by the Investigator(s) or other authorised site personnel. An audit trail documents all changes to the data over the entire study period. A comment must be supplied in the query response, stating the reason for the change. Once queries have been resolved by the site staff, the resolutions are assessed by Data Management or study monitors. If the query response provided confirms the data as correct, the discrepancy will be closed. If the response does not adequately address the question raised, a new query will be issued for further clarification. Manual checks will be performed, and programs run throughout the study until the data is clean and the database is ready for lock. All discrepancies will be resolved prior to database lock.

9.3 Data Handling

The final data will be transferred to the SAS-system for data analyses in accordance with the SAP. The MedDRA dictionary will be used for coding of AEs and concomitant diseases. Concomitant medication will be coded using the World Health Organization Drug Dictionary. Coding will be started with latest available versions of dictionary and documented in DMP.

9.3.1 Deviations from the Protocol

Deviations from the protocol will be judged during the study and/or when an individual subject's eCRF is completed (monitored).

Before unblinding the data, a blinded data review meeting (BDRM) will take place where protocol deviations will be classified (major/minor protocol deviations) for statistical analysis.

9.4 Data Quality Assurance

The Sponsor and/or their representative (i.e. Monitor engaged by the contract research organisation [CRO] company) will conduct a site visit to verify the qualifications of each investigator, inspect the site facilities, and inform the investigator of responsibilities and the procedures for ensuring adequate and correct documentation. The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. All information recorded on the eCRFs for this study must be consistent with the subjects' source documentation (i.e. medical records).

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Study Initiation Activities

The investigator(s) are informed about study objectives and methods, the inclusion and exclusion criteria, the time-schedule, and study procedures at a Pre-Study Visit by the monitor (if necessary), an investigators' meeting, and during the Site Initiation Visit by the monitor.

10.2 Training of Site Staff

The investigator will ensure that everyone assisting with the clinical study is adequately informed about the protocol, the investigational product(s), and their study-related duties and functions. Furthermore, the investigator will maintain a list of qualified persons to whom the investigator has delegated study-related duties.

10.3 Documentation and Filing

10.3.1 eCRF System

The investigator and persons authorised by the investigator will be instructed about how to complete the eCRF. Entries in the eCRF must only be made by the investigator or persons authorised by the investigator. A list of all persons who are allowed to make entries in the eCRF must be available in each study site.

The investigator must ensure that all data entries in the eCRF are complete, accurate, legible and reported in a timely manner. Data reported on the eCRF should be consistent with the source documents or the discrepancies should be explained. Entries will be checked against appropriate source documentation by the monitor.

10.3.2 List of Subjects (subject identification log)

The investigator will keep a confidential list of names of all subjects participating in the study, so that the subjects' records can be identified if necessary.

In addition, the investigator will keep a list of all subjects screened on a screening log to document identification of subjects who were consented and entered study screening. If someone is not eligible to participate in the study, a reason must be provided.

10.3.3 Source Data

Per ICH, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents which comprise clinical documentation, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, ECG recordings, memoranda, subjects' eDiary or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study). When a copy is used to replace an original document, the copy should fulfil the requirements for certified copies.

10.3.4 Investigator Site File / Regulatory Binder

Before site initiation Ergomed will provide an Investigator Site File (ISF) to each site. The ISF will include essential documents as defined by the ICH GCP guideline and applicable local requirements that are required for study initiation at the investigational site.

From that point onwards, the investigator will be responsible for the update and maintenance of the ISF, which will be reviewed periodically by the monitor(s). These documents will be reviewed during an audit by the Sponsor or an inspection by the Regulatory Authorities.

All study-related documents are to be archived and stored according to the local regulatory requirements and agreement with the study Sponsor.

Details pertaining to the retention and archiving of study documents are found in Section 11.4.

10.4 Monitoring

The monitor is responsible for checking the quality of data and ensuring that the investigative site is adhering to the study protocol. Additionally, the monitor ensures that the site is following the legal and ethical requirements as stated in local laws and the principles of GCP.

The interval between monitoring visits will depend on the recruitment rate and the complexity of the study.

Source data verification is an essential part of the monitoring process and the investigator must grant direct access to the original subject's source documents.

The extent and nature of monitoring will be described in detail in the monitoring plan.

10.5 Audits and Inspections

Audits will be performed according to the corresponding audit program. The Sponsor or their representative may visit the investigative site to audit the performance of the study, as well as all study documents. Audits may also be performed by contract auditors who will be instructed about the timing and extent of the audits. In the event of an audit at the investigational site, the monitor will usually accompany the auditor(s).

Inspections by Regulatory Authority representatives and IECs are possible at any time, even after the end of the study. The investigator is to notify the Sponsor immediately of any such inspection. The investigator and institution will permit study-related monitoring, audits, reviews by the IEC and/or Regulatory Authorities and will allow direct access to original source documents for monitoring, audits, and inspections.

11 ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

11.1 Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the Sponsor and investigator abide by the principles of the Good Clinical Practice guidelines of the International Council for Harmonization (ICH), and of the Declaration of Helsinki. The study also will be carried out in keeping with local legal requirements.

11.2 Informed Consent

Before the first study-specific screening procedure can be performed, informed consent must be obtained from each subject (or his/her legally authorised representative) according to the regulatory and legal requirements of the participating country (i.e., the Declaration of Helsinki, ICH GCP, and other applicable local regulations). This consent form must be approved by responsible IEC and must be signed and dated by subject and authorised consenter and retained by the investigator as part of the study records. The investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. The terms of the consent and when it was obtained must also be documented in the subjects' medical records.

If a protocol amendment is required, the informed consent form may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the appropriate IEC and signed by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

11.3 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/ Competent Authorities, in accordance with local regulatory requirements. The Sponsor must ensure that all ethical and regulatory requirements have been met before the first subject is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IEC/Competent Authority approval prior to implementation (if appropriate), unless a protocol deviation is required in the event of an urgent safety need.

All amendments will be distributed to all protocol recipients, with appropriate instructions.

11.4 Archiving Study Records

According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local

regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

11.5 Premature Termination of the Study

If the Investigator, the Sponsor, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to subjects if the study continues, the study may be terminated after appropriate consultation between the relevant parties. The study may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study;
- Failure to enrol subjects at an acceptable rate;
- A decision on the part of the Sponsor to suspend or discontinue development of the drug.

11.6 Confidentiality

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

The anonymity of participating subjects must be maintained. Subjects will be identified on eCRFs and other documents by their subject number allocated in the trial, not by name. Documents that identify the subject (e.g., the signed informed consent, subject identification list) must be maintained by the investigator as part of the ISF in a secure and confidential manner.

11.7 Liability and Insurance

The Sponsor will take out reasonable third-party liability insurance cover in accordance with all local legal requirements. The civil liability of the investigator, the persons instructed by him and the hospital, practice or institute in which they are employed and the liability of the Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable law.

The Sponsor will arrange for subjects participating in this study to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study.

11.8 Publication Policy

By signing the study protocol, the investigator agrees with the use of results of the study for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. If necessary, the

authorities will be notified of the investigator's name, address, qualifications and extent of involvement.

An investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with the Sponsor in advance and gained written approval.

12 REFERENCE LIST

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APPENDIX 1: LIST OF INSTITUTIONS INVOLVED IN THE STUDY

Sponsor	Göran Tornling, MD, PhD Gesynta Pharma AB Wallingatan 24, SE-111 24 Stockholm, Sweden Phone: +46 730 963131
Coordinating Investigator	Professor Ariane Herrick Centre for Musculoskeletal Research University of Manchester Oxford Road, Manchester M13 9PT, United Kingdom Phone: +44 161 275 5993
Contract Research Organization	Ergomed Plc 1 Occam Court, Occam Road Surrey Research Park Guildford GU2 7HJ, United Kingdom Phone: +44 (0) 1483 307 920
Medical Monitor	Piotr Dzialak Ergomed Sp. z.o.o. ul. Armii Krajowej 18 30-150 Kraków, Poland Phone: +44 (0) 20 8819 6901
Adverse Event Reporting	PrimeVigilance Ltd 1 Occam Court, Occam Road Surrey Research Park Guildford GU2 7HJ, United Kingdom Phone: +44 (0) 1483 307920 Fax: +44 (0) 800 471 5289 E-mail: GesyntaPV@primevigilance.com
Central Laboratory	Medicover Integrated Clinical Services 27, Siemensstraße, 12247 Berlin, Germany
Other Laboratory	Lablytica Life Science AB Virdings allé 16, SE-754 50 Uppsala, Sweden

APPENDIX 2: OVERALL SCHEDULE OF ASSESSMENTS

	Visit 1 Screening Visit	**Visit 2 Baseline Visit**	**Visit 3**	**Visit 4 EoT Visit**	**Visit 5 Follow-up or Early Termination Visit***
Activity	Enrolment	Treatment start	Treatment	End of Treatment	Follow-up
Day	-21 to -14	1	15 (±2 days)	28 (-2/+1 days)	42-49
Confirmation of Signed Informed consent	X				
Demographics	X				
Medical and surgical history	X				
Concomitant medication	X	X	X	X	X
Physical examination	X	X [a]	X [a]	X [a]	X
Nailfold capillaroscopy	X [b]				
Vital signs (BP, heart rate)	X	X	X	X	X
Weight/height	X				X [c]
ECG	X	X [d]	X		X
Clin chem and haematology	X	X	X	X	X
Thyroid hormones (free T3/T4, tot T4, TSH)	X				
Urinalysis – dipstick	X	X	X	X	X
SSc-related autoantibodies [e]	X				
Pregnancy test (WOCBP) [f]	X	X		X	X[p]
Inclusion/exclusion criteria	X	X			
Hepatitis B, C, HIV-test	X				
Drug screen [g]	X	X		X	
eDiary	X [h] ←			→	X [i]
ASRAP questionnaire (PRO)		X	X	X	X
Global Impression of Change (Subject/Physician)				X	
Adverse events	X	X	X	X	X
Randomisation		X			
IMP administration at site [j]		X		X	
IMP dispense to subjects		X	X		

	Visit 1 Screening Visit	**Visit 2 Baseline Visit**	**Visit 3**	**Visit 4 EoT Visit**	**Visit 5 Follow-up or Early Termination Visit***
Activity	Enrolment	Treatment start	Treatment	End of Treatment	Follow-up
Day	-21 to -14	1	15 (±2 days)	28 (-2/+1 days)	42-49
IMP collection and compliance			X	X	
PK sampling (sparse)		X	X	X	
AA metabolites, and urine creatinine [k]		X		X	
Blood biomarker sampling [l]		X		X	
Biobank samples – urine and blood		X		X	
Assessments below will be conducted at pre-selected sites					
Finger temperature		X			
Cold challenge, thermography		X [m]		X	
PK sampling (rich)				X	
PGE_2 levels in whole blood		X		X	
Platelet activation (FACS) [n]		X		X	
Microvascular volume (D-OCT)		X [o]	X	X [o]	X

* Also, the Early Termination visit, if applicable.

a. Abbreviated examination (minimally to include statement regarding DUs).
b. Could be performed at Visit 2 if not feasible at Visit 1.
c. Only weight (not height) to be recorded at this visit.
d. Two ECG assessments will be performed, one pre- and another 170 min post-IMP administration.
e. Analysis of antinuclear antibodies (ANA), Scl-70 antibody (anti-topoisomerase I) and anti-centromere antibodies (ACA)
f. Urine dipstick pregnancy test in WOCBP. At Visit 1, FSH assessment will be performed for women not of childbearing potential.
g. For presence of alcohol or prohibited substances, e.g. cocaine
h. Subjects will be given access to an eDiary and given instructions on how to use it at study enrolment. The eDiary will include the RCS, NRS pain scale, record of attacks (start time and finish time and date), IMP administration timepoints and reminders to subject,
i. eDiaries will be completed for the final time and then "closed" so that no further data are entered.
j. IMP administered together with food at the study site.
k. Subjects bring a urine sample (first urination of the day) from home to the study site in the container provided.
l. Predefined biomarkers (including hsCRP, Endothelin-1, sE-selectin, xICAM1, TNF, IL-1b, IL-4, IL-6, IL-10, s-PECAM1 CXCL-4, CD40L and von Willebrand factor).
m. Two cold challenges will be performed, one pre- and another 180 mins post-IMP administration, see Appendix 2.1.
n. Analysis of surface markers of platelet activation performed at a local laboratory.
o. Two D-OCT assessments will be performed, one pre- and another 175 mins post-IMP administration
p. WOCBP will receive a home pregnancy test to be used 35-40 days after their last dose of IMP.

APPENDIX 3: DETAILED SCHEDULE OF ASSESSMENTS – VISIT 2

		Minutes *(time window +/- 5 minutes, exact time recorded in eCRF)*									
	≥30-0	**0**	**30**	**60**	**90**	**120**	**150**	**170**	**175**	**180** (180-195)	**200**
Arrival at site	X										
Morning urine sample collection (AA-metabolites, urine creatinine)	X										
Physical examination (minimum DU)	X										
Vital signs (BP, heart rate)	X										
ECG	X							X			
Nailfold capillaroscopy (if not performed at Visit 1)	(X)										
Pregnancy test (WOCBP) (urine dipstick)	X										
Drug Screen [a]	X										
Urinalysis (dipstick)	X										
Review of eDiary compliance	X										
Concomitant medication	X										
Inclusion/exclusion criteria	X										
Clin chem and haematology	X										
Biomarkers (blood)[b]	X										
Collect blood and urine for Biobank	X										
Randomisation	X										
Adverse Event	X[c]										
IMP administration		X [d]									
ASRAP questionnaire			X								
PK sampling sparse									X		
IMP dispensation											X
Assessments below will be conducted at pre-selected sites											
PGE2 levels in whole blood	X										
Platelet activation (FACS) [e]	X										
Microvascular volume (D-OCT)	X								X		

a. For presence of alcohol or prohibited substances, e.g. cocaine
b. hsCRP, Endothelin-1, sE-selectin, ICAM1, TNF, IL-1b, IL-4, IL-6, IL-10, s-PECAM1 CXCL-4, CD40L and von Willebrand factor

c. AE collection reflecting the time from the previous visit as well as any AEs experienced during the day.
d. IMP will be administered with food.
e. Analysis of surface markers of platelet activation performed by FACS analysis at a local laboratory.

DETAILED SCHEDULE OF ASSESSMENTS COLD CHALLENGE/THERMOGRAPHY – VISIT 2

The detailed schedule of assessment below describes the **additional** assessments at Visit 2 if the subject is enrolled to Cold Challenge.

		Session 1[1]					**Session 2[2]**									
		Minutes *(time window +/- 5 minutes, exact time recorded in eCRF)*														
	≥30-0	**0** (0-15)	**30**	**80**	**100**	**120[3]**	**0**	**30**	**60**	**90**	**120**	**150**	**170**	**175**	**180** (180-195)	**200**
Cold Challenge / Thermography																
Finger temperature	X															
Cold challenge with thermography every 15 seconds		X													X	
Thermography				X	X	X	X	X	X	X	X	X				

[1] Session 1 is conducted after randomization and prior to IMP administration.
[2] Session 2 starts at the same time as IMP administration, see DETAILED SCHEDULE OF ASSESSMENTS – VISIT 2.
[3] Estimated that skin temperature has returned to normal at 120 minutes, otherwise wait until it has returned to normal.

APPENDIX 4: DETAILED SCHEDULE OF ASSESSMENTS – VISIT 4

Assessment	**Minutes** ***(time window +/- 5 minutes, exact time recorded in eCRF)***												
	≥30-0	**-5**	**0**	**30**	**60**	**90**	**120**	**150**	**175**	**180** (180-195)	**240**	**360**	**480**
Arrival at site	X												
Morning urine sample collection (AA-metabolites, urine creatinine)	X												
Physical examination (minimum DU)	X												
Vital signs (BP, heart rate)	X												
Drug screen [a]	X												
Urinalysis (dipstick)	X												
Pregnancy test (WOCBP) (urine dipstick)	X												
Review of eDiary	X												
Collect blood and urine for Biobank	X												
Adverse Event [b]	X												
Concomitant medication	X												
IMP collection	X												
ASRAP questionnaire				X									
Clin chem and haematology	X												
Biomarkers (blood) [c]	X												
Patient Global Impression of Change [d]	X												
Physician Global Impression of Change	X												
PK sample, sparse		X					X [e]		X [e]				
IMP administration [f]			X										

Assessment	**Minutes** ***(time window +/- 5 minutes, exact time recorded in eCRF)***												
	≥30-0	**-5**	**0**	**30**	**60**	**90**	**120**	**150**	**175**	**180** (180-195)	**240**	**360**	**480**
Assessments below will be conducted at pre-selected sites													
Thermography		X											
Cold challenge with thermography every 15 seconds										X			
PK sample, rich [g]		X		X	X	X	X		X		X	X	X
PGE_2 levels in whole blood	X												
Platelet activation (FACS) [h]	X												
Microvascular volume (D-OCT)	X								X				

a. For presence of alcohol or prohibited substances, e.g. cocaine
b. AE collection for past study period as well as any experienced during the day.
c. hsCRP, Endothelin-1, sE-selectin, ICAM1, TNF, IL-1b, IL-4, IL-6, IL-10, s-PECAM1 CXCL-4, CD40L and von Willebrand factor.
d. If not already completed by subjects in the morning at home (diary).
e. The PK sampling for subjects enrolled to cold challenge assessment is to be drawn at 175 mins, for all other subjects at 120 mins.
f. IMP will be administered with food.
g. The schedule includes sparse PK sampling that is also drawn from subjects enrolled in rich PK. If feasible, a PK sample should be drawn at 480 min, or as late as possible.
h. Analysis of surface markers of platelet activation performed by FACS.

APPENDIX 5: COLD CHALLENGE AND THERMOGRAPHY

Preparation for cold challenge

All measurements will be performed in a temperature-controlled room (23ºC ±2°C) or a temperature-monitored room. The room temperature will be recorded in order to monitor any changes and their effects on the data. Subjects will be requested to wear light clothing and must refrain from vigorous exercise, caffeine and alcohol for at least 4 hours prior to the assessment. Upon arrival subjects will be seated comfortably in the temperature-controlled (or temperature-monitored) room for 20 minutes and acclimatised.

Cold challenge protocol

This involves 1 minute's exposure to 15ºC water for both hands (in case of DU, only the hand with no DU), and rewarming at an ambient temperature of 23ºC (±2ºC). Immediately prior to the cold challenge, a baseline image of both hands will be taken with the thermal camera with the subject's hands placed on a black, thermally insulated surface. Two standard containers of water at 15 ± 1°C (measured by thermometer) will be prepared and placed on either side of the subject. Both hands will then be gloved and immersed for 1 minute in the cooled water. The hands will be submerged to the metacarpophalangeal joints. After the cold challenge, the gloves will be removed, and the hands returned to their original position on the insulating surface. Reperfusion/rewarming after cold challenge will be imaged simultaneously during the 15 minutes following hand removal from the water. Thermography images will be captured at 4 frames per minute (to allow faster changes to be observed than at slower rates). At the end of the 15 minutes one extra image will be taken to allow the gradient of the last data point to be calculated; thus, a total of 61 images/scans are obtained for both assessments during the 15 minutes of measurement.

Thermography

Thermography images will be securely transferred electronically to the University of Manchester for automated analysis. The region of interest is defined as 2 dorsal regions: one on the dorsum of each hand and all 8 distal phalanges (excluding thumbs). At baseline before cooling, a distal dorsal difference (DDD) is defined for all 4 fingers on each hand in relation to the dorsum of the same hand (4 values for each hand, i.e., 8 in total). These are then averaged to give one DDD per hand or one for both hands. During and after cold challenge only the fingers are assessed. At each time point, the value for the 8 fingers can be plotted individually, but the areas under the curve (AUC) and maximum values are averaged for all 8 fingers. Thus, providing one DDD and one AUC and MAX per subject per cold challenge. This will be performed in a semi-automated way using software (based on observer-defined regions).

APPENDIX 6: MICROVASCULAR VOLUME

Microvascular volume will be assessed at the nailfold of the third finger of the dominant hand, at the proximal phalanx of the same finger and dorsum of the dominant hand. For the purpose of Microvascular volume assessment, subjects will undergo D-OCT scan using VivoSight scanner equipped with a 20-kHz swept-source laser and D-OCT processing software (Michelson Diagnostics, Kent, UK).
Each scan includes 500 frames with a width of 3 mm and will last approximately 60 seconds. The capillary pattern will be visualised in horizontal D-OCT images ("en-face view").
All the D-OCT images will be collected by a delegated member of staff previously trained, and subsequently analysed by the built-in software tool (Michelson Diagnostics Ltd.) (Themstrup et al; 2016). The "flow at depth" signal will be measured until the peak and extracted from each D-OCT scan, quantified as area under the curve and defined as "MicroVascular Volume" (MVV).

APPENDIX 7: NAILFOLD CAPILLAROSCOPY

Nailfold capillaroscopy is a technique used routinely to assess the degree of microvascular abnormality in subjects with SSc. It involves examining the small blood vessels (capillaries) in the skin at the base of the fingernail.

It is anticipated that all participating centres will have their own nailfold capillaroscopy system as this technique is routinely used for SSc diagnosis in all centers.

At Visit 1 (could be performed at Visit 2 if the assessment was not feasible at Visit 1), after a period of 20 minutes' acclimatisation at standard room temperature, preferably all 8 fingers (thumbs excluded) will be assessed , and images (up to 4 images taken at each nailfold; 2 from either side of midline) will be stored for potential subsequent analysis.

The investigator will assess the capillaroscopy pattern as ‘normal’, 'early', 'active' or 'late' (Herrick AL and Cutolo M, 2010).

Images will be securely transferred to University of Manchester for potential automated analysis of capillary density and dimension.

APPENDIX 8: METHODS OF ASSESSMENT FOR EFFICACY ENDPOINTS

Assessment	Description	Evaluation	Visit	Method of Collection
RP attack (eDiary)	A PRO Number and duration of attacks (for each attack: date, start time, stop time). Pain NRS for each attack.	-Mean number of RP attack during 7 days prior to Visit 4 compared with the mean number of RP attacks 7 days prior to Visit 2. -Cumulative duration of RP attacks during 7 days prior to Visit 4 minus the cumulative duration of RP attack during 7 days prior to Visit 4. - Mean change in NRS during 7 days prior to Visit 4 minus the mean NRS during 7 days prior to Visit 2	Daily from Visit 1 through to Visit 5	eDiary
Raynaud's Condition Score (RCS)	A PRO RCS is a validated numeric rating scale 0-10 (0 = No difficulty; 10 = Extreme difficulty) answering the question "What difficulty did you have today with your Raynaud's condition". To measure disease activity and Functional status	Mean score during 7 days prior to Visit 4 compared with mean score during 7 days prior to Visit 2.	Daily from Visit 1 through to Visit 5	eDiary
Physician Global Impression of Change	The clinician is answering the question "Considering all the ways in which Raynaud's symptoms affect your patient, compared to the start of treatment, how do you rate your patient's Raynaud's?" using a scale of; 1 = much better, 2 = a little better, 3 = no change, 4 = a little worse, 5= much worse.	The score at Visit 4 to be used	Visit 4	eCRF
Patient Global Impression of Change	A PRO The subject is answering the question "Considering all the ways in which Raynaud's symptoms affect you, compared to the start of treatment, how do you	The score at Visit 4 to be used	Visit 4	eDiary

Assessment	Description	Evaluation	Visit	Method of Collection
	rate your Raynaud's currently?" using a scale of; 1= much better, 2 = a little better, 3 = no change, 4 = a little worse, 5 = much worse.			
ASRAP Questionnaire	A PRO	A newly developed outcome measure to assess the impact of RP physically and mentally, and how it impacts on subjects' daily life.	Visit 2 Visit 3 Visit 4 Visit 5	Paper
Nailfold capillaroscopy	Nailfold capillaroscopy on 4 fingers on each hand according to a standardised method to assess severity of the micro vasculopathy.	Baseline evaluation of severity of condition, including classification into designated patterns (normal, early, active, late). Pictures will also be captured and sent for central reading with automated analysis which will compute density and size.	Visit 1 (or Visit 2 pre-randomization)	Central reader (density and width) - eCRF (vasculopathy)
Assessments conducted at pre-selected sites				
Peripheral vascular blood flow before cold challenge	Thermography Images will be obtained before first cold challenge at Visit 2 and before IMP is administered at Visit 4.	Change in peripheral blood flow from first assessment at Visit 2, to assessed before IMP administration at Visit 4.	Visit 2 Visit 4	Thermography images by central reader - eCRF
Peripheral vascular blood flow post IMP dose	Thermography images will be obtained in accordance with SoA.	Change in peripheral blood flow from before IMP to after IMP on Visit 2	Visit 2	Thermography images by central reader - eCRF
Peripheral vascular blood flow after cold challenge	Reperfusion/rewarming following the cold challenge will be imaged by thermography every 15 seconds (4 frames per minute), for 15 minutes.	Change in recovery of peripheral blood flow after cold challenge	Visit 2 (Session 1) Visit 2 (Session 2)	Thermography images by central reader - eCRF
Peripheral vascular blood flow after cold challenge	Reperfusion/rewarming following the cold challenge will be imaged by thermography every 15 seconds (4 frames per minute), for 15 minutes.	Change in recovery of peripheral blood flow after cold challenge from Visit 2 to Visit 4	Visit 2 (Session 1) Visit 4	Thermography images by central reader - eCRF

Assessment	Description	Evaluation	Visit	Method of Collection
Microvascular volume	Dynamic Optical Coherence Tomography (D-OCT) assessment of skin/nailfold		Visit 2 Visit 3 Visit 4 Visit 5	Equipment at site (eCRF)
Blood samples				
PK sparse			Visit 2 Visit 3 Visit 4	Central lab Lablytica
Biomarkers for inflammation and endothelium dysfunction	hsCRP, endothelin-1, sE-selectin, ICAM1, TNF, IL-1b, IL-4, IL-6, IL-10, s-PECAM1 CXCL-4, CD40L, and von Willebrand factor.		Visit 2 Visit 4	Central laboratory
Potential future analysis of inflammatory biomarkers and endothelial dysfunction.			Visit 2 Visit 4	Central laboratory (KI Biobank)
Blood samples conducted at pre-selected sites				
PK rich			Visit 4	Central lab Lablytica
PGE_2 levels in whole blood			Visit 2 Visit 4	Central lab Lablytica
Expression of platelet surface markers	FACS analysis		Visit 2 Visit 4	Local laboratory
Urine samples				
AA-metabolites (PGEM, PGIM, TXM)	Subjects will bring a urine sample (first urination of the morning).		Visit 2 Visit 4	Central lab Lablytica
Potential future analysis of inflammatory biomarkers and endothelial dysfunction			Visit 2 Visit 4	Central lab (KI Biobank)

APPENDIX 9: DEFINITIONS OF DIAGNOSES

The American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis (SSc)*

Item	Sub-item(s)	Weight/score†
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (sufficient criterion)	-	9
Skin thickening of the fingers (only count the higher score)	Puffy fingers Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	2 4
Fingertip lesions (only count the higher score)	Digital tip ulcers Fingertip pitting scars	2 3
Telangiectasia	-	2
Abnormal nailfold capillaries	-	2
Pulmonary arterial hypertension and/or interstitial lung disease (maximum score is 2)	Pulmonary arterial hypertension Interstitial lung disease	2 2
Raynaud's phenomenon	-	3
SSc-related autoantibodies (anticentromere, anti–topoisomerase I [anti–Scl-70], anti–RNA polymerase III) (maximum score is 3)	Anticentromere Anti–topoisomerase I Anti–RNA polymerase III	3

Adapted from Van den Hoogen F, et al. Arthritis & Rheumatism, 2013;65(11):2737-47.

* These criteria are applicable to any patient considered for inclusion in an SSc study. The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, generalised morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy).
† The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of ≥9 are classified as having definite SSc.

Definitions of items/sub-items in the American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis (SSc)

Item	Definition
Skin thickening	Skin thickening or hardening not due to scarring after injury, trauma, etc.
Puffy fingers	Swollen digits—a diffuse, usually nonpitting increase in soft tissue mass of the digits extending beyond the normal confines of the joint capsule. Normal digits are tapered distally with the tissues following the contours of the digital bone and joint structures. Swelling of the digits obliterates these contours. Not due to other causes such as inflammatory dactylitis.
Fingertip ulcers or pitting scars	Ulcers or scars distal to or at the proximal interphalangeal joint not thought to be due to trauma. Digital pitting scars are depressed areas at digital tips as a result of ischemia, rather than trauma or exogenous causes.

Item	Definition
Telangiectasia	Telangiectasiae are visible macular dilated superficial blood vessels, which collapse upon pressure and fill slowly when pressure is released. Telangiectasiae in a scleroderma-like pattern are round and well demarcated and found on hands, lips, inside of the mouth, and/or are large mat-like telangiectasiae. Distinguishable from rapidly filling spider angiomas with central arteriole and from dilated superficial vessels.
Abnormal nailfold capillary pattern consistent with systemic sclerosis	Enlarged capillaries and/or capillary loss with or without pericapillary hemorrhages at the nailfold. May also be seen on the cuticle.
Pulmonary arterial hypertension	Pulmonary arterial hypertension diagnosed by right-sided heart catheterization according to standard definitions.
Interstitial lung disease	Pulmonary fibrosis seen on high-resolution computed tomography or chest radiography, most pronounced in the basilar portions of the lungs, or occurrence of "Velcro" crackles on auscultation, not due to another cause such as congestive heart failure.
Raynaud's phenomenon	Self-reported or reported by a physician, with at least a 2-phase color change in finger(s) and often toe(s) consisting of pallor, cyanosis, and/or reactive hyperemia in response to cold exposure or emotion; usually one phase is pallor.
SSc-related autoantibodies	Anticentromere antibody or centromere pattern seen on antinuclear antibody testing, antitopoisomerase I antibody (also known as anti–Scl-70 antibody), or anti–RNA polymerase III antibody. Positive according to local laboratory standards.

Adapted from Van den Hoogen, 2013.

APPENDIX 10: eDIARY

MEDICATION

At what time did you take study medication today? HH-MM [24hr clock]

If, for some reason, you did not take all 3 capsules today, please let your Study Nurse/Doctor know.

ENDPOINT

Previous Attack Detail:

1. Did you have any attacks yesterday? Yes / No

If 1. is answered as yes -->a) Did you record them in the diary? Y/N

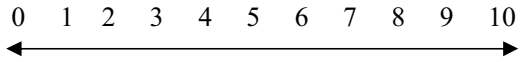
If a) is answered as No -- > Please proceed to record the attack(s) you had yesterday in the form for yesterday. You can find this form in the home screen.

If a) is answered as Yes -- > Thank you for your confirmation! Please proceed to record the attack(s) you have today. You can find this form in the "Show all events" tab.

Raynaud's Attack Form:

Date of attack:	DD/MMM/YY [Auto]
What time did your Raynaud attack start?	HH-MM [24hr clock]
What time did your Raynaud attack stop?	HH-MM [24hr clock]

Please record the score that best indicates the pain you experienced with **this** attack: _____



0=No pain

10=Worst imaginable pain

Thank you for completing this assessment.

To report another Raynaud Attack, please start another Raynaud Attack Form after submitting this form, on the next page.

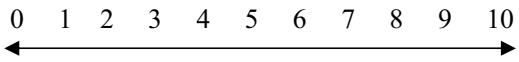
Raynaud's Condition Score: (To be completed EVERY evening)

The Raynaud's Condition Score is your rating of how much difficulty you had with your Raynaud's **TODAY**.

When choosing your score, please consider how many attacks you had and how long they lasted. Please also consider how much pain, numbness, or other symptoms the Raynaud's caused in your fingers (including painful sores) and how much the Raynaud's ALONE affected the use of your hands today.
Please record the score using the scale below that best indicates the difficultly you had today with your Raynaud's condition:

0=No difficulty

10=Extreme difficulty



Thank you for completing your Raynaud's Condition Score today.

Patient Global Impression of Change (Visit 4)

Kindly fill this form only on the day of Visit 4

"*Considering all the ways in which Raynaud's symptoms affect you, compared to the start of treatment, how do you rate your Raynaud's currently?"*

- *much better*
- *a little better*
- *no change*
- *a little worse*
- *much worse.*

APPENDIX 11: ASRAP QUESTIONNAIRE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Study ID ☐☐ - ☐☐☐☐

Todays Date ☐☐ / ☐☐ / ☐☐
dd/mm/yyyy

The ASRAP (Assessment of Scleroderma-associated RAynaud's Phenomenon) questionnaire

The following questions relate to your experience of Raynaud's symptoms over the last 7 days. When considering your Raynaud's symptoms, we want you to think about the effects of reduced blood flow (reduced circulation) in your fingers. This might include symptoms that are present most of the time, as well as "attacks" of worsening symptoms in response to cold exposure or stress that many people experience.

Please **try to avoid** considering symptoms being caused by sores (finger ulcers), skin tightening and/or calcinosis (calcium deposits in the skin) that may also affect your fingers, when choosing your response.

For each question, please indicate your response by placing an 'x' in the box/selecting the box that best describes your experiences relating to your Raynaud's symptoms **over the last 7 days**. Raynaud's symptoms can change from day to day and during the day. You may feel unsure about how to answer a question, but please give the best answer you can.

THE FOLLOWING QUESTIONS ASK ABOUT THE PHYSICAL SYMPTOMS OF RAYNAUD'S

In the PAST 7 DAYS ...	Not at all	A little bit	Somewhat	Quite a bit	Very much / a lot
1. Raynaud's symptoms have caused pain in my fingers	☐	☐	☐	☐	☐
2. Raynaud's symptoms have caused numbness in my fingers	☐	☐	☐	☐	☐
3. Raynaud's symptoms have caused tingling in my fingers	☐	☐	☐	☐	☐
4. Raynaud's symptoms have made my fingers tender / hypersensitive to touch	☐	☐	☐	☐	☐
5. Raynaud's symptoms have caused a burning sensation in my fingers	☐	☐	☐	☐	☐
6. Raynaud's symptoms have made my fingers feel cold	☐	☐	☐	☐	☐
7. Raynaud's symptoms have made my fingers change one or more colours (white/blue/ red/purple etc.)	☐	☐	☐	☐	☐
8. Raynaud's symptoms have made it difficult to use my fingers	☐	☐	☐	☐	☐

NOW CONSIDER THE FREQUENCY AND DURATION OF YOUR RAYNAUD'S ATTACKS:

In the PAST 7 DAYS					
9. On average, how often have you experienced attacks of Raynaud's symptoms?	None ☐	1-2 times per day ☐	3-4 times per day ☐	5-10 times per day ☐	over 11 times per day ☐
10. On average, how much total time per day have you experienced attacks of Raynaud's symptoms?	None ☐	Less than 15 minutes per day ☐	15 minutes to an hour per day ☐	1-2 hours per day ☐	over 2 hours per day ☐
11. On average, how long has a typical attack of Raynaud's lasted?	None ☐	Less than 5 minutes ☐	5-10 minutes ☐	11-25 minutes ☐	over 25 minutes ☐

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THE FOLLOWING QUESTIONS ASK ABOUT THE EMOTIONAL IMPACT OF YOUR RAYNAUD'S SYMPTOMS

In the PAST 7 DAYS	Not at all	A little bit	Somewhat	Quite a bit	Very much / a lot
12. Raynaud's symptoms have made me tearful	☐	☐	☐	☐	☐
13. Raynaud's symptoms have made me worry about my ability to do things	☐	☐	☐	☐	☐
14. Raynaud's symptoms have made me frustrated	☐	☐	☐	☐	☐
15. Raynaud's symptoms have made me irritable	☐	☐	☐	☐	☐
16. Raynaud's symptoms have caused feelings of despair / loss of hope	☐	☐	☐	☐	☐
17. Raynaud's symptoms have made me embarrassed	☐	☐	☐	☐	☐
18. Raynaud's symptoms have made me sad/depressed	☐	☐	☐	☐	☐
19. Being unable to do normal things because of Raynaud's symptoms has bothered me	☐	☐	☐	☐	☐
20. Raynaud's symptoms have beaten me/got the better of me	☐	☐	☐	☐	☐

THE FOLLOWING QUESTIONS ASK ABOUT THE IMPACT OF YOUR RAYNAUD'S SYMPTOMS ON DAILY LIFE

In the PAST 7 DAYS	Not at all	A little bit	Somewhat	Quite a bit	Very much / a lot
21. Raynaud's symptoms have made it difficult when I have been shopping	☐	☐	☐	☐	☐
22. Raynaud's symptoms have made it difficult to do work around the house	☐	☐	☐	☐	☐
23. Raynaud's symptoms have made social events / doing exercise difficult	☐	☐	☐	☐	☐
24. Raynaud's symptoms have made it difficult to do my job (paid or unpaid)	☐	☐	☐	☐	☐
25. Raynaud's symptoms have had an effect on my home / family life	☐	☐	☐	☐	☐
26. Raynaud's symptoms have had an effect on my personal / private life	☐	☐	☐	☐	☐

THE FOLLOWING QUESTIONS ASK ABOUT THE IMPACT OF COLD AND OTHER RELEVANT FACTORS ON YOUR RAYNAUD'S SYMPTOMS

In the PAST 7 DAYS ...	Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
27. I have been able to reduce (control) the intensity of my Raynaud's symptoms?	☐	☐	☐	☐	☐

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In the PAST 7 DAYS ....

	Never	Rarely	Sometimes	Often	Always	This activity not undertaken
28. Being inside a grocery store / super-market has caused Raynaud's symptoms	☐	☐	☐	☐	☐	☐
29. Household activities e.g. taking things out of the refrigerator/washing vegetables has triggered Raynaud's symptoms	☐	☐	☐	☐	☐	☐
30. Being in air-conditioned rooms has triggered Raynaud's symptoms	☐	☐	☐	☐	☐	☐
31. Stressful situations have triggered Raynaud's symptoms	☐	☐	☐	☐	☐	☐
32. Being outdoors without gloves has triggered Raynaud's symptoms	☐	☐	☐	☐	☐	☐

THE FOLLOWING QUESTIONS ASK ABOUT APPROACHES YOU HAVE TAKEN TO MANAGE YOUR RAYNAUD'S SYMPTOMS

In the PAST 7 DAYS ....

	Never	Rarely	Somewhat	Often	Always
33. I have used gloves / extra clothing to control Raynaud's symptoms	☐	☐	☐	☐	☐
34. I have used techniques (e.g. hand warmers/putting hands in warm water/sitting on hands) to control/ manage Raynaud's symptoms'	☐	☐	☐	☐	☐
35. I have avoided doing things (e.g. going outside / doing things I enjoy) to avoid making my Raynaud's symptoms worse	☐	☐	☐	☐	☐

THE FOLLOWING QUESTIONS RELATE TO ADAPTATIONS YOU MAY HAVE MADE TO HELP YOU MANAGE YOUR RAYNAUD'S SYMPTOMS

In the PAST 7 DAYS ....

	Never	Rarely	Somewhat	Often	Always
36. Raynaud's symptoms have made me have to do things differently	☐	☐	☐	☐	☐
37. Raynaud's symptoms have made me need to seek help from others	☐	☐	☐	☐	☐

THE FOLLOWING QUESTIONS RELATE TO UNCERTAINTY CAUSED BY YOUR RAYNAUD'S SYMPTOMS

In the PAST 7 DAYS ....

	Not at all	A little bit	Somewhat	Quite a bit	Very much / a lot
38. Raynaud's symptoms have caused me to worry about my future health	☐	☐	☐	☐	☐
39. A change in my normal routine has caused me to worry about possible worsening of my Raynaud's symptoms	☐	☐	☐	☐	☐

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APPENDIX 12: WOCBP AND HIGHLY EFFECTIVE CONTRACEPTION

WOCBP:

A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile (Clinical Trials Facilitation Group, 2014). Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Highly Effective Contraception:

Methods that can achieve a failure rate of <1% per year when used consistently and correctly are considered as highly effective birth control methods (Clinical Trials Facilitation Group, 2014). Such methods include combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1,5] (oral, Intravaginal, and/or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation[1,5] (oral, injectable, and/or implantable[2]); intrauterine device (IUD)[2]; intrauterine hormone-releasing system (IUS)[2]; bilateral tubal occlusion[2]; vasectomised partner[2,3]; sexual abstinence[4].

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method

[2] Contraception methods that in the context of this guidance are considered to have low user dependency.

[3] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

[4] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

[5] WOCBP using a hormonal method of contraception should also use a barrier form of contraception during the study and for one month after discontinuation of dosing

Appendix 13: List with examples of moderate and strong CYP3A4 inhibitors

Generic drug/compound	*ATC*	*Classification*
aprepitant	A04A	Antiemetics and antinauseants
dronedarone	C01B	Class 1 and 3 antiarrhythmic drugs
conivaptan	C03	Diuretics
diltiazem	C08	Calcium channel blockers
verapamil	C08	Calcium channel blockers
ciprofloxacin	J01	Antibacterial drugs
clarithromycin	J01	Antibacterial drugs
erythromycin	J01	Antibacterial drugs
telithromycin	J01	Antibacterial drugs
troleandomycin	J01	Antibacterial drugs
fluconazole	J02	Antibacterial drugs
itraconazole	J02	Antimycotic drugs
ketoconazole	J02	Antimycotic drugs
posaconazole	J02	Antimycotic drugs
voriconazole	J02	Antimycotic drugs
cyclosporine	J04	Antimycobacterials
boceprevir,	J05	Antiviral drugs
cobicistat,	J05	Antiviral drugs
danoprevir and ritonavir	J05	Antiviral drugs
elvitegravir and ritonavir	J05	Antiviral drugs
indinavir and ritonavir	J05	Antiviral drugs
lopinavir and ritonavir	J05	Antiviral drugs
nelfinavir	J05	Antiviral drugs
paritaprevir and ritonavir and (combative and/or dasabuvir)	J05	Antiviral drugs
ritonavir	J05	Antiviral drugs
saquinavir and ritonavir	J05	Antiviral drugs
telaprevir	J05	Antiviral drugs
tipranavir and ritonavir	J05	Antiviral drugs
crizotinib	L01	Antineoplastic drugs
idelalisib	L01	Antineoplastic drugs
imatinib	L01	Antineoplastic drugs
tofisopam	N05	Psycholeptics
fluvoxamine	N06A	Antidepressants
nefazodone	N06A	Antidepressants
grapefruit juice		

More information available from: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers