Clinical Study Protocol	
EudraCT No.	2019-000815-98
Investigational Medicinal Product	GS-248
Sponsor study code	GS-1001
CTC study code	225-45-2018
Protocol Version and Date	Final Version 2.0, 29MAY2019

A Phase I, placebo-controlled, double-blind, first-in-human study to investigate safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of GS-248 solution in healthy subjects and patients with systemic sclerosis (SSc)

Phase	I, first-in-human (FIH)
Indication	Digital ulcers, Systemic sclerosis
Test product	GS-248
Reference product	Celecoxib
Sponsor signatory	Göran Tornling, MD, PhD, MSc Gesynta Pharma AB Fogdevreten 2 SE-171 65 Solna, Sweden
Principal Investigator	Folke Sjöberg, MD, PhD, Professor CTC Clinical Trial Consultants AB Uppsala University Hospital, Entrance. 85, 2nd level SE-751 85 Uppsala, Sweden
Clinical study conduct and management	CTC Clinical Trial Consultants AB Uppsala University Hospital, Entrance. 85, 2nd level SE-751 85 Uppsala, Sweden CTC Clinical Trial Consultants AB Dag Hammarskjölds väg 10B SE-752 37 Uppsala, Sweden

1 STUDY SYNOPSIS

Study title A Phase I, placebo-controlled, double-blind, first-in-human (FIH) study to investigate safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of GS-248 solution in healthy subjects and patients with systemic sclerosis (SSc)	
Study code GS-1001	**EudraCT No** 2019-000815-98
Planned study period Q2 2019 to Q2 2020	**Phase of development** I, FIH
Principal Investigator Folke Sjöberg, MD, PhD, Professor CTC Clinical Trial Consultants AB Uppsala University Hospital, Entrance. 85, 2nd level SE-751 85 Uppsala, Sweden	

Study design

This is a FIH, double-blind, parallel-group, randomised, placebo-controlled study designed to evaluate the safety, tolerability, PK and PD of single and multiple ascending oral doses of GS-248 in healthy subjects and in patients with SSc. In addition, an exploratory comparison of the PD effects between celecoxib and GS-248 will be performed.

The study will be conducted in 4 parts:

Part I (single ascending dose [SAD]): safety, tolerability, PK and PD of single ascending oral doses of GS-248 in healthy male and female subjects.

Part II (multiple ascending dose [MAD]): safety, tolerability, PK and PD of multiple ascending oral doses of GS-248 in healthy male and female subjects during 10 days administration.

Part III (SSc patients): safety, tolerability, PK and PD of multiple oral doses of GS-248 in patients with SSc during 10 days administration.

Part IV (celecoxib): PD of multiple oral doses of celecoxib (200 mg BID) in healthy males and females during 10 days administration.

Objectives

Primary objective

- To determine the safety and tolerability following oral single and multiple ascending doses of GS-248 (solution) in healthy subjects and patients with SSc

Secondary objectives

- To evaluate the PK of GS-248 in healthy subjects and patients with SSc

Exploratory objectives

- To evaluate the PD effects of GS-248 and celecoxib by determination of microsomal Prostaglandin E synthase-1 (mPGES-1) activity (Prostaglandin E_2 [PGE_2] levels) in a whole blood assay (WBA)

- To explore the PD effects of GS-248 in plasma (asymmetric dimethylarginine [ADMA]) and urine (arachidonic acid [AA] metabolites) and additional exploratory inflammatory biomarkers in healthy subjects and patients with SSc
- To explore the PD effects of celecoxib in plasma (ADMA) and urine (AA metabolites) and additional exploratory inflammatory biomarkers in healthy subjects after 10 days twice daily dosing to enable exploratory comparisons with GS-248 treated subjects
- To explore potential metabolites of GS-248 in plasma and urine (including metabolites in safety testing [MIST])

Endpoints

Primary endpoints

- Frequency, severity and seriousness of adverse events (AEs)
- Clinically significant changes in:
  - 12-lead electrocardiogram (ECG)
  - Vital signs
  - Safety laboratory parameters
  - Physical examinations

Secondary endpoints

- PK parameters:
  - Part I: area under the curve from time 0 to time t (AUC_{0-t}), AUC from time 0 to infinity ($AUC_{0-\infty}$), terminal half-life ($T_{½}$), maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), dose proportionality (based on AUC and C_{max}), apparent total body clearance following extravascular administration (CL/F) and apparent volume of distribution following extravascular administration (V_z/F)
  - Part II and III after first dose interval: AUC_{0-t}, $T_{½}$, T_{max}, C_{max}, dose proportionality (based on AUC and C_{max})
  - Part II and III after last dose interval: AUC_{0-t}, AUC at steady state (AUC_{ss}), $T_{½}$, T_{max}, C_{max}, observed concentration at the end of a dosing interval, immediately before next administration (C_{trough} from the 2 doses preceding the last dose), dose proportionality (based on AUC_{ss} and C_{max}), CL/F, V_z/F and accumulation ratio

Exploratory endpoints

- *Ex vivo* determination of mPGES-1 activity (PGE_2 levels) in a WBA
- AA metabolites in urine captured pre-dose administration and during 24 h post-dose:
  - 11-alfa-hydroxy-9,15-dioxo-13,14-dihydro-2,3,4,5, tetranor-prostan-1,20-dioic acid (PGEM)
  - 2, 3-dinor-6-ketoprostaglandin F1α (PGIM)
  - 11-dehydro-thromboxane B_2 (TXM)
- ADMA in plasma
- Collection of plasma and urine for future analysis of potential metabolites after single and multiple dosing with GS-248

- Plasma and urine samples will be saved for future biomarker analyses e.g. further AA metabolite profiling in plasma and urine and inflammatory biomarkers in plasma and urine

The outcome of the WBA will be reported in the clinical study report (CSR) whereas the other exploratory endpoints may be reported separately from the CSR.

Number of subjects/patients planned

Part I (SAD): 48 subjects will be randomised and dosed (6 cohorts, each of 8 subjects with 6 subjects receiving GS-248 and 2 receiving placebo).

Part II (MAD): 32 subjects will be randomised and dosed (4 cohorts, each of 8 subjects with 6 subjects receiving GS-248 and 2 receiving placebo).

Part III (SSc patients): 10 SSc patients will be randomised and dosed (1 cohort with 10 subjects of which 8 will receive GS-248 and 2 will receive placebo).

Part IV (celecoxib): 8 subjects will be randomised and dosed (1 cohort with 8 subjects receiving celecoxib).

If indicated by emerging data and recommended by the internal safety review committee (iSRC), 2 additional cohorts (8+8 subjects) may be added to Part I, 1 cohort (8 subjects) may be added to Part II and 1 cohort (10 patients) may be added to Part III.

Diagnosis and main eligibility criteria

Part I (SAD), II (MAD) and IV (celecoxib):

- Healthy male and female subjects aged 18-70 years inclusive (Part I) and 40-75 years inclusive (Part II and IV).
- Has provided a signed informed consent and are considered eligible to participate in the study.
- Body Mass Index (BMI) ≥ 19 and ≤ 30 kg/m^2.
- Agree to use sufficient contraception as defined in this clinical study protocol (CSP).
- Females must not be pregnant, breast feeding or plan to be pregnant.
- Use of corticosteroids (inhaled and systemic), non-steroidal anti-inflammatory drugs (NSAIDs including e.g. coxibs and aspirin), antacids, proton pump inhibitors (PPIs) or any medication that changes gastric pH is prohibited within 14 days of the first IMP administration until the end-of study visit of each part.

Part IV (celecoxib) only:

- Subjects with a history of salicylate hypersensitivity or NSAID hypersensitivity or subjects who have experienced asthma, urticaria or other allergic reactions after taking aspirin or other NSAIDs will be excluded from study participation.

Part III (SSc patients):

- Male and female SSc patients aged 40-75 years inclusive diagnosed according to the European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) criteria. Patients must not satisfy more than one set of ACR criteria for rheumatic disease.
- SSc disease duration less than 60 months based on the time from the first non-Raynaud phenomenon manifestation.
- Raynaud's Phenomenon with a typical frequency of attacks during the winter months of on average 5 per week.

- Has provided a signed informed consent and are considered eligible to participate in the study.
- Agree to use sufficient contraception as defined in this CSP.
- Females must not be pregnant, breast feeding or plan to be pregnant.
- Use of iloprost or corticosteroids (inhaled and systemic) or other immunosuppressive therapies including, but not restricted to cyclophosphamide, azathioprine, mycophenolic acid, methotrexate, or cyclosporine is prohibited within 4 weeks of the first IMP administration until the end-of study visit.
- Use of NSAIDs (including e.g. coxibs and aspirin), antacids, PPIs or any medication that changes gastric pH is prohibited within 14 days of the first IMP administration until the end-of study visit.

Methodology

Part I (SAD)
In the SAD part of the study, single oral doses of GS-248 will be administered in 6 sequential cohorts, each of 8 subjects. Within each cohort, subjects will be randomised in a 3:1 ratio to receive either GS-248 (n=6) or placebo (n=2) in a blinded fashion. The proposed starting dose is 1 mg. Up to 2 additional dose cohorts can be explored based on the safety, tolerability and PK of the drug if recommended by the iSRC.

Subjects will come for 3 visits to the clinic. Screening (Visit 1) will take place from Day -28 to Day -1. At Visit 2, subjects will be admitted to the clinic on Day -1 and will remain at the clinic until Day 3 for single dose IMP administration, safety, PK and PD (PD from cohort 3) assessments. The subjects must fast for at least 10 h before the anticipated dosing time on Day 1. Water, but no other drinks, is allowed as desired except for 1 h before and 1 h after dosing. The first 2 subjects in each cohort will be dosed in a sentinel fashion; 1 subject will receive GS-248 and the other will receive placebo as randomised. The subjects will be carefully monitored by clinical staff during and after dosing. Vital signs and ECG will be checked at regular intervals. There is immediate access to equipment, qualified staff and an intensive care unit (ICU) in case of an acute emergency. To give sufficient time for observation of any reactions, there will be at least 24 h before dosing of the third and fourth subject, who will be dosed on the same day approximately 2 h apart. The remaining 4 subjects will also be dosed 2 by 2, i.e. 2 subjects will be dosed on the same day approximately 2 h apart. A final end-of-study visit (Visit 3) will take place on Day 8 (±2 days) or after early withdrawal.

In all cohorts, safety and PK will be assessed before and after dose. Exploratory blood sampling for WBA and potential future metabolite analysis will be performed before and after dose from cohort 3 and onwards.

Before initiating a new cohort, all subjects in the previous cohort must have been treated and 48 h safety, tolerability and PK data for all treated subjects must have been evaluated by the iSRC. Once Day 3 safety, tolerability and PK data for the last subject in each cohort has been collected, there will be at least 1week between dose escalations.

Part II (MAD)
Part II of the study will explore multiple ascending dosing of GS-248. The initial dose, dose escalation and dosing schedule will be based on emerging knowledge of safety, tolerability and PK of GS-248 observed in the SAD part of the study (Part I). The proposed starting dose is 25 mg/day.

GS-248 is planned to be administered once daily for 10 days. Each dose level during the MAD part will be selected such that the predicted maximum exposure will not exceed the maximum exposure (based on AUC and C_{max}) in previously evaluated SAD cohorts. The starting dose, subsequent dose levels and time points and visits for PK sampling may be adjusted based on safety and PK evaluation in the SAD and MAD part.

GS-248 will be administered in 4 sequential cohorts, each of 8 subjects. Within each cohort, subjects will be randomised in a 3:1 ratio to receive GS-248 (n=6) or placebo (n=2) in a blinded fashion. Up to 1 additional dose cohort can be explored based on the safety, tolerability and PK of the drug if recommended by the iSRC.

Subjects will come for 9 visits to the clinic. Screening (Visit 1) will take place from Day -28 to Day -2. At Visit 2, subjects will be admitted to the clinic in the morning of Day -1 for pre-dose assessments including a 24 h baseline urine collection and will remain at the clinic until Day 3 for IMP administration and safety, PK and PD assessments. Up to 4 subjects will be dosed on the same day. There will be at least 30 minutes between the dosing of each subject. The subjects will be carefully monitored by clinical staff during and after dosing. Vital signs and ECG will be checked at regular intervals. There is immediate access to equipment, qualified staff and an ICU in case of an acute emergency.

Outpatient visits for IMP administration, safety and PK assessments are planned for Day 4 to Day 8. (Visit 3 to Visit 7). On Day 9 (Visit 8), subjects will come to the unit in the morning for IMP administration and PK sampling and will return again in the evening for admission. For practical reasons, and if preferred by the subject, he or she may remain at the clinic during the whole Day 9.

Subjects will be admitted to the clinic between Day 9 and Day 12 (Visit 8) for IMP administration, safety, PK and exploratory PD assessments. The last dosing day is Day 10. Urine collection for exploratory PD analysis will be performed during 24 h after the last dose. A final end-of-study visit (Visit 9) is planned to take place on Day 19 (±2 days) or after early withdrawal.

Before initiating a new cohort, all subjects in the previous cohort must have been treated and 11 days safety, tolerability and PK data (i.e. data up to and including 24 h post last dose) for all treated subjects must have been evaluated by the iSRC. Once Day 11 safety, tolerability and PK data for the last subject in each cohort has been collected, there will be at least 1 week between dose escalations.

Part III (SSc patients)
Part III of the study will explore multiple dosing of GS-248 in SSc patients with Raynaud's Phenomenon. The dose will be based on emerging knowledge of safety, tolerability and PK of GS-248 observed in the preceding SAD and MAD parts of the study (Part I and II).

GS-248 is planned to be administered once daily for 10 days. The dose level in part III will be selected such that the predicted maximum exposure will not exceed the maximum exposure (based on AUC and C_{max}) in previously evaluated cohorts in healthy volunteers (Part I and Part II). The dose and time points and visits for PK sampling may be adjusted based on PK evaluation in the SAD and MAD parts.

Ten SSc patients will be included in Part III of the study. The patients will be randomised in a 4:1 ratio to receive GS-248 (n=8) or placebo (n=2) in a blinded fashion. One additional cohort may be added as needed to test e.g. additional doses or dosing schemes.

Patients will come for 9 visits to the clinic. Screening (Visit 1) will take place from Day -42 to Day -2. At Visit 2, patients will be admitted to the clinic in the morning of Day -1 for pre-dose assessments including a 24 h baseline urine collection and will remain at the clinic until Day 3 for IMP administration and safety, PK and PD assessments. Up to 2 subjects will be dosed on the same day. The patients will be carefully monitored by clinical staff during and after dosing. Vital signs and ECG will be checked at regular intervals. There is access to equipment, qualified staff and an ICU in case of an acute emergency.

Outpatient visits for IMP administration, safety and PK assessments are planned for Day 4 to Day 8 (Visit 3 to Visit 7). On Day 9 (Visit 8), patients will come to the unit in the morning for IMP administration and PK sampling and will return again in the evening for admission. For practical reasons, and if preferred by the patient, he or she may remain at the clinic during the whole Day 9. Subjects will be residential at the clinic between Day 9 and Day 12 (Visit 8) for IMP administration,

safety, PK and exploratory PD assessments. The last dosing day is Day 10. Urine collection for exploratory PD analysis will be performed during 24 h after the last dose. A final end-of-study visit (Visit 9) is planned to take place on Day 19 (±2 days) or after early withdrawal.

Part IV (celecoxib)
In Part IV of the study, 200 mg celecoxib will be administered to 8 healthy volunteers twice daily for 10 days (i.e. 400 mg/day for 10 days).

Subjects will come for 5 visits to the clinic. Screening (Visit 1) will take place from Day -28 to Day -2. At Visit 2, subjects will be admitted to the clinic in the morning of Day -1 for pre-dose assessments including a 24 h baseline urine collection and will remain at the clinic until Day 2 for IMP administration and PD assessments. Subjects will be discharged from the clinic after the morning dose on Day 2.

From the evening of Day 2 to the evening of Day 8, subjects will self-administer celecoxib at home twice daily (morning and evening) and register each administration in an electronic diary (ViedocMe). Any reactions or use of concomitant medication will also be registered in ViedocMe. On Day 5 (Visit 3), the subjects will be contacted by phone for a drug accountability and AE check-up.

Subjects will again be residential at the clinic between Day 9 and Day 11 (Visit 4) for IMP administration and exploratory PD assessments. The last dosing day is Day 10. Urine collection for exploratory PD analysis will be performed during 24 h after the last morning dose on Day 10. A final end-of-study visit (Visit 5) will take place on Day 19 (±2 days) or after early withdrawal.

Investigational Medicinal Product (IMP), dosage, mode of administration and duration of treatment

GS-248 is an oral solution of pH 3. Placebo contains the same components as the GS-248 solution except the active substance.

Part I (SAD), planned dosage: single doses of 1 mg, 5 mg, 25 mg, 75 mg, 225 mg and 450 mg GS-248

Part II (MAD), planned dosage: once daily dosing of 25 mg, 75 mg, 225 mg and 450 mg GS-248 for 10 days

Part III (SSc patients), planned dosage: the dose in Part III will be based on safety, tolerability and PK data collected during Part I and II of the study and will be documented in a substantial amendment, which must be approved by the regulatory authorities and the ethics committee prior to start of Part III. The dose is planned to be administered once daily for 10 days.

Reference product, dosage, mode of administration and duration of treatment

Celecoxib is a registered product provided as oral capsules (200 mg).

Part IV (celecoxib) dosage: 200 mg twice daily for 10 days.

Duration of each subject's/patient's involvement in the study

Part I (SAD): Each subject is expected to participate in the study for approximately 36 days including a 28-day screening period.

Part II (MAD): Each subject is expected to participate in the study for approximately 47 days including a 27-day screening period.

Part III (SSc patients): Each patient is expected to participate in the study for approximately 61 days including a 41-day screening period.

Part IV (celecoxib): Each subject is expected to participate in the study for approximately 47 days including a 27-day screening period.

Safety assessments (Part I, II and III) AE reporting, 12-lead ECG monitoring, vital signs (blood pressure and pulse), body temperature, physical examination, use of concomitant medications, urinalysis and blood sampling for haematology, clinical chemistry and coagulation parameters.
Pharmacokinetic (PK) assessments (Part I, II and III) Blood sampling for bioanalysis and subsequent determination of GS-248 PK parameters
Exploratory assessments • Blood sampling for analysis of mPGES-1 activity (PGE_2 levels) in an *ex vivo* WBA (all parts, Part I from cohort 3) • Blood and urine sampling for analysis of ADMA in plasma and AA metabolites in urine (Part II, III and IV) • Blood and urine sampling for future analysis of GS-248 metabolites (Part I [plasma only] and Part II, Part II includes MIST). • Blood and urine sampling to be saved for future biomarker analyses e.g. further AA metabolite profiling in plasma and urine and inflammatory biomarkers in plasma (all parts, Part I from cohort 3) and urine (Part II, III and IV).
Statistical methods No formal sample size calculation has been performed. The proposed sample size is considered sufficient to provide adequate information for the study objectives. A statistical analysis plan (SAP) will be prepared and signed prior to the first database lock which will take place after completion of Part I, II and IV. Safety, PK and PD data will be summarised by descriptive statistics as appropriate.
Study reporting After completion of the study, an ICH-E3 compliant CSR will be prepared.

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3 LIST OF ABBREVIATIONS AND DEFINTIONS OF TERMS

Abbreviation or term	Explanation
AA	Arachidonic acid
ADL	Activities of daily living
AE	Adverse event
ACE	Angiotensin Converting Enzyme
ACR	American College of Rheumatology
ADMA	Asymmetric dimethylarginine
ADR	Adverse drug reaction
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC_{0-t}	Area under the curve from time 0 to time t
$AUC_{0-\infty}$	Area under the curve from time 0 to infinity
AUC_{ss}	Area under the curve at steady state
AUE	Area under the effect curve
BMI	Body mass index
CA	Competent authority
CDC	Centres for Disease Control and Prevention
CIOMS	Council for International Organisations of Medical Sciences
C_{max}	Maximum plasma concentration
CNS	Central nervous system
COX	Cyclooxygenase
CRM	Clinical research manger
CRP	C-reactive protein
CSP	Clinical study protocol
CSR	Clinical study report
CTC	Clinical Trial Consultants AB
CTCAE	Common terminology criteria for adverse events
CTC PV	CTC's Pharmacovigilance
C_{trough}	Observed concentration at the end of a dosing interval, immediately before next administration
CV	Coefficient of variation
DBL	Database lock
DMP	Data management plan
DRF	Dose range finding

DSUR	Development safety update report
DU	Digital ulcer
ECG	Electrocardiogram
eCRF	Electronic CRF
eGFR	Estimated glomerular filtration rate
EDC	Electronic data capture
EEA	European Economic Area
ePRO	Electronic patient reported outcome
EULAR	European League Against Rheumatism
FAS	Full analysis set
FDA	U.S. Food and Drug Administration
FIH	First-in-human
FSH	Follicle stimulating hormone
GCP	Good clinical practice
GDPR	General data protection regulation
gGT	Gamma glutamyl transferase
GI	Gastrointestinal
GMP	Good manufacturing practice
h	hour
Hb	Haemoglobin
HBsAG	Hepatitis B surface antigen
HCG	Human chorionic gonadotropin
HCVAb	Hepatitis C virus antibodies
HED	Human Equivalent Dose
HIV	Human immunodeficiency virus
IB	Investigator's brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International conference on harmonisation
ICU	Intensive care unit
IEC	Independent ethics committee
IMP	Investigational medicinal product
ISF	Investigator site file
iSRC	Internal safety review committee
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LD	Lactate dehydrogenase
LLOQ	Lower limit of quantification
LPS	Lipopolysaccharide

MABEL	Minimum Anticipated Biological Effect Level
MAD	Multiple ascending dose
MCV	Mean corpuscular volume
MEC	Molar extinction coefficient
MedDRA	Medical dictionary for regulatory activities
min	minute
MIST	Metabolites in Safety Testing
MPA	Medical products agency
MTD	Maximum tolerated dose
mPGES-1	Microsomal Prostaglandin E synthase-1
N	number
NCA	Non-compartmental analysis
NCI	National Cancer Institute
NIH	National Institute of Health
NOAEL	No observed adverse effect level
NSAID	Non-steroidal anti-inflammatory drug
OTC	Over the counter
PD	Pharmacodynamic(s)
PDE-5	Phosphodiesterase type 5
PG	Prostaglandin
PGE_2	Prostaglandin E2
PGH_2	Prostaglandin H2
PGI_2	Prostaglandin I2 (prostacyclin)
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
PK(INR)	Prothrombin complex international normalised ratio
PII	Personally identifiable information
PPS	Per protocol set
PPI	Proton pump inhibitor
PT	Preferred term
QC	Quality control
RBM	Risk-based monitoring
RCS	Raynaud's Condition Score
SAD	Single ascending dose
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAP	Statistical analysis plan

SD	Standard deviation
SDV	Source data verification
SmPC	Summary of product characteristics
SOC	System organ class
SOP	Standard operating procedure
SPF	Sun protection factor
SSc	Systemic sclerosis
SUSAR	Suspected unexpected serious adverse reaction
T_{max}	Time to C_{max}
TMF	Trial master file
TPC	Thrombocyte particle concentration
TSH	Thyroid Stimulating hormone
TXM	11-dehydro-thromboxane B_2
$T_{½}$	Terminal half life
ULN	Upper limit of normal
UVA	Ultraviolet A
UVB	Ultraviolet B
WBA	Whole blood assay, *ex vivo* measurements of mPGES-1 activity in LPS-stimulated whole blood
WHO	World Health Organization
WOCBP	Women of childbearing potential

4 IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

4.1 Medical emergencies contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. A medical emergency usually constitutes a serious adverse event (SAE) and is to be reported as such. Detailed SAE reporting procedures are described in Section 11.3.1.12.

In the case of a medical emergency the Investigator may contact the Medical Monitor.

Name	Function in the study	Telephone number and e-mail
Cornelia Lif-Tiberg	Medical monitor and adjunct member of the internal Safety Review Committee (iSRC)	Telephone: +46 (0)73 978 94 45 E-mail: cornelia-lif-tiberg@ctc-ab.se

5 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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Part I and II will be conducted at the FIH Uppsala University Hospital clinic. Part III and IV may be conducted either at the clinic at Uppsala University Hospital or at the clinic on Dag Hammarskjölds väg 10B.

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Laboratory (Safety)	Clinical Chemistry and Pharmacology Uppsala University Hospital Entrance 61, 2nd level SE-751 85 Uppsala, Sweden
Laboratory (Bioanalysis, ADMA in plasma, AA metabolites in urine)	Recipharm OT Chemistry AB Virdings allé 18 SE-754 50 Uppsala, Sweden
Laboratory (*ex vivo* WBA, MIST and other exploratory analyses)	To be decided.
Investigational medicinal product (IMP) manufacturing, packaging and labelling	RISE Research Institutes of Sweden AB Forskargatan 18 SE-151 36 Södertälje, Sweden.
Pharmacy	Apoteket Clinical Trial Unit Dag Hammarskjölds väg 18 SE-751 85 Uppsala, Sweden
Electronic data capture (EDC) system provider:	PCG Solutions AB S:t Persgatan 6 SE-753 20 Uppsala, Sweden

Signatures are provided in Section 19.

6 INTRODUCTION

6.1 Background

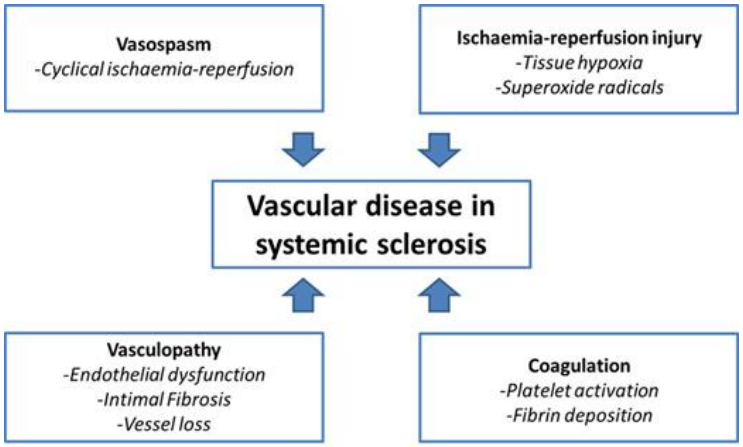
6.1.1 *Systemic Sclerosis*

Systemic Sclerosis (SSc) is an autoimmune disease with microvascular injury and endothelial cell activation that results in vascular damage. Pathophysiological consequences of the vasculopathy are vasospasm, ischemia-reperfusion injury and coagulation, which manifest as Raynaud's Phenomenon in more than 95% of the patients, and around half of patients report a history of Digital Ulcers (DUs). Most subjects make at least one life adjustment due to Raynaud's Phenomenon, and quality of life is significantly reduced. DUs are painful, heal slowly and are difficult to treat. In an international survey only 16% of those with current or previous use of medications for Raynaud's Phenomenon reported at least one medication being effective. Although clinical studies have demonstrated phosphodiesterase type 5 (PDE-5) inhibitors and bosentan can improve healing and prevent development of new DUs, the efficacy is modest, and more than half of the patients with chronic DUs need hospitalisation for intravenous treatment with iloprost.

6.1.2 *Raynaud's phenomenon and digital ulcers in Systemic sclerosis*

Microvascular injury and endothelial cell activation that results in vascular damage are considered to be the earliest, and possibly primary, events in SSc [1]. Changes in capillary morphology as investigated with nailfold videocapillaroscopy demonstrate a distinct and typical pattern [2] , but also small and medium size arteries are involved [3]. There are four pathophysiological components of the vascular disease in SSc (Figure 6.1-1; [4]).

Figure 6.1-1 The pathophysiology of vascular disease in SSc (Hughes & Herrik, 2017)



Peripheral blood flow after cold challenge can reliably be assessed also in multi-centre clinical studies with laser speckle contrast imaging and thermography [5]. Other methods to assess peripheral blood flow in a human experimental setting include microdialysis [6].

Raynaud's phenomenon, an episodic painful ischemic event affecting primarily fingers and toes in response to cold exposure or to emotional stress, is a very common manifestation of

SSc. In the large EUSTAR database, including 9,182 patients with SSc, more than 95% reported Raynaud's Phenomenon [7]. The mean age at onset of Raynaud's Phenomenon, which usually is the first symptom of SSc, was 42 years and preceded symptoms from other organ manifestations within mean 4 years [8]. In an international survey of patients with Raynaud's Phenomenon, most subjects (78%) reported making at least one life adjustment due to Raynaud's Phenomenon, and quality of life was significantly reduced. Further, of those with current or previous use of medications for Raynaud's Phenomenon, only 16% reported at least one medication being effective [9]. Raynaud's Condition Score (RCS), a patient-reported outcome, is a validated method to assess and document disease activity and functional status in patients during clinical trials [10].

DUs are a common and disabling manifestation of the underlying vasculopathy in SSc; around half of patients report a history of DUs [4], with male sex being associated with higher risk [7]. DU in the course of SSc are painful, heal slowly (3–15 months) and are difficult to treat [11]. More than half of the patients with chronic DUs need hospitalisation for intravenous treatment with prostacyclin analogues of their ulcers or complications. DU is also a marker for a more severe course of SSc with increased frequency of organ manifestations such as heart, lung, kidney and the gastrointestinal tract [12].

Raynaud's Phenomenon and DUs are closely related sharing the same pathophysiology with impaired peripheral circulation. Raynaud's Phenomenon in patients with connective tissue disease, especially in those with SSc, can sometimes progress to digital ulceration or critical ischemia [13]. In line with this, Raynaud's phenomenon has been demonstrated to be a risk factor for the development of DUs [11], and the connection between the 2 conditions is further supported by the observation that the RCS is worse in patients with digital ulcers than in those without [10].

6.2 Product characteristics

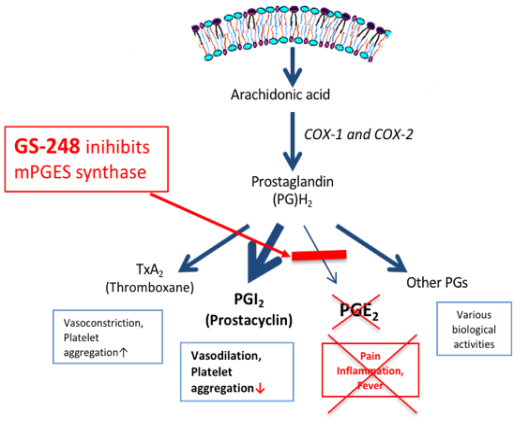
The Drug Substance, GS-248, is isolated as stable, highly crystalline hydrogen sulphate salt. It is an achiral substance with a *trans*-orientation of the 4-trifluoromethylcyclohexyl-group. The parent is a weak base with pKa 4.8 (protonation at the benzimidazole moiety) and the water solubility is low and pH-dependant.

The Drug Product to be used in the study is an oral solution where GS-248 is dissolved in an acidic vehicle at pH 3.0.

6.3 Mechanism of action

GS-248 is a selective and potent inhibitor of the microsomal Prostaglandin E synthase-1 (mPGES-1). Microsomal PGES-1 is an inducible enzyme that catalyses the second step in the prostaglandin E2 (PGE_2) formation from arachidonic acid (AA) and is also an anticipated drug target to treat inflammation (Figure 6.3-1).

Figure 6.3-1 Schematic view of arachidonic acid cascade and shunting of the substrate PGH_2 from PGE_2 production to PGI_2 formation



Selective mPGES-1 inhibitors are suggested to be safer than traditional non-steroidal anti-inflammatory drugs (NSAID)s or Coxibs, which target the upstream cyclooxygenases (COX-1 and COX-2, respectively) for general inhibition in prostanoid production (Figure 6.3-1). Genetic deletion of mPGES-1, as well as its pharmacological inhibition, has been proven to be protective in several models of inflammatory disorders such as stroke, multiple sclerosis, atherosclerosis, osteo- and rheumatoid arthritis [14]. Prostaglandin I_2 (PGI_2), another AA metabolite, induces vasodilatation and inhibits platelet aggregation. PGI_2 is formed from common substrate, prostaglandin H_2 (PGH_2), by the enzyme prostacyclin synthase, which is mainly expressed in the vascular endothelium.

The aim of the present project is to achieve an anti-inflammatory effect by reducing production of the proinflammatory mediator PGE_2 and concomitantly, by substrate shunting, elicit a vasodilatory and platelet inhibitory effect by increased prostacyclin (PGI_2) production.

6.4 Non-clinical summary

GS-248 inhibits mPGES-1 enzyme with a half maximal inhibitory concentration (IC_{50}) of 2 nM, while having no effect on COX-1 or COX-2 when tested up to 100 uM. In a human whole blood assay (WBA), GS-248 inhibited PGE_2 synthesis with an IC_{50} of 0.4 nM. Efficacious enzyme inhibition *in vivo* has been demonstrated in a Thermal Hyperalgesia model in the guinea-pig in which GS-248 reversed the lipopolysaccharide (LPS)-induced hyperalgesia in a dose dependent manner with maximal effect at 30 mg/kg p.o., 3 h post-dose.

The core battery safety pharmacology studies performed showed that GS-248 had no central nervous system (CNS), respiratory or cardiovascular effects after single or repeated administration at doses of up to 1000 mg/kg in rats or 80 mg/kg in dogs.

GS-248 in rat demonstrated an intermediate clearance compound with a large volume of distribution, with an oral bioavailability of 37% and a terminal half-life ($T_{½}$) of 2.5 h in the fasted state. The overall steady state toxicokinetic data in the rat and dog showed that the exposure increased less than dose proportionally, except for female dogs between the low and intermediate doses on test day 1 and between the intermediate and high doses on test day 18/28, where the increase was dose proportional. The mean exposure (male and female dogs) at the no observed adverse effect level (NOAEL) were 2500 nmol/L for maximum plasma

concentration (C_{max}) and 23000 nmol*h/L for $AUC_{(0\text{-last})}$. No accumulation was observed in the rat, whereas an accumulation was observed over the number of treatment days in the dog.

GS-248 showed a high plasma protein binding in all investigated species, with human serum albumin as the major determined protein in human plasma. Radiolabelled GS-248 was extensively distributed with the highest concentrations found in the liver, adrenals, brown fat, kidneys, salivary glands, and pancreas. After reaching the maximum, radioactivity in tissues and organs depleted rapidly within the first 8 h.

An *in vitro* metabolism species comparison showed no major difference in metabolic pathways between rat, dog, cynomolgus and human hepatocytes. GS-248 has been shown to be a potent in vitro inhibitor for CYP 2C8, 2C9 and 2C19.

The major part of GS-248 in rats was eliminated in faeces via the bile whereas urinary excretion was negligible. Overall, the elimination was fast and almost complete after 48 h.

Mild increases in serum cholesterol levels were noted in both rats and dogs at all dose levels included in the 28-day toxicity studies, but these changes were of a low degree and were therefore not considered to be adverse effects. The same applies for mild decreases in serum protein levels noted at the low and intermediate dose levels in the dog study.

Testicular degeneration was noted histopathologically in the 3 male dogs at the highest dose level that were necropsied pre-terminally on Day 21 of the 28-day toxicity study. These were most probably an exacerbation of effects that can be seen spontaneously in adult dogs, as a result of the poor physiological condition of these animals prior to their pre-terminal necropsy. Thus, these changes may well be secondary effects and therefore not directly related to GS-248 treatment. No such changes were noted at the NOAEL of 20 mg/kg (the intermediate dose level).

Clear adverse effects on the liver and biliary system indicating cholestasis and inflammation noted in the dogs in the dose range finding (DRF) and pivotal 28-day toxicity studies are the toxicity findings that set the limits for human exposure in the current Phase I study. Pronounced and serious effects were seen at the highest dose of 80/40 mg/kg, and thus this dose regimen was clearly above the maximum tolerated dose (MTD) for repeated treatment with GS-248 in dogs. At the intermediate dose level of 20 mg/kg, a single female showed mild to moderate increases in the majority of liver biomarkers, which were followed at regular intervals during the study. These changes were primarily observed during the first 2 weeks of dosing, subsequently decreased during continued dosing and had finally returned to within the normal range at the end of the 28-day dosing period. No treatment-related histopathological changes of any type were noted in this animal. Therefore, as the changes in these clinical pathology parameters were short-lived, returned to within the normal range during continued and uninterrupted dosing and no treatment-related histopathological changes were noted in these animals, the NOAEL in this study was set at this dose level, i.e. 20 mg/kg.

This test compound was shown to be negative for genotoxicity in the Ames test and mouse lymphoma assay in vitro and the micronucleus test in rats in vivo, following 14 days' treatment at 1000 mg/kg plus an additional 14 days' treatment at 2000 mg/kg.

Both the molar extinction coefficient (MEC) value of GS-248 and the fact that it also showed a weak and comparatively short-lived potential binding of radioactivity to melanin-containing tissues of the ocular bulb indicate a phototoxic potential.

For details on the non-clinical studies performed, refer to the Investigator's Brochure (IB) of GS-248.

6.5 Clinical experience

The present study is a first-in-human (FIH) study, hence there is no clinical experience of GS-248 administration to humans. However, substances targeting the same enzyme have previously been investigated in Phase I studies; no target related toxicity was observed in the study with LY3023703 [15], but the development was discontinued due to liver toxicity related to formation of reactive metabolites formed from those compounds [16]. Similar metabolites have not been observed from GS-248 and are unlikely to be formed based on the chemical structure of the molecule.

6.6 Study rationale

GS-248 is intended to be used for the prevention and treatment of DUs in patients with systemic sclerosis. Current oral therapies for DUs have limited efficacy, and there is a high medical need for new therapeutic alternatives.

This is a FIH study including healthy volunteers and patients with SSc. It is not expected that the healthy volunteers will gain any benefit from GS-248. However, should patients included in the cohort(s) with systemic sclerosis potentially experience improvement of symptoms related to Raynaud's phenomenon, this will be captured by posing relevant questions to the patients during the study.

The aim of the present project is to achieve an anti-inflammatory effect by reducing production of the proinflammatory mediator PGE_2 and concomitantly, by substrate shunting, to elicit a vasodilatory and platelet inhibitory effect by increased PGI_2 production.

The study will collect information about safety, tolerability and pharmacokinetics (PK) following single and multiple administration of GS-248 to healthy subjects and patients with SSc. In addition, an exploratory comparison of the pharmacodynamic (PD) effects between celecoxib and GS-248 will be performed.

It is considered desirable to obtain safety and tolerability data in the target SSc patient population early in the clinical program. In addition, specific reasons to include patient cohort(s) are:

- More than 50% of patients with SSc have gastrointestinal involvement, which may influence uptake of study drug
- Inclusion of patients will allow early assessment of PD effects based on ex vivo whole blood PGE_2 synthesis. The mPGES enzyme is upregulated in inflammatory tissues such as in patients with SSc. Thus, the levels of active prostaglandin (PG)-metabolite may differ between healthy subjects and patients with SSc.

The rationale for the study design is outlined in Section 8.2.

6.7 Risk/benefit assessment

Part I, II and III

The healthy volunteers in Part I and II (single ascending dose [SAD] and multiple ascending dose [MAD], respectively) in this study will, except for thorough health examinations, have no medical benefit from participation and their safety and wellbeing are of outmost importance. The study involves the first administration of GS-248 to humans, and there are no previous data on the effects of the drug in humans. It is therefore difficult to make predictions about possible adverse drug reactions (ADRs).

Pronounced and serious effects on the liver and biliary system were noted in dogs at the highest dose in the 28-day toxicity study. However, no findings that were considered to constitute an adverse effect were noted at the intermediate dose level, primarily based on the total lack of treatment-related histopathological findings at this dose level, and the NOAEL in this study was therefore set at 20 mg/kg.

The liver biomarkers will be closely monitored during the present study, providing the possibility to stop dosing in individuals with signs on emerging liver toxicity. The medical monitor will continuously review individual subjects to decide if dosing should be discontinued. An internal safety review committee (iSRC) will review both individual subjects and trends between dosing groups as recommended in the U.S. Food and Drug Administration (FDA) Guidance on Drug-Induced Liver Injury [25] to decide if dosing should be continued, and in that case at which dose level, see Section 9.7.3. Stopping of further dosing or adjustments from the intended dosing scheme can be considered also if the stopping rules recommended in the Guidance are not fulfilled.

Mild increases in serum cholesterol levels have been noted in both rats and dogs at all dose levels included in the 28-day toxicity studies. However, these changes were of a low degree and were therefore not considered to be adverse effects. The likelihood of any clinically relevant increases in serum cholesterol in the present study is low, but serum cholesterol will be monitored throughout the study in order to discern any evolving effects.

Testicular degeneration was noted histopathologically in the 3 male dogs at the highest dose level in the 28-day study that were necropsied pre-terminally on Day 21. These changes were interpreted as most probably being secondary effects as a result of the poor physiological condition of these animals, and therefore not directly related to GS-248 treatment. Furthermore, as no such changes were noted at the NOAEL (the intermediate dose level) in this study, there will be sufficient safety margins to such effects in the present study.

The phototoxicity of GS-248 has not been investigated, but based on the MEC value obtained from absorbance studies and the weak and comparatively short-lived potential binding of radioactivity to melanin-containing tissues of the ocular bulb, a phototoxic potential cannot be excluded. Thus sun protection, as defined in Section 9.5.2, should be used during the study.

The selection of starting-dose and dose-escalation steps represents a careful approach to administer GS-248 for the first time in humans (see Section 8.3). Sentinel dosing will apply for the first 2 subjects in each SAD cohort.

SSc patients participating in the study may experience some symptom relief. The risks for SSc patients are considered to be comparable to those identified for the healthy volunteers participating in Part I and Part II of the study with the exception that patients may experience

discomfort following withdrawal of e.g. proton pump inhibitors (PPIs) and other medications (see below).

In Part I, II and III, use of antacids, PPIs or any medication that changes gastric pH is disallowed from 14 days prior to IMP administration and during the study since GS-248 is a low solubility compound with pH dependent solubility. A high pH may decrease exposure.

Use of NSAIDs, coxibs and aspirin is prohibited from 14 days prior to IMP administration and during the study to avoid interference with the GS-248 signal transduction pathway and evaluation of study results.

The iSRC will monitor emerging safety and PK data over the course of the study and must give a favourable recommendation prior to any dose escalation, see Section 8.3.7 and Section 8.3.8 for stopping criteria for dose escalation and for further information about the iSRC.

Subjects will remain in the research clinic for approximately 48 h after the single dose in Part I (SAD) and will be closely monitored by medical staff. In Part II (MAD) and Part III (SSc patients), subjects/patients will be residential at the clinic for approximately 48 h after the first dose (Day 1) and the last dose (Day 10) for safety surveillance and PK/PD sampling. In addition, subjects will visit the clinic in the morning of each day in between the residential stays for IMP administration and safety check-up. The duration of the residential periods may be amended if indicated by PK and/or safety data, see Section 8.3.8.

Part IV

The healthy volunteers in Part IV will receive the registered product celecoxib. Subjects with a history of salicylate hypersensitivity or NSAID hypersensitivity or subjects who have experienced asthma, urticaria or other allergic reactions after taking aspirin or other NSAIDs will not be included in Part IV of the study.

No specific safety surveillance following intake of celecoxib is considered necessary, but subjects will stay at the clinic for 24 h following the first and last dose of celecoxib, for PD assessments. On the remaining dosing days (from the evening dose on Day 2 until the evening dose on Day 8), subjects will self-administer celecoxib at home. The intake, and the time for intake, of celecoxib as well as any reactions or use of concomitant medications will be registered in an electronic diary (ViedocMe), see Section 16.3.

All parts

In all parts, subjects/patients will be admitted to the clinic the day before each residential stay. Visits at the clinic may be prolonged in case the Investigator finds it medically warranted for safety reasons. Each volunteer will be provided with a subject information card with information detailed in Section 14.4.

Overdosing of GS-248 is not likely to occur since GS-248 will be administered by site personnel under medical surveillance. In cases of accidental overdose, appropriate supportive medical care should be provided, see Section 11.3.1.15. In the event of suspected overdose of celecoxib, which will be self-administered by the subjects from the evening of Day 2 to the evening of Day 8, appropriate supportive medical care should be provided, see Section 11.3.1.15. The maximum recommended total daily dose is 400 mg, which corresponds to the intended dose in this study (2x200 mg/day).

The Principal Investigator at the research clinic will ascertain that adequate facilities and procedures are available to handle emergency situations should they occur during the study.

The medical staff at CTC have extensive experience from early Phase I and FIH studies and there are adequate procedures in place to handle unexpected and expected adverse reactions in the study subjects. The research clinic is located adjacent and on the same floor as the Intensive Care Unit (ICU) at the University Hospital in Uppsala. CTC has a separate agreement with the ICU for support in case of emergencies. CTC has been regularly inspected by the Swedish Medical Products Agency (MPA) and is authorised to conduct FIH studies.

Besides the risks related to the IMPs as described above, there may also be risks related to the medical devices used in the study e.g. indwelling venous catheters. However, these are devices that are used in routine medical care and the risk associated with their use is considered low and ethically justifiable. Study specific evaluations and sampling procedures, like blood-pressure measurements using a blood pressure cuff and frequent blood sampling, may cause transient discomfort but the risk is deemed to be low and ethically justifiable.

Overall, while keeping the above-mentioned risk factors at a minimum level in order to not expose the subjects participating in the study for risks that would not be ethically justifiable it is concluded that the planned study assessments are sufficient to meet the scientific and medical goals for the study. It is therefore concluded that the potential benefits from the study will outweigh the potential risks for the treated subjects/patients.

More detailed information about the known and expected benefits and risks and reasonably expected ADRs of GS-248 and celecoxib is found in the IB of GS-248 and in the Summary of Product Characteristics (SmPC) of celecoxib (Celebra, Pfizer) respectively.

7 STUDY OBJECTIVES AND ENDPOINTS

7.1 Primary objective

- To determine the safety and tolerability following oral single and multiple ascending doses of GS-248 (solution) in healthy subjects and patients with SSc

7.1.1 *Primary endpoints*

- Frequency, severity and seriousness of adverse events (AEs)
- Clinically significant changes in:
  - 12-lead electrocardiogram (ECG)
  - Vital signs
  - Safety laboratory parameters
  - Physical examinations

7.2 Secondary objective

- To evaluate the PK of GS-248 in healthy subjects and patients with SSc

7.2.1 *Secondary endpoints*

- PK parameters:
  - **Part I:** area under the curve from time 0 to time t (AUC_{0-t}), AUC from time 0 to infinity ($AUC_{0-\infty}$), $T_{½}$, C_{max}, time to C_{max} (T_{max}), dose proportionality (based on AUC and C_{max}), apparent total body clearance following extravascular administration (CL/F) and apparent volume of distribution following extravascular administration (V_z/F)
  - **Part II and III** after first dose interval: AUC_{0-t}, $T_{½}$, T_{max}, C_{max}, dose proportionality (based on AUC and C_{max})
  - **Part II and III** after last dose interval: AUC_{0-t}, AUC at steady state (AUC_{ss}), $T_{½}$, T_{max}, C_{max}, observed concentration at the end of a dosing interval, immediately before next administration (C_{trough} from the 2 doses preceding the last dose), dose proportionality (based on AUC_{ss} and C_{max}), CL/F, V_z/F and accumulation ratio

7.3 Exploratory objectives

- To evaluate the PD effects of GS-248 and celecoxib by determination of mPGES-1 activity (PGE_2 levels) in a WBA
- To explore the PD effects of GS-248 in plasma (asymmetric dimethylarginine [ADMA]) and urine (AA metabolites) and additional exploratory inflammatory biomarkers in healthy subjects and patients with SSc

- To explore the PD effects of celecoxib in plasma (ADMA) and urine (AA metabolites) and additional exploratory inflammatory biomarkers in healthy subjects after 10 days twice daily dosing to enable exploratory comparisons with GS-248 treated subjects
- To explore potential metabolites of GS-248 in plasma and urine (including metabolites in safety testing [MIST])

7.3.1 *Exploratory endpoints*

- *Ex vivo* determination of mPGES-1 activity (PGE_2 levels) in a WBA
- AA metabolites in urine captured pre-dose administration and during 24 h post-dose:
  - 11-alfa-hydroxy-9,15-dioxo-13,14-dihydro-2,3,4,5, tetranor-prostan-1,20-dioic acid (PGEM)
  - 2, 3-dinor-6-ketoprostaglandin F1α (PGIM)
  - 11-dehydro-thromboxane B_2 (TXM)
- ADMA in plasma
- Collection of plasma and urine for future analysis of potential metabolites after single and multiple dosing with GS-248
- Plasma and urine samples will be saved for future biomarker analyses e.g. further AA metabolite profiling in plasma and urine and inflammatory biomarkers in plasma and urine

The outcome of the WBA will be reported in the clinical study report (CSR) whereas the other exploratory endpoints may be reported separately from the CSR.

8 STUDY DESIGN

8.1 Overall study design and schedule of events

This is a FIH, double-blind, parallel-group, randomised, placebo-controlled study designed to evaluate the safety, tolerability, PK and PD of single and multiple ascending oral doses of GS-248 in healthy subjects and in patients with SSc. In addition, an exploratory comparison of the PD effects between celecoxib and GS-248 will be performed.

The study will be conducted in 4 parts:

Part I (SAD): safety, tolerability, PK and PD (PD from cohort 3) of single ascending oral doses of GS-248 in healthy male and female subjects (Section 8.1.1).

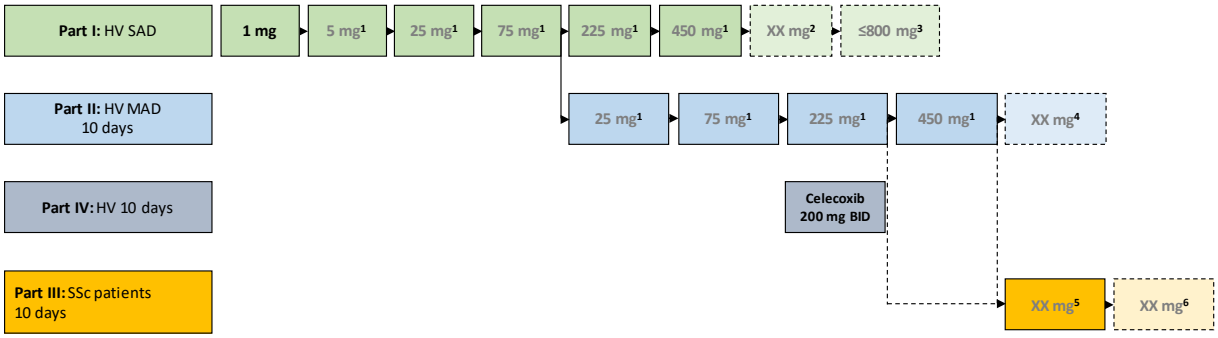
Part II (MAD): safety, tolerability, PK and PD of multiple ascending oral doses of GS-248 in healthy male and female subjects during 10 days administration (Section 8.1.2).

Part III (SSc patients): safety, tolerability, PK and PD of multiple oral doses of GS-248 in patients with SSc during 10 days administration (Section 8.1.3)

Part IV (celecoxib): PD of multiple oral doses of celecoxib (200 mg BID) in healthy males and females during 10 days administration (Section 8.1.4).

An overview of the study design is shown in Figure 8.1-1.

Figure 8.1-1 Overview of the study design



1. Tentative dose levels (grey). Final doses will be set based on emerging data.
2. Optional cohort. The dose may be set to between 450 mg and 800 mg, may be a repeated dose or another intermediate dose.
3. Optional cohort. 800 mg corresponds to the maximum dose to be administered in the study.
4. Optional cohort.
5. Dose in Part III to be set based on emerging data and will be documented in a substantial amendment, which must be approved prior to start of the cohort.
6. Optional cohort.

8.1.1 *Part I: Single Ascending Dose (SAD)*

In the SAD part of the study, single oral doses of GS-248 will be administered in 6 sequential cohorts, each of 8 subjects. Within each cohort, subjects will be randomised in a 3:1 ratio to receive either GS-248 (n=6) or placebo (n=2) in a blinded fashion. The proposed starting dose is 1 mg. The rationale for the starting dose and the planned dose escalation is detailed in

Section 8.3. Up to 2 additional dose cohorts can be explored based on the safety, tolerability and PK of the drug if recommended by the iSRC.

Subjects will come for 3 visits to the clinic. Screening (Visit 1) will take place from Day -28 to Day -1. For details on assessments, refer to Table 8.1-1. At Visit 2, subjects will be admitted to the clinic on Day -1 and will remain at the clinic until Day 3 for single dose IMP administration, safety, PK and PD (PD from cohort 3) assessments (Table 8.1-1 and Table 8.1-2). The subjects must fast for at least 10 h before the anticipated dosing time on Day 1. Water, but no other drinks, is allowed as desired except for 1 h before and 1 h after dosing. The first 2 subjects in each cohort will be dosed in a sentinel fashion; 1 subject will receive GS-248 and the other will receive placebo as randomised. The subjects will be carefully monitored by clinical staff during and after dosing. Vital signs and ECG will be checked at regular intervals as detailed in Table 8.1-2. There is immediate access to equipment, qualified staff and an ICU in case of an acute emergency. To give sufficient time for observation of any reactions, there will be at least 24 h before dosing of the third and fourth subject, who will be dosed on the same day approximately 2 h apart. The remaining 4 subjects will also be dosed 2 by 2, i.e. 2 subjects will be dosed on the same day approximately 2 h apart. A final end-of-study visit (Visit 3) will take place on Day 8 (±2 days) or after early withdrawal.

In all cohorts, safety and PK will be assessed before and after dose as outlined in Table 8.1-1 and detailed in Table 8.1-2. Exploratory blood sampling for WBA and future biomarker analysis (from cohort 3 and onwards) and potential future metabolite analysis will be performed before and after dose (Table 8.1-1 and Table 8.1-2).

Before initiating a new cohort, all subjects in the previous cohort must have been treated and 48 h safety, tolerability and PK data for all treated subjects must have been evaluated by the iSRC, see Section 8.3.8. Once Day 3 safety, tolerability and PK data for the last subject in each cohort has been collected, there will be at least 1week between dose escalations.

Each subject is expected to participate in the study for approximately 36 days including a 28-day screening period.

The schedule of events for Part I is shown in Table 8.1-1 and detailed for Visit 2 in Table 8.1-2. Study assessments are described in Section 11.

Safety assessments include: AE reporting, 12-lead ECG monitoring, vital signs (blood pressure and pulse), body temperature, physical examination, use of concomitant medications and blood sampling for haematology, clinical chemistry and coagulation parameters, see Section 11.3.

PK assessments include: blood sampling for bioanalysis and subsequent determination of PK parameters, see Section 11.4.

Exploratory assessments include: blood sampling for analysis of mPGES-1 activity (PGE_2 levels) in an *ex vivo* WBA, for future biomarker analysis (from cohort 3 and onwards) and for future exploratory analysis of metabolites, see Section 11.5.

Table 8.1-1 Schedule of events Part I (SAD)

	Screening	Residential period				End-of-study
Visit	**Visit 1**	**Visit 2[1]**				**Visit 3**
Assessment	Day -28 to Day -1[2]	Admission Day -1[2]	Day 1	Day 2	Day 3	Day 8 (±2 days)
Informed Consent	X					
Inclusion/exclusion criteria	X		X[3]			
Weight/height/BMI	X					X[4]
Medical/surgical history	X					
Demographics	X					
HIV, hepatitis B and C	X					
Urine Drug Screen[5]	X	X				X
Alcohol breath test	X	X				X
Pregnancy Test (WOCBP)[6]	X	X				X
Physical Examination	X		X[7, 8]			X
Clinical Laboratory Profile[9]	X	X			X	X
Vital signs[10]	X	X	X[11]	X	X	X
Body temperature			X[8]			
12-lead ECG	X		X[8, 11]	X	X	X
Telemetry			X[12]			
Randomisation			X			
IMP administration[13]			X			
PK blood sampling[14]			X[11]	X[11]	X[11]	
Blood sampling for WBA[15]			X[15]	X[15]		
Blood sampling for future biomarker analyses[15]			X[15]	X[15]		
Meals[16]		X	X	X	X	
Baseline symptoms	X	X				
AEs and SAEs			X[17]			
Prior and concomitant medications	X					

1. Details in separate flow chart (Table 8.1-2). The duration of the residential period may be amended following review of data from earlier cohorts.
2. Screening and admission to the clinic may be conducted on the same day.
3. Confirmation of eligibility prior to randomisation. Day -1 or Day 1.
4. Weight only.
5. Random drug screening test may also be performed at the discretion of the investigator.
6. Screening: plasma/serum tests, other visits: urine test.
7. Short version of physical examination on Day 1.
8. Pre-dose assessments may be performed pre-dose Day 1 or on Day -1.
9. Clinical chemistry, haematology, coagulation, urinalysis (dip-stick), see Section 11.3.6.
10. Blood pressure and pulse, see Section 11.3.3.
11. For timing of assessments, refer to Table 8.1-2.
12. Ambulatory ECG telemetry for up to 24 h after IMP administration.
13. Administered under fasting conditions, i.e. fasting for 10 h before IMP administration until 4 h post administration.
14. Includes sampling for future exploratory analyses of potential GS-248 metabolites.
15. Sampling for WBA analysis and for future biomarker analyses starts at cohort 3. For timing of assessments, refer to Table 8.1-2.
16. Breakfast, lunch, snack, dinner and evening snack. Standardised meals during 24 h after dose. For timing of meals, refer to Table 8.1-2. No breakfast on Day 1. Breakfast only on Day 3.
17. From administration of IMP.

Table 8.1-2 Detailed schedule of events for Visit 2, Part I (SAD)

	Day -1	Day 1													Day 2		Day 3
Assessment/time-point	**Admission**	**Pre-dose**	**0**	**0.25h**	**0.5h**	**1h**	**1.5h**	**2h**	**3h**	**4h**	**6h**	**8h**	**12h**	**16h**	**24h**	**36h**	**48 h**
Inclusion/exclusion criteria		X[1]															
Pregnancy test (WOCBP)	X																
Urine drug screen	X																
Alcohol breath test	X																
Physical examination		X[1,2]															
Clinical laboratory profile	X																X
Vital signs	X	X				X		X		X	X	X	X		X	X	X
Body temperature		X[1]															
12-lead ECG		X[1]						X				X			X		X
Telemetry			X														
Randomisation		X															
IMP administration			X														
PK blood sampling[4]		X[3]		X	X	X	X	X	X	X	X	X	X	X	X[5]		X
Blood sampling for WBA[6]		X[3]						X				X			X		
Blood sampling for future biomarker analyses[6]		X[3]						X				X			X		
Breakfast[7]															X		X
Meals	X[9]									X[8, 9]					X[9]		X[9]
Baseline symptoms	X	X															
AEs and SAEs			X														
Prior and concomitant medications	X																

1. Day -1 or pre-dose Day 1 prior to randomisation.
2. Short version of physical examination.
3. Within 60 minutes prior to dose.
4. Includes sampling for future exploratory analyses of potential GS-248 metabolites.

5. The 24 h PK sample is taken pre-dose Day 2 within 10 minutes of the of the nominal time for the dosage interval. For details regarding time windows for PK sampling, refer to Section 11.4.1.
6. From cohort 3 and onwards.
7. Fasting on Day 1. Breakfast on Day 2 and Day 3 after PK blood sampling.
8. Standardised lunch at least 4 h post-dose.
9. Standardised lunch, snack, dinner and evening snack at approximately 4, 7 and 9 and 11 h post-dose on Day 1 until 24 h after dose. Non-standardised lunch, snack, dinner and evening snack at approximately 4, 7 and 9 and 11 h post breakfast on Day 2. Dinner and evening snack on Day -1. Breakfast only on Day 3.

8.1.2 *Part II: Multiple Ascending Dose (MAD)*

Part II of the study will explore multiple ascending dosing of GS-248. The initial dose, dose escalation and dosing schedule will be based on emerging knowledge of safety, tolerability and PK of GS-248 observed in the SAD part of the study (Part I). The proposed starting dose is 25 mg/day. The rationale for the starting dose and the planned dose escalation is detailed in Section 8.3.

GS-248 is planned to be administered once daily for 10 days. Each dose level during the MAD part will be selected such that the predicted maximum exposure will not exceed the maximum exposure (AUC and C_{max}) in previously evaluated SAD cohorts. The starting dose, subsequent dose levels and time points and visits for PK sampling may be adjusted based on safety and PK evaluation in the SAD and MAD part as outlined in Section 8.3.8.

GS-248 will be administered in 4 sequential cohorts, each of 8 subjects. Within each cohort, subjects will be randomised in a 3:1 ratio to receive GS-248 (n=6) or placebo (n=2) in a blinded fashion. Up to 1 additional dose cohort can be explored based on the safety, tolerability and PK of the drug if recommended by the iSRC.

Subjects will come for 9 visits to the clinic. Screening (Visit 1) will take place from Day -28 to Day -2. For details on assessments, refer to Table 8.1-3. At Visit 2, subjects will be admitted to the clinic in the morning of Day -1 for pre-dose assessments including a 24 h baseline urine collection and will remain at the clinic until Day 3 for IMP administration and safety, PK and exploratory PD assessments (Table 8.1-3 and Table 8.1-4). Up to 4 subjects will be dosed on the same day. There will be at least 30 minutes between the dosing of each subject. The subjects will be carefully monitored by clinical staff during and after dosing. Vital signs and ECG will be checked at regular intervals as detailed in Table 8.1-4. There is immediate access to equipment, qualified staff and an ICU in case of an acute emergency.

Outpatient visits for IMP administration, safety and PK assessments are planned for Day 4 to Day 8. (Visit 3 to Visit 7), see Table 8.1-3 and Table 8.1-4. On Day 9 (Visit 8), subjects will come to the unit in the morning for IMP administration and PK sampling and will return again in the evening for admission. For practical reasons, and if preferred by the subject, he or she may remain at the clinic during the whole Day 9.

Subjects will be admitted to the clinic between Day 9 and Day 12 (Visit 8) for IMP administration, safety, PK and exploratory PD assessments. The last dosing day is Day 10. Urine collection for exploratory PD analysis will be performed during 24 h after the last dose. A final end-of-study visit (Visit 9) is planned to take place on Day 19 (±2 days) or after early withdrawal.

Before initiating a new cohort, all subjects in the previous cohort must have been treated and 11 days safety, tolerability and PK data (i.e. data up to and including 24 h post last dose) for all treated subjects must have been evaluated by the iSRC, see Section 8.3.8. Once Day 11 safety, tolerability and PK data for the last subject in each cohort has been collected, there will be at least 1 week between dose escalations.

Each subject is expected to participate in the study for approximately 47 days including a 27-day screening period.

The schedule of events for Part II is shown in Table 8.1-3 and is detailed for Visit 2 and Visit 9 in Table 8.1-4. Study assessments are described in Section 11.

Safety assessments include: AE reporting, 12-lead ECG monitoring, vital signs (blood pressure and pulse), body temperature, physical examination, use of concomitant medications and blood sampling for haematology, clinical chemistry and coagulation parameters, see Section 11.3.

PK assessments include: blood sampling for bioanalysis and subsequent determination of GS-248 PK parameters, see Section 11.4.

Exploratory assessments include: blood sampling for analysis of mPGES-1 activity (PGE_2 levels) in an *ex vivo* WBA, blood and urine sampling for analysis of ADMA in plasma and AA metabolites in urine, blood and urine sampling for future exploratory analysis of GS-248 metabolites and for future exploratory biomarker analyses, see Section 11.5.

Table 8.1-3 Schedule of events Part II (MAD)

	Screening	Residential period				Daily visits	Residential period				End-of-study
Visit	**Visit 1**	**Visit 2[1]**				**Visit 3 to 7**	**Visit 8[1]**				**Visit 9**
Assessment	Day -28 to Day -2	Admission Day -1	Day 1	Day 2	Day 3	Day 4 to 8	Admission Day 9	Day 10	Day 11	Day 12	Day 19 (±2
Informed Consent	X										
Inclusion/exclusion criteria	X		X[2]								
Weight/height/BMI	X										X[3]
Medical/surgical history	X										
Demographics	X										
HIV, hepatitis B and C	X										
Urine Drug Screen[4]	X	X					X				X
Alcohol breath test	X	X					X				X
Pregnancy Test (WOCBP)[5]	X	X					X				X
Physical Examination	X		X[6, 7]							X[6]	X
Clinical Laboratory Profile[8]	X	X		X[9]	X	X[9]	X			X	X
Vital signs[10]	X	X	X[11]	X[11]	X		X	X[11]	X[11]	X	X
Body temperature			X[7]					X[7]			
12-lead ECG	X		X[7, 11]	X	X			X[7,11]		X	X
Randomisation			X								
IMP administration[12]			X	X	X	X	X	X			
PK blood sampling			X[11]	X[11]		X[14]	X[11, 14]	X[11, 14]	X	X	
Blood sampling for GS-248 MIST[13]			X[11]	X[11]				X[11]	X[11]		
Blood sampling for WBA			X[11]	X[11]				X[11]	X[11]		
Blood sampling for ADMA analysis			X[11]	X[11]				X[11]	X[11]		
Blood sampling for future biomarker analyses[15]			X[11]	X[11]				X[11]	X[11]		

	Screening	Residential period				Daily visits	Residential period				End-of-study
Visit	**Visit 1**	**Visit 2[1]**				**Visit 3 to 7**	**Visit 8[1]**				**Visit 9**
Assessment	Day -28 to Day -2	Admission Day -1	Day 1	Day 2	Day 3	Day 4 to 8	Admission Day 9	Day 10	Day 11	Day 12	Day 19 (±2
Urine collection		X[16]						X[16]			
Meals[17]		X	X	X	X		X	X	X	X	
Baseline symptoms	X	X									
AEs and SAEs			X[18]								
Prior and concomitant medications	X										

1. Details in separate flow chart (Table 8.1-4). The duration of the residential period may be amended following review of data from earlier cohorts.
2. Confirmation of eligibility prior to randomisation. Day -1 or Day 1.
3. Weight only.
4. Random drug screening test may also be performed at the discretion of the investigator.
5. WOCBP only. Screening: plasma/serum tests, other visits: urine test.
6. Short version of physical examination on Day 1 and Day 12.
7. Pre-dose assessments may be performed pre-dose Day 1/Day 10 or on Day -1/Day 9.
8. Clinical chemistry, haematology, coagulation, urinalysis (dip-stick), see Section 11.3.6.
9. Clinical chemistry only on Day 2 and Day 6. Approximately 8 h post-dose on Day 2 and pre-dose on Day 6. No clinical laboratory sampling on Day 4, 5, 7 and 8.
10. Blood pressure and pulse, see Section 11.3.3.
11. For timing of assessments, refer to Table 8.1-4.
12. Once daily administration of IMP. On Day 1 and Day 10, administration under fasting conditions, i.e. fasting for 10 h before IMP administration until 4 h post administration. On Days 2 to 9, administration prior to breakfast at the same time each morning (±1 h).
13. Includes sampling for future exploratory analyses of potential GS-248 metabolites.
14. Pre-dose PK samples on Day 8, 9 and 10 must be taken within 5 minutes before dose.
15. Future exploratory analyses of biomarkers e.g. inflammatory biomarkers.
16. Urine for analysis of AA metabolites and for future analysis of GS-248 metabolites and biomarkers will be collected at the following intervals: 0 to 6 h, 6 to 12 h and 12-24 h post administration of study drug on Day 1 and Day 10. In addition, baseline urine is collected -24 h to -12 h and -12 h to 0 h prior to the first IMP administration on Day -1/Day 1.
17. Breakfast, lunch, snack, dinner and evening snack. Standardised meals during 24 h after dose on Day 1 and Day 10. For timing of meals, refer to Table 8.1-4. No breakfast on Day 1 and Day 10. Breakfast only on Day 3 and Day 12.
18. From administration of IMP.

Table 8.1-4 Detailed schedule of events for Visit 2 and Visit 8, Part II (MAD)

	Day -1	Day 9	Day 1/Day 10											Day 2/Day 11		Day 3/ Day 12
Assessment/time-point	**Admission**		**Pre-dose**	**0**	**0.25h**	**0.5h**	**1h**	**2h**	**4h**	**6h**	**8h**	**12h**	**16h**	**24h**	**36h**	**48 h**
Inclusion/exclusion criteria			X[1]													
Pregnancy test (WOCBP)	X	X														
Urine drug screen	X	X														
Alcohol breath test	X	X														
Physical examination			X[1,2]													X[3]
Clinical laboratory profile	X	X												X[5]		X
Vital signs[6]	X	X	X				X	X	X	X	X	X		X	X	X
Body temperature			X[4]													
12-lead ECG			X[4]					X			X			X[7]		X
Randomisation			X[8]													
IMP administration		X		X										X[9]		X[9]
PK blood sampling		X[11]	X[10,11]		X	X	X	X	X	X	X	X	X	X[12]		X[13]
Blood sampling for GS-248 MIST[14]			X[11]		X	X	X	X	X	X	X	X	X	X[12]		
Blood sampling for WBA			X[10]					X			X			X		
Blood sampling for ADMA analysis			X[10]					X			X			X		
Blood sampling for future biomarker analyses			X[10]					X			X			X		
Urine collection[15]	X			X							X			X		
Breakfast[16]		X												X		X
Meals	X[17]	X[17,]							X[17,18]					X[17]		X[17]
Baseline symptoms	X		X													
AEs and SAEs				X												
Prior and concomitant medications	X															

1. Day -1 or pre-dose Day 1 prior to randomisation. Not Day 10.
2. Short version of physical examination.
3. Physical examination Day 12, not Day 3.
4. Day -1/Day 9 or pre-dose Day 1/Day 10
5. Day 2; clinical chemistry only. Approximately 8 h post-dose. Not Day 11.
6. Day 1 at time points indicated, Day 2, Day 3 and Day 10 (approximately 2 h post-dose only) and Day 12 prior to departure. Not Day 11.
7. ECG on Day 2, not Day 11.
8. Randomisation on Day 1.
9. IMP administration on Day 2 and Day 3, not Day 11 or Day 12.
10. Pre-dose sample on Day 1 should be taken within 60 minutes prior to dose.
11. Pre-dose samples on Day 8, 9 and 10 must be taken within 5 minutes before dose.
12. The 24 h PK sample is taken pre-dose Day 2 or 24 h post last dose on Day 11 within 10 minutes of the of the nominal time for the dosage interval. For details regarding time windows for PK sampling on Days 2, 8, 9 and 10, refer to Section 11.4.1.
13. 48 h after last dose on Day 12. Not Day 3.
14. Day 1 and Day 10 during 24 h in association with PK sampling. Includes sampling for future exploratory analyses of potential GS-248 metabolites.
15. Urine for analysis of AA metabolites and for future analysis of GS-248 metabolites and biomarkers will be collected at the following intervals: 0 to 6 h, 6 to 12 h and 12-24 h post administration of study drug on Day 1 and Day 10. In addition, baseline urine is collected -24 h to -12 h and -12 h to 0 h prior to the first IMP administration on Day -1/Day 1.
16. Fasting on Day 1 and Day 10. Non-standardised breakfast on Day 2, Day 3, Day 9, Day 11 and Day 12 after PK blood sampling.
17. Standardised lunch, snack, dinner and evening snack at approximately 4, 7 and 9 and 11 h post breakfast. Breakfast only on Day 3 and Day 12.
18. Standardised lunch at least 4 h post-dose.

8.1.3 *Part III: Patients with Systemic Sclerosis and Raynaud's Phenomenon*

Part III of the study will explore multiple dosing of GS-248 in SSc patients with Raynaud's Phenomenon. The dose will be based on emerging knowledge of safety, tolerability and PK of GS-248 observed in the preceding SAD and MAD parts of the study (Part I and II).

GS-248 is planned to be administered once daily for 10 days. The dose level in part III will be selected such that the predicted maximum exposure will not exceed the maximum exposure (based on AUC and C_{max}) in previously evaluated cohorts in healthy volunteers (Part I and Part II). The dose and time points and visits for PK sampling may be adjusted based on PK evaluation in the SAD and MAD parts.

Ten SSc patients will be included in Part III of the study. The patients will be randomised in a 4:1 ratio to receive GS-248 (n=8) or placebo (n=2) in a blinded fashion. One additional cohort may be added as needed to e.g. repeat the dose or to test additional doses or dosing schemes.

Patients will come for 9 visits to the clinic. Screening (Visit 1) will take place from Day -42 to Day -2 (for details on assessments, refer to Table 8.1-5). At Visit 2, patients will be admitted to the clinic in the morning of Day -1 for pre-dose assessments including a 24 h baseline urine collection and will remain at the clinic until Day 3 for IMP administration and safety, PK and exploratory PD assessments (Table 8.1-5 and Table 8.1-6). Up to 2 subjects will be dosed on the same day. The patients will be carefully monitored by clinical staff during and after dosing. Vital signs and ECG will be checked at regular intervals as detailed in Table 8.1-5. There is access to equipment, qualified staff and an ICU in case of an acute emergency.

Outpatient visits for IMP administration, safety and PK assessments are planned for Day 4 to Day 8 (Visit 3 to Visit 7), see Table 8.1-5 and Table 8.1-6. On Day 9 (Visit 8), patients will come to the unit in the morning for IMP administration and PK sampling and will return again in the evening for admission. For practical reasons, and if preferred by the patient, he or she may remain at the clinic during the whole Day 9. Subjects will be residential at the clinic between Day 9 and Day 12 (Visit 8) for IMP administration, safety, PK and exploratory PD assessments. The last dosing day is Day 10. Urine collection for exploratory PD analysis will be performed during 24 h after the last dose. A final end-of-study visit (Visit 9) is planned to take place on Day 19 (±2 days) or after early withdrawal.

Each patient is expected to participate in the study for approximately 61 days including a 41-day screening period.

The schedule of events for Part III is shown in Table 8.1-5 and is detailed for Visit 2 and Visit 9 in Table 8.1-6. Study assessments are described in Section 11.

Safety assessments include: AE reporting, 12-lead ECG monitoring, vital signs (blood pressure and pulse), body temperature, physical examination, use of concomitant medications and blood sampling for haematology, clinical chemistry and coagulation parameters, see Section 11.3.

PK assessments include: blood sampling for bioanalysis and subsequent determination of PK parameters, see Section 11.4.

Exploratory assessments include: blood sampling for analysis of mPGES-1 activity (PGE_2 levels) in an *ex vivo* WBA, blood and urine sampling for analysis of ADMA in plasma and AA metabolites in urine, and blood and urine sampling for future exploratory biomarker analyses, see Section 11.5.

Table 8.1-5 Schedule of events Part III (SSc patients)

	Screening	Residential period				Daily visits	Residential period				End-of-study
Visit	**Visit 1**	**Visit 2[2]**				**Visit 3 to 7**	**Visit 8[2]**				**Visit 9**
Assessment/time point	Day -42 to Day -2	Admission Day -1	Day 1	Day 2	Day 3	Day 4 to 8	Admission Day 9	Day 10	Day 11	Day 12	Day 19 (±2 days)
Informed Consent	X										
Inclusion/exclusion criteria	X		X[3]								
Weight/height	X										X[4]
Medical/surgical history	X										
Demographics	X										
HIV, hepatitis B and C	X										
Alcohol breath test	X	X					X				X
Pregnancy Test (WOCBP)[5]	X	X					X				X
Physical Examination	X		X[6, 7]							X[6]	X
Clinical Laboratory Profile[8]	X	X		X[9]	X	X[9]	X			X	X
Vital signs[10]	X	X	X[11]	X[11]	X		X	X[11]	X[11]	X	X
Body temperature			X[7]					X[7]			
12-lead ECG	X		X[7, 11]	X	X			X[7, 11]		X	X
Randomisation			X								
IMP administration[12]			X	X	X	X	X	X			
PK blood sampling			X[11]	X[11]		X[13]	X[11, 13]	X[11, 13]	X	X	
Blood sampling for WBA			X[11]	X[11]				X[11]	X[11]		
Blood sampling for ADMA analysis			X[11]	X[11]				X[11]	X[11]		
Blood sampling for future biomarker analyses[14]			X[11]	X[11]				X[11]	X[11]		
Urine collection		X[15]						X[15]			
Raynaud's questioning									X		
Meals[16]		X	X	X	X		X	X	X	X	

	Screening	Residential period				Daily visits	Residential period				End-of-study
Visit	**Visit 1**	**Visit 2[2]**				**Visit 3 to 7**	**Visit 8[2]**				**Visit 9**
Assessment/time point	Day -42 to Day -2	Admission Day -1	Day 1	Day 2	Day 3	Day 4 to 8	Admission Day 9	Day 10	Day 11	Day 12	Day 19 (±2 days)
Baseline symptoms	X	X									
AEs			X[17]								
SAEs	X										
Prior and concomitant medications	X										

1. The screening visits may be conducted as a single visit.
2. Details in separate flow chart (Table 8.1-6). The duration of the residential period may be amended following review of data from earlier cohorts.
3. Confirmation of eligibility prior to randomisation. Day -1 or Day 1.
4. Weight only.
5. Screening: plasma/serum tests, other visits: urine test.
6. Short version of physical examination on Day 1 and Day 12.
7. Pre-dose assessments may be performed pre-dose Day 1/Day 10 or on Day -1/Day 9.
8. Clinical chemistry, haematology, coagulation, urinalysis (dip-stick), see Section 11.3.6.
9. Clinical chemistry only on Day 2 and Day 6. Approximately 8 h post-dose on Day 2 and pre-dose on Day 6. No clinical laboratory sampling on Day 4, 5, 7 and 8.
10. Blood pressure and pulse, see Section 11.3.3.
11. For timing of assessments, refer to Table 8.1-6.
12. Once daily administration of IMP. On Day 1 and Day 10, administration under fasting conditions, i.e. fasting for 10 h before IMP administration until 4 h post administration. On Day 2 to Day 9, administration prior to breakfast at the same time each morning (±1 h).
13. Pre-dose PK samples on Day 8, 9 and 10 must be taken within 5 minutes before dose.
14. Future exploratory analyses of biomarkers e.g. further AA metabolite profiling and inflammatory biomarkers.
15. Urine for analysis of AA metabolites and for future analysis of biomarkers will be collected at the following intervals: 0 to 6 h, 6 to 12 h and 12-24 h post administration of study drug on Day 1 and Day 10. In addition, baseline urine is collected -24 h to -12 h and -12 h to 0 h prior to the first IMP administration on Day -1/Day 1.
16. Standardised breakfast, lunch, snack, dinner and evening snack. For timing of meals, refer to Table 8.1-6. No breakfast on Day 1 and Day 10. Breakfast only on Day 3 and 12.
17. From administration of IMP.

Table 8.1-6 Detailed schedule of events for Visit 2 and Visit 8, Part III (SSc patients)

	Day -1	Day 9	Day 1/Day 10											Day 2/ Day 11		Day 3/ Day 12
Assessment/time-point	**Admission**		**Pre-dose**	**0**	**0.25h**	**0.5h**	**1h**	**2h**	**4h**	**6h**	**8h**	**12h**	**16h**	**24h**	**36h**	**48h**
Inclusion/exclusion criteria			X[1]													
Pregnancy test (WOCBP)	X	X														
Alcohol breath test	X	X														
Physical examination			X[1,2]													X[3]
Clinical laboratory profile	X	X												X[5]		X
Vital signs[6]	X	X	X				X	X	X	X	X	X		X	X	X
Body temperature			X[4]													
12-lead ECG			X[4]					X			X			X[7]		X
Randomisation			X[8]													
IMP administration		X		X										X[9]		X[9]
PK blood sampling		X[11]	X[10, 11]		X	X	X	X	X	X	X	X	X	X[12]		X[13]
Blood sampling for WBA			X[10]					X			X			X		
Blood sampling for ADMA analysis			X[10]					X			X			X		
Blood sampling for future biomarker analyses			X[10]					X			X			X		
Urine collection[14]	X		X								X		X			
Raynaud's questioning														X[15]		
Breakfast[16]		X												X		X
Meals[17]	X[17]	X[17]							X[17,18]					X[17]		X[17]
Baseline symptoms	X		X													
AEs		X		X												
SAEs	X															
Prior and concomitant medications	X															

1. Day -1 or pre-dose Day 1 before randomisation. Not Day 10.
2. Short version of physical examination.
3. Physical examination on Day 12, not Day 3.
4. Day -1/Day 9 or pre-dose Day 1/Day 10
5. Day 2; clinical chemistry only. Approximately 8 h post-dose. Not Day 11.
6. Day 1 at time points indicated, Day 2, Day 3 and Day 10 (approximately 2 h post-dose only) and Day 12 prior to departure. Not Day 11.
7. ECG on Day 2, not Day 11.
8. Randomisation on Day 1.
9. IMP administration on Day 2 and Day 3, not Day 11 or Day 12.
10. Pre-dose sample on Day 1 should be taken within 60 minutes prior to dose.
11. Pre-dose PK samples on Day 8, 9 and 10 must be taken within 5 minutes before dose.
12. The 24 h sample is taken pre-dose Day 2 or 24 h post last dose on Day 11 within 10 minutes of the of the nominal time for the dosage interval. For details regarding time windows for PK sampling on Days 2, 8, 9 and 10, refer to Section 11.4.1.
13. 48 h after last dose on Day 12. Not Day 3.
14. Urine for analysis of AA metabolites and for future analysis of biomarkers will be collected at the following intervals: 0 to 6 h, 6 to 12 h and 12-24 h post administration of study drug on Day 1 and Day 10. In addition, baseline urine is collected -24 h to -12 h and -12 h to 0 h prior to the first IMP administration on Day -1/Day 1.
15. Day 11, not Day 2.
16. Fasting on Day 1 and Day 10. Standardised breakfast on Day 2, Day 3 and Day 9 after PK blood sampling.
17. Standardised lunch, snack, dinner and evening snack at approximately 4, 7 and 9 and 11 h post breakfast. Breakfast only on Day 3 and Day 12.
18. Standardised lunch at least 4 h post-dose.

8.1.4 *Part IV: Celecoxib – open cohort with healthy volunteers*

In Part IV of the study, 200 mg celecoxib will be administered to 8 healthy volunteers twice daily for 10 days (i.e. 400 mg/day for 10 days).

Subjects will come for 5 visits to the clinic. Screening (Visit 1) will take place from Day -28 to Day -2. For details on assessments, refer to Table 8.1-7. At Visit 2, subjects will be admitted to the clinic in the morning of Day -1 for pre-dose assessments including a 24 h baseline urine collection and will remain at the clinic until Day 2 for IMP administration and PD assessments (Table 8.1-7). Subjects will be discharged from the clinic after the morning dose on Day 2.

From the evening of Day 2 to the evening of Day 8, subjects will self-administer celecoxib at home twice daily (morning and evening) and register each administration in an electronic diary (ViedocMe). Any reactions or use of concomitant medication will also be registered in ViedocMe. On Day 5 (Visit 3), the subjects will be contacted by phone for a drug accountability and AE check-up.

Subjects will again be residential at the clinic between Day 9 and Day 11 (Visit 4) for IMP administration and exploratory PD assessments. The last dosing day is Day 10. Urine collection for exploratory PD analysis will be performed during 24 h after the last morning dose on Day 10. A final end-of-study visit (Visit 5) will take place on Day 19 (±2 days) or after early withdrawal.

Each subject is expected to participate in the study for approximately 47 days including a 27-day screening period.

The schedule of events for Part IV is shown in Table 8.1-7.

Study assessments are described in Section 11.

Safety assessments include: AE reporting and use of concomitant medications, see Section 11.3.

Exploratory assessments include: blood sampling for analysis of mPGES-1 activity (PGE_2 levels) in an *ex vivo* WBA, blood and urine sampling for analysis of ADMA in plasma and AA metabolites in urine, and blood and urine sampling for future exploratory biomarker analysis, see Section 11.5.

Table 8.1-7 Part IV Schedule of events, celecoxib

	Screening	Residential			At home	Telephone call	At home	Residential			End-of-study
Visit	**Visit 1**	**Visit 2**				**Visit 3**		**Visit 4**			**Visit 5**
Assessment	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3 & 4**	**Day 5**	**Day 6, 7 & 8**	**Day 9**	**Day 10**	**Day 11**	**Day 19 (±2 days)**
Informed Consent	X										
Inclusion/exclusion criteria	X		X[1]								
Weight/height/BMI	X										X[2]
Medical/surgical history	X										
Demographics	X										
HIV, hepatitis B and C	X										
Urine Drug Screen[3]	X	X						X			X
Alcohol breath test	X	X						X			X
Pregnancy Test[4]	X	X						X			X
Physical Examination	X										X
Clinical Laboratory Profile[5]	X										X
Vital signs	X										X
12-lead paper ECG	X										X
Celecoxib administration BID[6]			X	X	X	X	X	X	X		
Blood sampling for WBA[7]			X	X					X	X	
Blood sampling for ADMA analysis[7]			X	X					X	X	
Blood sampling for future biomarker analyses[7]			X	X					X	X	
Urine collection[8]		X	X	X					X	X	
Meals[9]		X	X	X				X	X	X	
Baseline symptoms	X	X									
AEs and SAEs[10]			X								
Prior and concomitant medications	X										

1. Confirmation of eligibility prior to randomisation. Day -1 or Day 1.
2. Weight only.
3. Random drug screening test may also be performed at the discretion of the investigator.
4. WOCBP only. Screening: plasma/serum tests, other visits: urine test.
5. Clinical chemistry, haematology, coagulation, urinalysis (dip-stick), see Section 11.3.6.
6. To be taken each morning and evening at the same time (±1 h). Self-administration at home from the evening of Day 2 to the evening of Day 8.
7. Blood samples for WBA, ADMA and future biomarker analyses are drawn 0 h (within 60 min pre-dose) and 2 h, 8 h and 24 h post administration of celecoxib on Day 1 and Day 10 (24 h samples taken pre-dose on Day 2 and 24 h post last dose on Day 11, respectively).
8. Urine for PD analysis will be collected at the following intervals: 0 to 6 h, 6 to 12 h and 12-24 h post administration of celecoxib on Day 1 and Day 10. In addition, baseline urine is collected -24 h to -12 h and -12 h to 0 h prior to the first celecoxib administration on Day -1/Day 1.
9. Breakfast, lunch, snack, dinner and evening snack. Breakfast only on Day 2 and 11.
10. From administration of IMP.

8.2 Rationale for study design

The design of the study is based on the aim to study safety, tolerability, PK and PD of selected doses of GS-248 in a limited number of healthy volunteers and patients. The design is adaptive, to allow for flexible dose escalation and involves careful monitoring of the subjects' well-being. The time points for PK blood sampling have been selected based on data obtained from pre-clinical studies but may be changed based on emerging data. Time points for PD sampling (blood and urine) is based on previous experience with selective inhibition of the mPGES-1 in a human Phase I study [15] and on predicted human PK.

A placebo control will be used in Parts I, II and III to establish the frequency and magnitude of changes in endpoints that may occur in the absence of active treatment.

Randomisation will be used in Part I, II and III to minimise bias in the assignment of subjects to dose groups and to increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) are evenly balanced across treatment groups.

Blinded treatment will be used in Part I, II and III to reduce potential bias during data collection and evaluation of endpoints.

Part IV will be non-placebo controlled, non-randomised and open. The purpose of Part IV is to collect PD data for comparison with GS-248.

Overall, the study will provide important data to support the design of further studies, both in healthy volunteers and in patients.

8.3 Selection of starting dose and rationale for planned dose escalation

8.3.1 *Selection of starting dose in the SAD part*

A single oral dose of 1 mg is proposed for the first cohort, since it is estimated that this will yield a pharmacological response close to the Minimum Anticipated Biological Effect Level (MABEL), which corresponds to 20% of the maximum attainable area under the effect (AUE; i.e. inhibition) curve 0-24 h as described in the IB.

In assessment of the pharmacological response in terms of mPGES-1 inhibition, one must consider both the duration and the magnitude of such inhibition, i.e. the AUE. In view of a target human dosing interval of at most 24 h and the projected PK of GS-248, it appears reasonable to apply the AUE from 0 to 24 h [$AUE_{(0-24)}$] as a function of dose in order to define MABEL. In this context, 20% of maximum attainable $AUE_{(0-24)}$ is chosen to constitute MABEL, and is projected to be achieved by a single oral dose of GS-248 between 0.9 and 1.7 mg, based on allometric scaling from dog and cynomolgus monkey, respectively.

The NOAEL in the 28-day dog toxicity study was set at 20 mg/kg, with mean C_{max} and $AUC_{0-24\ h}$ values at this dose level of 2500 nmol/L and 23000 h*nmol/L (in males and females combined), respectively. These values set the maximum limits for exposure in humans in this Phase I study.

The predicted exposure at the chosen starting dose in the SAD phase results in exposure margins for C_{max} and $AUC_{0-24\ h}$ of 250- and 290-fold, respectively, compared to the exposure at the lowest dose level in the dog study, and 450- and 740-fold, respectively, compared to the

exposure at the NOAEL (Table 8.3-1). All these margins are considered to constitute good safety margins between animals and man. However, it should be realised that the human exposure values used in these calculations are, of necessity, only estimated values.

Table 8.3-1 Exposure margins for mean C_{max} and AUC_{last} values between GS-248-treated animals in the pivotal 28-day toxicity studies and the predicted values in humans in the SAD

Species	Study No.	Dose level (mg/kg animals) (mg humans)	Duration (days)	Sex	C_{max} (nmol/L)	AUC[a] (h*nmol/L)	Exposure margin animals:man[e] (X-fold) C_{max}	Exposure margin animals:man[e] (X-fold) AUC[a]
Rats	36325	150/400/1000 (< NOAEL)	28	F[b]	ca. 2100[c]	ca. 30000[c]	-	-
Dogs	36327	5	28	M+F	1400	9000	-	-
		20 NOAEL	28	M+F	2500	23000	-	-
Humans	Predicted	1 Starting dose SAD[d]	1	-	4.6-5.6	19-31	250[f]	290[f]
							450[g]	740[g]

NOAEL = No observed adverse effect level
a $AUC_{0\text{-}24\ h}$ in rats and dogs; $AUC_{0\text{-}\infty}$ in humans
b Exposure was clearly higher in female rats than in males. Therefore, values in females only are included exposure
c Exposure was equivalent at all 3 dose levels in rats. Therefore, approximate mean values from all females combined are given
d See above in Section 8.3.1 for the rationale for the starting dose in the SAD phase of the study
e All exposure margins are calculated against the highest predicted exposure values in man
f Exposure margins based on the lowest dose level in the 28-day dog study
g Exposure margins based on NOAEL (the intermediate dose level) in the 28-day dog study

Additionally, an approximate comparison of the given doses in the preclinical repeat-dose studies expressed as mg/m^2 body surface area can be used to supplement comparison based on kinetic data. The mg/kg doses are converted to mg/m^2 body surface area by multiplying by a factor 20 for dogs and 37 for a 60 kg human in terms of Human Equivalent Dose (HED), as per FDA guideline on estimation of maximum safe starting dose in initial clinical trials [17].

This gives 0.62 mg/m^2 for the starting dose in the SAD part (1 mg) 100 mg/m^2 for the lowest dose level (5 mg/kg) and 400 mg/m^2 for NOAEL (20 mg/kg) in the 28-day dog study, with dose margins of 160- and 650-fold, respectively.

In view of the sizable margin against NOAEL in the 28-day dog study in terms of predicted human $AUC_{(0\text{-}inf)}$ (740-fold) and also in terms of HED (650-fold), together with the fact that the target, mPGES-1, has previously been subject to pharmacological intervention in clinical trials with no reported overt target-related side-effects [15] it was deemed reasonable not to apply any additional margins against MABEL in the first cohort. Furthermore, mPGES-1 -/- mice are viable and fertile and develop normally compared with wild-type controls [18],

hence have no specific phenotype under normal conditions, while being protected in various inflammatory disease models [14].

8.3.2 *Rationale for dose escalation in the SAD part*

The desired pharmacological effect of GS-248 in humans includes i) blocking the production of PGE_2 via mPGES-1, and ii) increased production of the vasodilatory and platelet-inhibitory PGI_2 via substrate shunting. The latter aspect calls for a pronounced level of inhibition of mPGES-1 over 24 h, to optimise for the desired shunting effect and intravascular PGI_2 synthesis.

A PK/exposure-driven dose escalation strategy will be applied such that the first cohort is expected to yield a systemic exposure corresponding to MABEL and the last cohort will achieve exposures close to the maximum exposure limits, as established by the 28-day dog toxicity study, unless safety or tolerability has previously limited escalation. The escalation steps will be smaller when the maximum exposure limits are approached.

Pharmacokinetics will be evaluated following each cohort and the escalation scheme can be modified based on the totality of acquired PK, safety and tolerability data. In case of sings of unpredictable PK (i.e. highly variable or non-linear PK) escalation steps will be decreased. In case the systemic exposure following the first cohort is appreciably smaller than predicted or below the lower limit of quantification (LLOQ), multiple maximum 8-fold dose escalations will be allowed until the exposure is within the predicted range of the study. If the systemic exposure following the first cohort is appreciably larger than projected, escalation steps will be decreased or, in case of limiting safety or tolerability, de-escalation may be performed. The decision on dose selection will be made by the iSRC, which will have access to all safety, tolerability and PK data (8.3.8).

A tentative dose escalation scheme based on target systemic exposures is shown in Table 8.3-2 where the first and last cohorts are determined by MABEL and maximum exposure limits, and the mid-range of maximum attainable $AUE_{(0\text{-}24)}$ is expected to be achieved between cohort 2 and 3.

Table 8.3-2 Tentative dose escalation schedule SAD

Cohort:	**1**	**2**	**3**	**4**	**5**	**6**	**(7)**
Tentative dose (mg)	**1**	5	25	75	225	450	≤ 800
Predicted $AUC_{0\text{-}inf}$	19-31	97-150	480 – 770	1500 – 2300	4400 – 6900	8700 – 14000	16000-25000

For details on the prerequisites for the transition from single to multiple dosing, refer to Section 8.3.5.

8.3.3 *Selection of starting dose and dose escalation in the MAD part*

The starting dose in the MAD part of the study will be selected with the aim to achieve an exposure similar to that observed in the third cohort in the SAD part, and is tentatively set to 25 mg. The doses in the second and third MAD cohorts will be selected to achieve an

escalation of exposure of approximately 3 times of what was observed in the previous cohort. The dose in the fourth (and potential fifth) MAD cohort will be selected to achieve an exposure twice of what was observed in the previous cohort. Tentative doses are displayed in Table 8.3-3.

Table 8.3-3 Tentative dose escalation schedule MAD

Cohort:	1	2	3	4
Maximum exposure escalation steps		3x	3x	2x
Tentative doses (mg)	25[1]	75	225	450[2]

1. Aimed to achieve an exposure similar to that in the third cohort of the SAD part.
2. Projected exposure not exceeding what was achieved by the study maximum dose given in the SAD part in terms of $AUC_{0-\infty}$.

If the systemic exposure following any of the first 3 cohorts is appreciably larger than projected, escalation steps will be decreased. In case of limiting safety or tolerability, de-escalation may be performed. The decision on dose selection will be made by the iSRC, which will have access to all safety, tolerability and PK data as outlined in Section 8.3.8.

PK information from the SAD part will give the terminal $T_{½}$ of the drug, which in turn, will indicate potential accumulation of GS-248. The dose, or dosing interval, will be adjusted accordingly if such is identified. If safety and tolerability allows, the aim is to, in the last MAD cohort, reach a maximum exposure in terms of AUC_{0-tau} not exceeding what was achieved by the study maximum dose given in the SAD part in terms of $AUC_{0-\infty}$.

8.3.4 *Maximum exposure and dose*

The maximum dose to be given is 800 mg/day. The maximum exposure in the study may not exceed 2500 nmol/L or 23 000 h*nmol/L in terms of C_{max} and AUC, respectively, based on C_{max} and AUC_{0-24} at the dog NOAEL (males and females combined).

8.3.5 *From single to multiple dosing*

Following completion of cohort 4 of Part I (SAD), the iSRC will evaluate all available safety, tolerability and PK data up until and including at least 48 h data from SAD cohort 4 and, if necessary, suggest adjustments to dose levels, dosing regimens or dosing duration in a written recommendation to the Sponsor. If no safety or tolerability concerns are identified, and provided that the PK of GS-248 is linear, cohort 1 of Part II (MAD) will be initiated approximately in parallel with cohort 5 of Part I (SAD) as decided by the Sponsor. The predicted exposure in the MAD will not exceed the maximum exposure (based on AUC and C_{max}) in any previously evaluated SAD cohort. The iSRC recommendation, as well as Sponsor's decision, will be documented in a non-substantial amendment to the clinical study protocol (CSP).

8.3.6 *From healthy volunteers to patients*

Prior to start of Part III (SSc patients), a substantial amendment containing a summary of blinded Part I and Part II safety, tolerability and PK data (all cohorts), the intended Part III dose, a dose rationale, the dosing duration and a request to start Part III, will be submitted to

the competent authority (CA) and an independent ethics committee (IEC). In case the systemic exposure of GS-248 is considered sufficiently high already after 3 MAD cohorts, or if indicated by safety and tolerability data, the fourth (and fifth) cohort(s) will not be conducted and the substantial amendment prior to start of Part III will be submitted following completion of the third MAD cohort. Part III will not start until after approval from the CA and IEC.

8.3.7 *Stopping criteria for dose escalation*

The iSRC (including the Principal Investigator; Section 8.3.8) will follow the recommendations and grading system of Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [19] see Section 11.3.1.7 but also take into account the recommendations published by Sibille *et al.* 2010 [20] which is an adaptation to FIH studies of the grading systems previously proposed by National Cancer Institute (NCI) [19], World Health Organization (WHO) [21], National Institute of Health (NIH) [22] and the FDA [23]. The grade, the frequency of AEs and the blindness will be considered.

A rolling review of emerging safety data will be performed throughout the study taking into account any AEs (in particular moderate AEs assessed as at least possibly related to the IMP administration), the number of subjects in whom they occur, concurrency of more than one event within the same subject and any trends. Changes from baseline measurements will also be considered and not just absolute cut-off based on upper- or lower limits of normal that might apply for healthy volunteers.

Trends or safety signals described above, which are not necessarily covered by the stopping criteria in Table 8.3-4 may warrant the scheduling of ad hoc iSRC meetings after which the iSRC will make recommendations to sponsor on e.g. whether to terminate the study or to stop dosing in individual subjects or a certain cohort.

Additional study specific withdrawal criteria are summarised in Section 9.7.

Table 8.3-4 Dose escalation and stopping rules, Part I and Part II

Stop criterion	Action taken
At individual and dose group level	
If no subject has an SAE considered at least possibly related to the IMP administration, i.e. a serious adverse drug reaction (SADR)	Escalate to the next higher dose level.
If 1 subject on active treatment has an SAE assessed as at least possibly related to IMP administration	1. Stop dosing of subject with a potential SADR. Withdrawal of subject. 2. Unblinding of subject with potential SADR. Only voting members of the iSRC will be unblinded. 3. Evaluation by iSRC. The iSRC makes recommendation to Sponsor. 4. Sponsor decides how to proceed: Subject met stop criterion: stop further dosing at this dose level for all subjects. Sponsor decides if the study will be terminated or if dosing will commence at a lower dose level or at an intermediate dose level.
If 2 subjects on active treatment have severe, non-serious AEs assessed at least possibly related to the IMP administration (independent of within or not within the same System organ class [SOC])	1. Stop dosing of subjects with severe, non-serious potential ADRs. 2. Unblinding of the subjects with potential ADRs. Only voting members of the iSRC will be unblinded. 3. Evaluation by iSRC. The iSRC makes recommendation to Sponsor. 4. Sponsor decides how to proceed: Both subjects meet stop criterion: stop further dosing at this dose level for all subjects. Sponsor decides if the study will be terminated or if dosing should commence at a lower dose level or at an intermediate dose level.
If 1 subject has an $AUC_{0-\infty}$ (single dose) or AUC_{0-tau} (repeated dose) higher than 23 000 h*nmol/L (corresponding to the NOAEL in male and female dogs)[1]	1. Evaluation by iSRC. The iSRC makes recommendation to Sponsor. 2. Sponsor decides if the study will be terminated or if dosing in the next cohort should commence at a lower dose level or at an intermediate dose level.
If 1 subject has a C_{max} higher than 2500 nmol/L (corresponding to the NOAEL in male and female dogs) [1]	1. Evaluation by iSRC. The iSRC makes recommendation to Sponsor 2. Sponsor decides if dosing in the next cohort should commence at a lower dose level or at an intermediate dose level.
Final dosing stop and termination of study	
If 2 subjects on active treatment in different cohorts have SAEs assessed as at least possibly related to IMP administration	1. Stop dosing of subjects with potential SADR. Withdrawal of subjects. 2. Unblinding of subjects with potential SADRs. Only voting members of the iSRC will be unblinded. 3. Evaluation by iSRC. The iSRC makes recommendation to Sponsor. 4. Subjects meet stop criterion: Termination of study.

1. When reviewing emerging data in relation to this criterion, the maximum exposure observed in individual subjects within a cohort rather than the mean exposure should be taken into account

8.3.8 *Internal safety review committee*

Before initiating a new cohort, all subjects in the previous cohort must have been treated and safety, tolerability and PK data (at least 48 h data in Part I [SAD] and data up until and including 24 h post last dose in Part II [MAD]) for all treated subjects must have been evaluated by the iSRC.

If GS-248 is considered safe and tolerable, a written recommendation on the next dose level based on the predicted exposure will be provided to the Sponsor. Likewise, the iSRC will recommend dose levels for Part II and III, respectively, based on review of data from earlier cohorts/study parts.

Details regarding timing of iSRC review and the data to be reviewed will be provided in a separate iSRC charter. Based on emerging safety and PK information, the amount of safety and PK data to be reviewed after a completed cohort might be adjusted.

The voting members of the iSRC will consist of the Principal Investigator and the Sponsor's medically responsible person or delegate. In addition, the study clinical research manager (CRM), the study pharmacokineticist, additional Sponsor representatives and further internal or external experts will be invited and consulted as appropriate.

An adaptive dosing strategy will be applied to allow for a flexible and safe dose escalation. The planned dose escalation is outlined in Section 8.3.2 and Section 8.3.3. The actual doses given in each cohort will be guided by the iSRC recommendations based on available safety, tolerability and PK data. Every dose step is thus adjustable and the recommendation to the Sponsor may be to continue with a higher or lower dose than the intended dose, repeat the same dose level, continue with an intermediate dose level or to stop dosing.

The recommendation of the iSRC on the next dose level will be taken in consensus between the iSRC members and documented as appropriate. In case there is disagreement between the 2 voting members, the most conservative approach will be recommended. It is not acceptable to repeat a dose level where any of the dose escalation stopping rules have been met.

In Part I and Part II, 2 or 1 additional cohort(s), respectively, may be added as needed to test additional doses or dosing schemes, repeat the dose given in a previous cohort, to establish the target dose for Part III and subsequent studies and/or to reach steady state. In Part III, 1 additional cohort (10 patients) may be added.

The duration of the residential periods in each part may be amended following review of data from earlier cohorts. The predicted $T_{½}$ of GS-248 is between 2 and 13 h, based on allometric scaling of preclinical data. A significantly shorter $T_{½}$ than expected, as determined following analysis of PK data in the study, may warrant a shortening of the residential period provided that no safety issues are indicated. Conversely, if indicated by safety and or PK data, the duration of the residential periods may be prolonged. Should the duration of any residential period change, subsequent changes to the timing of safety and PK assessments will be done as necessary. A significantly shorter $T_{½}$ than expected may also require a change in the dosing interval, i.e. twice daily GS-248 dosing rather than once daily dosing might be required in order to reach sufficient exposure. Such changes to the CSP (Part I, II or IV with healthy volunteers) will be documented in non-substantial amendments. A substantial amendment will be submitted to both the CA and the IEC prior to start of Part III (SSc patients) of the study, see Section 8.3.6.

The treatment code may be broken by the iSRC during the assessment process (partial un-blinding) in accordance with stopping criteria described in Table 8.3-4. The medical staff and the subjects will still be blinded for the treatments (active drug or placebo) to be administered in the subsequent dose groups/cohorts in order to minimise bias. If unblinding was considered necessary, the iSRC meeting will consist of a closed part and an open part.

9 STUDY POPULATION

Prospective approval of protocol deviations to eligibility criteria, also known as protocol waivers or exemptions, is not permitted.

9.1 Recruitment

Fort Part I, II and IV, the subjects will be recruited from CTC's database of healthy volunteers and from advertising in media (including social media).

Subjects may participate in more than one part of the study provided that the eligibility criteria for each part are met.

The patients for Part III will be identified by referring rheumatologists.

9.2 Screening and enrolment log

Investigators must keep a record of all screened subjects even if they were not subsequently included in the study. This information is necessary to verify that subjects were selected without bias. The reason for screening failure should be stated for all subjects screened but not included. The reason for withdrawal should be stated for all subjects included but not completed.

A screening number will be allocated to each subject in connection to the informed consent process at the Screening visit. The screening number is generated automatically in the electronic case report Form (eCRF). The screening number will allow identification of subjects irrespective of their possible eligibility for the study.

Subjects included and randomised will be assigned a randomisation number (1101, 1102 etc. in the Part I, cohort 1; 2101, 2102 etc. in the Part II, cohort 1 and so on). The first digit will correspond to the study part, the second digit will correspond to the cohort and the 3rd and 4th digits correspond to the subject number.

If a subject/patient cannot receive the planned dose of IMP within 27 days/41 days after screening (*i.e.*, the time interval between signing informed consent until dose administration) the subject should be re-screened before proceeding in the study.

9.3 Number of subjects/patients

Part I (SAD): 48 subjects will be randomised and dosed (6 cohorts, each of 8 subjects: 6 GS-248, 2 placebo).

Part II (MAD): 32 subjects will be randomised and dosed (4 cohorts, each of 8 subjects: 6 GS-248, 2 placebo).

Part III (SSc patients): 10 SSc patients will be randomised and dosed (1 cohort with 10 subjects: 8 GS-248, 2 placebo).

Part IV (celecoxib): 8 subjects will be randomised and dosed (1 cohort with 8 subjects receiving celecoxib).

If indicated by emerging data and recommended by the iSRC, 2 additional cohorts (8+8 subjects) may be added to Part I, 1 cohorts (8 subjects) may be added to Part II and 1 cohort (10 patients) may be added to Part III. In such cases, and to account for potential drop-outs, additional subjects might be included in the study.

For replacements of subjects who discontinue from the study, see Section 9.7.5.

9.4 Eligibility criteria

9.4.1 *Inclusion criteria Part I, II and IV: SAD, MAD and celecoxib in healthy volunteers*

For inclusion in Part I, II and IV of the study, subjects must fulfil the following criteria:

1. Willing and able to give written informed consent for participation in the study.
2. Male and female healthy subjects aged 18-70 years inclusive (Part I [SAD]) and 40-75 years inclusive (Part II [MAD] and Part IV [celecoxib])
3. Women of child bearing potential (WOCBP) must practice abstinence (only allowed when this is the preferred and usual lifestyle of the subject) or must agree to use a highly effective method of contraception with a failure rate of < 1% to prevent pregnancy (combined [oestrogen and progestogen containing] hormonal contraception associated with inhibition of ovulation [oral, intravaginal, transdermal], progestogen-only hormonal contraception associated with inhibition of ovulation [oral, injectable, implantable], intrauterine device [IUD]or intrauterine hormone-releasing system [IUS]) from at least 4 weeks prior to dose to 4 weeks after last dose. Their male partner must agree to use a condom during the same time frame.

   Women of non-childbearing potential are defined as pre-menopausal females who are sterilised (tubal ligation or permanent bilateral occlusion of fallopian tubes); or post-menopausal defined as 12 months of amenorrhea (in questionable cases a blood sample with simultaneous detection of follicle stimulating hormone [FSH] 25-140 IE/L and oestradiol <183 pmol/l is confirmatory).

   Male subjects must be willing to use condom or be vasectomised or practice sexual abstinence to prevent pregnancy and drug exposure of a partner and refrain from donating sperm from the date of dosing until 3 months after dosing with the IMP. Their female partner of child-bearing potential must use contraceptive methods with a failure rate of < 1% to prevent pregnancy (see above).
4. Body mass index (BMI) ≥ 19 and ≤ 30 kg/m^2.
5. Subjects must be in good health as determined by medical history, physical examination, vital signs, 12-lead ECG and clinical laboratory assessments at the time of screening, as judged by the Investigator.

9.4.2 *Exclusion criteria Part I, II and IV: SAD, MAD and celecoxib in healthy volunteers*

Subjects must not enter the study if any of the following exclusion criteria are fulfilled:

1. Known allergy to any components of the GS-248 formulation.
2. Females who are breast feeding or plan to be pregnant.

3. Positive serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) at screening and within 24 h prior to the first administration of IMP.
4. Use of corticosteroids (inhaled and systemic), NSAIDs (including e.g. coxibs and aspirin), antacids, PPIs or any medication that changes gastric pH within 2 weeks prior to the (first) administration of IMP.
5. Regular use of any prescribed or non-prescribed medication including analgesics, herbal remedies, vitamins and minerals within 2 weeks prior to the (first) administration of IMP, except hormonal contraception and occasional intake of paracetamol (maximum 2000 mg/day; and not exceeding 3000 mg/week) and nasal decongestants without cortisone, antihistamine or anticholinergics for a maximum of 10 days, at the discretion of the Investigator.
6. Inherited or acquired disorders of platelet function, bleeding or coagulation.
7. Presence of any clinically relevant acute or chronic disease that could interfere with the subject's safety during the clinical study or expose the subject to undue risk.
8. After 10 minutes supine rest at the time of screening, any vital signs values outside the following ranges:
    - Systolic blood pressure <90 or >140 mmHg, or
    - Diastolic blood pressure <50 or >90 mmHg, or
    - Pulse <40 or >90 bpm
9. Any positive result on screening for serum hepatitis B surface antigen (HBsAg), hepatitis C virus antibodies (HCVAb) or human immunodeficiency virus (HIV) 1 and/or 2 antibodies at screening.
10. Presence or history of drug and/or alcohol abuse and/or excessive intake of alcohol and/or history, or current use, of anabolic steroids, as judged by the Investigator.
11. Any positive result for drug abuse and/or alcohol at screening or on admission to the unit prior to administration of the IMP.
12. Participation in another clinical study with an experimental drug within 3 months before the administration of IMP.
13. Consumption of grapefruit or grapefruit juice within 14 days of study drug administration.
14. Any clinically significant illness, medical/surgical procedure or trauma within 4 weeks of the first administration of IMP.
15. Malignancy within the past 5 years with the exception of in situ removal of basal cell carcinoma or resected benign colonic polyps.
16. Any planned major surgery within the duration of the study.
17. Prolonged QTcF (>450 ms), cardiac arrhythmias or any clinically significant abnormalities in the resting ECG at the time of screening, as judged by the Investigator.

18. Current smokers or users of nicotine products. Irregular use of nicotine (e.g. smoking, snuffing, chewing tobacco) less than 3 times per week is allowed before screening visit.
19. Regular excessive caffeine consumption defined by a daily intake of >5 cups of caffeine containing beverages.
20. Intake of xanthine and/or taurine containing energy drinks within 2 days prior to screening.
21. Plasma donation within one month of screening or blood donation (or corresponding blood loss) during the three months prior to screening.
22. Investigator considers the subject unlikely to comply with study procedures, restrictions and requirements.

Part IV, celecoxib only:

History of salicylate hypersensitivity or NSAID hypersensitivity or subjects who have experienced asthma, urticaria or other allergic reactions after taking aspirin or other NSAIDs.

9.4.3 *Inclusion criteria Part III: SSc patients*

1. Willing and able to give written informed consent for participation in the study.
2. Male and female SSc patients aged 40-75 years inclusive.
3. SSc disease duration less than 60 months based on the time from the first non-Raynaud phenomenon manifestation.
4. Systemic Sclerosis diagnosed according to European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) criteria [24].
5. Raynaud's Phenomenon as determined by the investigator, and with a typical frequency of attacks during the winter months of on average 5 per week (re-confirmed on admission to the study unit Day-1).
6. WOCBP must practice abstinence (only allowed when this is the preferred and usual lifestyle of the subject) or must agree to use a highly effective method of contraception with a failure rate of < 1% to prevent pregnancy (combined [oestrogen and progestogen containing] hormonal contraception associated with inhibition of ovulation [oral, intravaginal, transdermal], progestogen-only hormonal contraception associated with inhibition of ovulation [oral, injectable, implantable], IUD or IUS) from at least 4 weeks prior to dose to 4 weeks after last dose. Their male partner must agree to use a condom during the same time frame.

   Women of non-childbearing potential are defined as pre-menopausal females who are sterilised (tubal ligation or permanent bilateral occlusion of fallopian tubes); or post-menopausal defined as 12 months of amenorrhea (in questionable cases a blood sample with simultaneous detection of FSH 25-140 IE/L and oestradiol <183 pmol/l is confirmatory).

   Male subjects must be willing to use condom or be vasectomised or practice sexual abstinence to prevent pregnancy and drug exposure of a partner and refrain from donating sperm from the date of dosing until 3 months after dosing with the IMP.

Their female partner of child-bearing potential must use contraceptive methods with a failure rate of < 1% to prevent pregnancy (see above).

9.4.4 *Exclusion criteria part III: SSc patients*

1. Females who are breast feeding or plan to be pregnant.
2. Positive serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) at screening and within 24 h prior to the first administration of IMP.
3. Mixed connective tissue disease or "overlap" (i.e. those who satisfy more than one set of ACR criteria for a rheumatic disease).
4. Ongoing treatment with immunosuppressive therapies including, but not restricted to; cyclophosphamide, azathioprine, mycophenolic acid, methotrexate, or cyclosporine, or use of those medications within 4 weeks prior to first dose.
5. Use of inhaled or systemic corticosteroids within 4 weeks prior to first dose.
6. Use of iloprost within 4 weeks prior to first dose.
7. Concurrent serious medical condition which in the opinion of the investigator makes the patient inappropriate for this study such as uncontrollable Congestive heart failure, significant arrhythmia, severe pulmonary or systemic hypertension, severe gastrointestinal (GI) involvement, significant hepatic impairment, serum creatinine of greater than 2.0, active infection, severe diabetes, unstable atherosclerotic cardiovascular disease, malignancy, or severe peripheral vascular disease. Ongoing DUs are allowed at the discretion of the Investigator but must not need iloprost treatment and should not be infected.
8. Have known allergies to any components of the GS-248 formulation.
9. Use of NSAIDs (including e.g. coxibs and aspirin), antacids, PPIs or any medication that changes gastric pH within 2 weeks prior to the (first) administration of IMP.
10. Regular use of any prescribed or non-prescribed medication including analgesics, herbal remedies, vitamins and minerals within 2 weeks prior to the (first) administration of IMP, except hormonal contraception and occasional intake of paracetamol (maximum 2000 mg/day; and not exceeding 3000 mg/week) and nasal decongestants without cortisone, antihistamine or anticholinergics for a maximum of 10 days, at the discretion of the Investigator.
11. Any positive result on screening for HBsAg, HCVAb or HIV 1 and/or 2 antibodies.
12. Presence or history of drug or alcohol abuse or excessive intake of alcohol, as judged by the Investigator.
13. Any positive result for drug abuse and/or alcohol at screening or on admission to the unit prior to administration of the IMP.
14. Participation in another clinical study with an experimental drug within 3 months before the administration of IMP.
15. Consumption of grapefruit or grapefruit juice within 14 days of study drug administration.

16. Any clinically significant illness, medical/surgical procedure or trauma within 4 weeks of the first administration of IMP.
17. Malignancy within the past 5 years with the exception of in situ removal of basal cell carcinoma or resected benign colonic polyps.
18. Any planned major surgery within the duration of the study.
19. Prolonged QTcF (>450 ms), cardiac arrhythmias or any clinically significant abnormalities in the resting ECG at the time of screening, as judged by the Investigator.
20. Current smokers or users of nicotine products. Irregular use of nicotine (e.g. smoking, snuffing, chewing tobacco) less than 3 times per week is allowed before screening visit.
21. Unable or unwilling to reduce caffeine consumption to a daily intake of >5 cups of caffeine containing beverages.
22. Intake of xanthine and/or taurine containing energy drinks within 2 days prior to screening.
23. Plasma donation within one month of screening or blood donation (or corresponding blood loss) during the three months prior to screening.
24. Investigator considers the subject unlikely to comply with study procedures, restrictions and requirements.

9.5 Restrictions during the study

The subjects must be willing to comply to the below restrictions during the entire study duration *i.e.*, from screening to the end-of-study visit (or longer if specified).

9.5.1 *Restrictions all parts*

Contraception Requirements: All WOCBP must use effective contraception (defined in inclusion criterion No 3) or practice abstinence (only allowed when this is the preferred and usual lifestyle of the subject) from at least 4 weeks prior to dose until 4 weeks after last dose. Their male partners must agree to use a condom during the same time frame.

The male volunteers are expected to use condom and their female partner of child-bearing potential must use a contraceptive method with a failure rate of < 1% to prevent pregnancy (for details, refer to inclusion criterion No 3) and drug exposure of a partner and refrain from donating sperm from the date of dosing until 3 months after the last IMP administration.

Meals and Dietary Restrictions:

Part I: The IMP will be administered in the fasted state (at least 10 h of fasting) together with 240 mL of tap water.

Part II and Part III: On Day 1 and Day 10, the IMP will be administered in the fasted state (at least 10 h of fasting) together with 240 mL of tap water. On other dosing days, the IMP will be administered at the clinic just prior to breakfast.

Part IV: On Day 1 and Day 10, the morning dose will be administered in the fasted state (at least 10 h of fasting) together with 240 mL of tap water. From Day 2 (evening dose) to Day 9 (evening dose) there are no food restrictions in relation to intake of celecoxib. However, the IMP should be taken at approximately the same time (±1 h) each morning and evening.

During residential stays, standardised meals will be served on PK/PD sampling days (24 h after dose on Day 1 [Part I], Day 1 and Day 10 [Part II, III and IV]). Breakfast will be served just after dose (except on Day 1 and Day 10 of Part II, III and IV) and lunch will be served 4 h post-dose. Snack, dinner and evening snack will be served approximately 7, 9 and 11 h post-dose, respectively. Water is allowed ad libitum at the clinic except 1 h before dose and 1 h after dose on PK and PD sampling days.

For details on IMP administration in terms of food restrictions, refer to Section 10.6.

Fasting: The subjects should be fasting overnight (10 h) before Day 1 of Part I and before Day 1 and Day 10 of Part II, III and IV until 4 h post-dose.

Alcohol: Consumption of alcohol is not allowed within 48 h prior to the screening visit and all subsequent visits to the clinic including the end-of-study visit of each part. In addition, consumption of alcohol is disallowed during residential stays.

Coffee: Not more than 5 cups of coffee per day is allowed during the study from screening to end-of-study visit of each part.

Xanthine or taurine containing products/beverages: Energy drinks (e.g. Redbull) are not allowed during the study from screening until the end-of-study visit of each part.

Nicotine: Smoking or use of nicotine-containing products is not allowed during the study from screening until the end-of-study visit of each part.

Grapefruit and grapefruit containing products: Consumption of grapefruit and/or grapefruit containing products, Seville oranges is not allowed during the study from 14 days prior to IMP administration until the end-of-study visit of each part.

Blood donation: The subjects must not donate blood or plasma during the study until 3 months after the final medical examination at the end-of-study visit of each part.

Participation in other clinical studies: Study subjects are not allowed to participate in any other interventional clinical study during the study period.

Exercise: Subjects will abstain from strenuous exercise for 72 h before each blood collection for clinical laboratory tests.

9.5.2 *Restrictions Part I, II and III*

Sun protection is required in Part I, Part II and Part III from the first administration of IMP until the end-of-study visit of each part to follow the recommendations given by Centres for Disease Control and Prevention (CDC): https://www.cdc.gov/cancer/skin/basic_info/sun-safety.htm:

- Stay in the shade, especially during peak hours of 10 AM to 4 PM.
- Wear clothing that covers arms and legs
- Use a hat or cap that shades the face, head, ears and neck
- Wear sunglasses that block both ultraviolet A (UVA) and ultraviolet B (UVB) rays
- Proper use of a broad-spectrum sunscreen with a sun protection factor (SPF) of 15 or higher.
- Abstain from use of tanning beds.

9.5.3 *Prior and concomitant therapy*

9.5.3.1 Prohibited medication Part I, II and IV

Use of any prescribed or non-prescribed medication including corticosteroids (inhaled and systemic), NSAIDs (including e.g. coxibs and aspirin), antacids, PPIs or any medication that changes gastric pH, herbal remedies, vitamin supplements and minerals and other over-the counter (OTC) medicines is prohibited within 14 days of IMP administration until the end-of study visit of each part.

9.5.3.2 Prohibited medication Part III

Use of iloprost or corticosteroids (inhaled and systemic) is disallowed from 4 weeks prior to the first IMP administration until the end-of study visit as are treatment with other immunosuppressive therapies including, but not restricted to, cyclophosphamide, azathioprine, mycophenolic acid, methotrexate, or cyclosporine.

Use of any prescribed or non-prescribed medication including NSAIDs (including e.g. coxibs and aspirin), antacids, PPIs or any medication that changes gastric pH, herbal remedies, vitamin supplements and minerals and other OTC medicines is prohibited within 14 days of IMP administration until the end-of study visit of each part.

9.5.3.3 Allowed medication (all parts)

- Paracetamol in doses up to 4000 mg/day for a maximum of 3 consecutive days. If this amount of paracetamol is not sufficient for treatment of the subjects, withdrawal should be considered.
- Nasal decongestants without cortisone, antihistamine or anticholinergics for a maximum of 10 days.

Other medications considered necessary for the subject´s safety and wellbeing may be given at the discretion of the Investigator during the residential period. Following consultation with

the Sponsor, the Investigator will determine whether or not the subject should continue in the study.

9.6 Screening failures

Screening failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomised in the study. A minimal set of screening failure information is required to ensure transparent reporting of screening failure subjects. Minimal information includes documentation of signed and dated ICF and reason(s) for screening failure.

Subjects/patients who do not meet the criteria for participation in this study may be re-screened.

Re-screening can be performed once if any of the following were reasons for screening failure or non-randomisation (as judged by the Investigator):

- Practical reasons.
- No significant medical conditions (e.g. influenza, nasopharyngitis).
- Reserve subject in previous cohort.
- Plasma or blood donation outside allowed time windows.

For subjects who are re-screened, a new screening number will be assigned and a new, signed ICF will be collected.

9.7 Subject/patient withdrawal

9.7.1 *General withdrawal criteria*

Subjects/patients are free to discontinue their participation in the study at any time and for whatever reason without affecting their right to an appropriate follow-up investigation or their future care. If possible, the reason for withdrawal of consent should be documented.

Subjects/patients may be discontinued from the study at any time at the discretion of the Investigator for any of the following reasons:

- Severe non-compliance to study protocol procedures, as judged by the Investigator and/or Sponsor
- Subject/patient is lost to follow-up
- Significant AEs posing a risk for the subject/patient, as judged by the Investigator and/or Sponsor
- Withdrawal of informed consent to the use of biological samples
- Pregnancy

Meeting of an exclusion criterion during the study, which, in the opinion of the Investigator, may pose a risk for the subject/patient.

9.7.2 *QTc withdrawal criteria*

A subject meeting the criteria below will be withdrawn from the study. The same QT correction formula will be used to determine discontinuation throughout the study.

- QTcF > 500 ms
- Change from baseline (i.e. the last measurement prior to the first dose) QTc > 60 ms

Withdrawal decisions will be based on an average QTc value of triplicate ECGs. If an ECG demonstrated a prolonged QT interval, two more ECGs will be obtained over a brief period and the averaged QTc values of the three ECGs used to determine whether the subject should be discontinued from the study.

9.7.3 *Liver chemistry withdrawal criteria*

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event aetiology. Study treatment will be stopped if any of the following liver chemistry stopping criteria, defined in the FDA Guidance on Drug-Induced Liver Injury [25], is met:

- Alanine aminotransferase (ALT) 3 x Upper Limit of Normal (ULN) and total bilirubin ≥ 2xULN (>35% direct bilirubin); **or** ALT 3xULN and INR > 1.5)

  NOTE: plasma bilirubin fractionation will be performed. Bilirubin is also measured via urine dipstick (a measurement of direct bilirubin, which would suggest liver injury).

- ALT 5xULN.
- ALT 3xULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).

Subjects with ALT 3xULN **and** < 5xULN **and** bilirubin < 2xULN, who do not exhibit hepatitis symptoms or rash, will be allowed to continue study treatment as long as they are monitored weekly for four weeks.

9.7.4 *Procedures for discontinuation of a subject/patient from the study*

A subject who prematurely discontinues participation in the study will always be asked about the reason(s) for discontinuation and the presence of any AEs. If a subject withdraws consent, the investigator must ask the subject if he/she is willing, as soon as possible, to be assessed according to the procedures scheduled for the end-of-study visit in each part. Any ongoing AEs will be followed as described in Section 11.3.1.14.

The primary reason for discontinuation/early withdrawal must be specified in the eCRF and final drug accountability must be performed.

9.7.5 *Subject/patient replacement*

Part I: Based on recommendations given by the iSRC and as decided by the Sponsor, subjects who were randomised but not dosed may be replaced.

Part II, III and IV: Based on recommendations given by the iSRC and as decided by the Sponsor, subjects/patients who were randomised but not dosed may be replaced as may subjects who were prematurely withdrawn from the study for any reason except the occurrence of AEs assessed at least possibly related to the IMP.

9.8 Randomisation

Part I, II and III: On Day 1, subjects in each cohort will be randomised in a 3:1 ratio to receive either GS-248 (n=6) or placebo (n=2). The first 2 subjects in a cohort will be randomised to GS-248 (n=1) or placebo (n=1). A computer-generated randomisation list will be created using SAS Proc Plan, SAS Version 9.4. The randomisation list will contain subject number and treatment and will be kept by the randomiser in a sealed envelope until database lock. A copy of the randomisation list will be kept by an unblinded pharmacist at the site.

Sealed individual, treatment code envelopes will be kept in a locked and restricted area at the clinic in case of need for emergency unblinding

Sealed individual, treatment code envelopes will also be kept at CTC's Pharmacovigilance (CTC PV) department in a locked and restricted area.

Part IV of the study is open and non-randomised. All subjects will receive celecoxib.

9.9 Blinding

Part I, II and III of the study will be conducted in double-blind fashion and the allocation of treatments will not be disclosed until clean file has been declared and the database has been locked, see Section 16.8.

GS-248 and the placebo are identical in appearance, taste and smell.

Part IV of the study is open. All subjects will receive celecoxib.

9.10 Emergency unblinding during the study

The treatment code may only be broken by the Principal Investigator or delegate in case of emergency when knowledge of the treatment received is necessary for the proper medical management of the subject/patient. The code breaking procedure should be carefully documented.

The randomisation code may be broken by the iSRC during the assessment process (partial un-blinding) to enable their decision on continued dosing of further cohorts or to stop the dose escalation, see Section 8.3.7. The medical staff and the subjects will still be blinded for the treatments (active drug or placebo) to be administered in the subsequent cohorts in order to minimise bias (see Section 8.3.8).

For unblinding procedures in case of a potential suspected unexpected serious adverse reaction (SUSAR), refer to Section 11.3.1.13.

10 TREATMENTS

10.1 Identity of investigational medicinal products

The Drug Substance, GS-248 SU, is isolated as stable, highly crystalline hydrogen sulphate salt. It is an achiral substance with a *trans*-orientation of the 4-trifluoromethylcyclohexyl-group. The parent is a weak base with pKa 4.8 (protonation at the benzimidazole moiety) and the water solubility is low and pH-dependant.

The Drug Product to be used in the study is an oral solution where GS-248 is dissolved in an acidic vehicle at pH 3.0.

GS-248 is a low solubility compound with pH dependent solubility and therefore an aqueous, acidic solution was developed for the formulation.

Placebo has the same composition as the GS-248 solution but without the active substance and will be provided as a frozen stock solution of pH 3.

GS-248 and placebo will be used in Part I, II and III of the study.

10.2 Identity of reference product

Celecoxib will be used as a reference product in Part IV of the study. Oral capsules, 200 mg for twice daily dosing will be used. Celecoxib will be purchased from the Swedish market (Celebra, Pfizer). For details on celecoxib, refer to the product's SmPC.

10.3 Manufacturing, packaging and labelling

GS-248 and placebo are manufactured, packaged, labelled and released by RISE, Research Institutes of Sweden, Södertälje, Sweden. Labels will comply with applicable Good Manufacturing Practice (GMP) requirements [26]. The IMP (GS-248 and placebo) will be shipped to the research clinic (CTC) in brown bottles. GS-248 will be provided in 2 different strengths; 1 mg/mL and 10 mg/mL with respect to the GS-248 parent.

CTC will add a subject specific label to the bottle or syringe with dispensed IMP. CTC staff present during dispensing will thus be unblinded.

Celecoxib (Celebra, Pfizer) will be labelled by the Hospital Pharmacy, Akademiska Sjukhuset, Uppsala, Sweden. Once labelled, the Hospital Pharmacy will provide celecoxib to CTC.

10.4 Conditions for storage

GS-248 and placebo will be stored frozen at -20ºC ±5 °C in an access-controlled storage area at CTC. The GS-248 solutions are sensitive to light. Prior to dispensing, the solutions will be thawed. Details regarding thawing conditions and storage of the thawed and dispensed solution, will be specified in a separate Pharmacy manual.

Celecoxib should not be stored above 30°C.

Temperature logs will be kept for the area where the IMP is stored. The temperature should be noted on a daily basis (working days only unless automatic temperature readings are available).

10.5 Dispensing and accountability

IMP dispensing will be done by trained personnel, i.e. a site pharmacist or a registered nurse, in a dedicated room at CTC. There will be two unblinded persons working together, one person will handle the IMP and perform the dispensing according to the randomisation list and the other person will supervise the process.

Dispensing details will be specified in a separate Pharmacy manual. No dilution steps are required, for each dose level a different volume will be dispensed.

CTC and the Investigator will maintain a Storage and Accountability Log as well as a Drug Dispensing Log detailing the dates and quantities of study medication received, dispensed to and used by each subject and study medication returned or destroyed at the end of the study. Any discrepancies between dispensed and returned IMP must be explained and documented. Products deliberately and/or accidentally destroyed by the site or the subject must be accounted for.

10.6 Treatment administration

Part I (SAD): Subjects in the SAD part will be administered a single oral dose of either GS-248 or placebo as randomised.

The IMP will be administered with 240 mL of water following an overnight fast of at least 10 h. No food is allowed until 4 h post-dose. Water, but no other drinks, is allowed as desired except for 1 h before and after IMP administration.

Part II (MAD) and Part III (SSc patients): Subjects in the MAD part and in the SSc part will be administered single oral doses of GS-248 or placebo as randomised for 10 consecutive days.

On Day 1 and Day 10, the IMP will be administered with 240 mL of water following an overnight fast of at least 10 h. No food is allowed until 4 h post-dose. Water, but no other drinks, is allowed as desired except for 1 h before and after IMP administration.

On other treatment days (Day 2 to Day 9), the IMP will be administered at the clinic before breakfast each morning at approximately the same time each day (±1 h).

Part IV (celecoxib): Subjects in the celecoxib cohort will receive twice daily oral doses of celecoxib (200 mg) for 10 consecutive days. Doses on Day 1, Day 2 (morning dose), Day 9 and Day 10 will be administered at the clinic. Other study days (Day 2 [evening dose] and Day 3 to Day 8) will be self-administered by the subjects at home at 12 h intervals (with or without food). An electronic diary (ViedocMe) will be used to document the time of administration and any deviations each day.

10.7 Continuation of treatment with Investigational Medicinal Product

No subject or patient will continue treatment with GS-248 after the end-of-study participation.

10.8 Treatment compliance

Part I, SAD: all IMP will be administered at the research clinic under medical supervision to ensure compliance.

Part II, MAD: all IMP will be administered at the research clinic under medical supervision to ensure compliance.

Part III, SSc patients: all IMP will be administered at the research clinic under medical supervision to ensure compliance.

Part IV, celecoxib: celecoxib will be administered at the research clinic under medical supervision On Day 1, Day 2 (morning dose), Day 9 and Day 10. On other study days, subjects will self-administer celecoxib twice daily and document the time of administration and any deviations in an electronic diary (ViedocMe). Compliance will also be confirmed by a telephone call at Visit 5 and by counting any unused celecoxib on Day 9.

In all parts, the administration of IMP will be documented in the eCRF. ViedocMe data is an integrated part of the eCRF.

10.9 Return and destruction of investigational medicinal products

Any unused study medication and all empty containers will be destructed at the site upon confirmation from the Sponsor. The Monitor will perform final IMP accountability reconciliation at the study end to verify that all used and unused IMP is adequately documented and destroyed.

11 STUDY ASSESSMENTS

The study assessments are described in the sections below and the timing of these assessments are detailed in the schedule of events:

Part I (SAD): Table 8.1-1 and Table 8.1-2.

Part I (MAD): Table 8.1-3 and Table 8.1-4.

Part III (SSc patients): Table 8.1-5 and Table 8.1-6.

Part IV (celecoxib): Table 8.1-7.

11.1 Recording of data

The Principal Investigator will provide the Sponsor with all data produced during the study from the scheduled study assessments. He/she ensures the accuracy, completeness, legibility, and timeliness of the data reported to Sponsor in the eCRF and in all required reports.

It is important that PK and PD blood sampling occurs as close as possible to the scheduled time. In order to achieve this, the timing priority order at a particular time point is:

1. Blood samples for PK and explorative GS-248 metabolite analysis (includes MIST in Part II)
2. Blood samples for PD (WBA, ADMA, future analyses)
3. Standard 12-lead ECG
4. Safety laboratory samples
5. Vital signs

Time points for PK and PD blood sampling, PD urine sampling, safety laboratory samples, standard 12-lead ECG and vital signs are outlined in Table 8.1-2 for Part I, Table 8.1-4 for Part II, Table 8.1-6 for Part III and Table 8.1-7 for Part IV (PD only).

Actual time for PK/PD sampling must not deviate more than ±10% from the planned time. For further details regarding time windows for PK sampling, refer to Section 11.4.1.

11.2 Demographics and other baseline characteristics

11.2.1 *Informed consent*

Signed informed consent must be obtained before any screening procedures are initiated. The informed consent procedure is further described in Section 14.3.

11.2.2 *Eligibility criteria*

Eligibility criteria should be checked during screening and verified before randomisation and IMP administration. The criteria are specified in Section 9.4.

11.2.3 *Demographic information*

The following demographic data will be recorded: gender, age, ethnicity and race.

11.2.4 *Weight and height*

Weight and height will be measured without shoes at screening. BMI will be calculated from the height and weight recorded. Weight will also be measured at the end-of-study visit of each part.

11.2.5 *Medical/surgical history*

Medical/surgical history will be obtained by subject interview in order to verify that the eligibility criteria are met.

The date (month) for onset of SSc will be documented in the eCRF as will the typical frequency of Raynaud's Phenomenon attacks.

11.2.6 *Prior and concomitant medication*

Prior medications taken will be obtained by subject interview in order to verify that the eligibility criteria are met (see also Section 9.5.3).

Medications are classified as prior if the stop date was before or on the day of the first dose administration (pre-dose) and as concomitant if ongoing on the day of the first dose administration, stopped after the first dose administration or started after the first dose administration. To distinguish between prior and concomitant medications on Day 1 in each part (i.e. the first dosing day), the start time of any newly introduced medication or the stop time of any previously ongoing medication must be recorded in the eCRF.

Any use of concomitant medication from 2 weeks before the first IMP administration until the end-of-study visit of each part must be documented appropriately in the subject's/patient's eCRF. Relevant information (*i.e.* name of medication, dose, unit, frequency, start and stop dates, reason for use) must be recorded. All changes in medication should be noted in the eCRF.

11.2.7 *HIV and Hepatitis B/C*

Subjects will be tested for HIV and hepatitis B/C prior to inclusion into the study. Any positive result will exclude the patient from participating in the study.

11.2.8 *Pregnancy test*

All WOCBP will do a pregnancy test at screening (blood/serum) and at visits specified in Table 8.1-1, to Table 8.1-7 (urine dipstick).

FSH and oestradiol levels will be determined as needed to confirm postmenopausal females.

11.2.9 *Urine drug screen*

Urine will be screened for drugs of abuse at time points in Part I, II and IV as outlined in the schedule of events (Table 8.1-1 to Table 8.1-4 and Table 8.1-7) using the Alere^{TM} Drug

Screen Test Panel. Random drug tests can be performed during the study period in all parts of the study including Part III.

11.2.10 *Alcohol breath test*

An alcohol breath test will be performed at time points outlined in the schedule of events (Table 8.1-1 to Table 8.1-7). Additional random tests can be performed during the study period.

11.2.11 *Baseline symptoms*

A baseline symptom is defined as an event that occurs between the subject's/patient's signing of the ICF until the first administration of IMP (i.e. an event that occurs during the screening period). Such events are not AEs and will be recorded as baseline symptoms in the Medical History Log in the eCRF.

11.3 Assessments related to primary endpoints: safety and tolerability

11.3.1 *Adverse events*

The Principal Investigator is responsible for ensuring that all medical staff involved in the study is familiar with the content of this section and the content of CTC's standard operating procedures (SOPs) regarding emergencies and FIH studies.

11.3.1.1 Definition of adverse event

An AE is defined as any untoward medical occurrence in a subject/patient who has received an IMP. The event does not necessarily need to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including clinically significant abnormal values from relevant tests, such as clinical safety laboratory tests, ECGs, vital signs), symptom, or disease temporally associated with the use of an IMP, regardless of whether it is considered related to the IMP.

11.3.1.2 Definition of serious adverse event

An SAE is any AE that:

- results in death
- is life-threatening (this refers to an event in which the subject/patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe)
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is medically important (this refers to an event that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the subject/patient or may require intervention to prevent any of the SAEs defined above)

Examples of medically important events are intensive treatment in an emergency room for allergic bronchospasm or blood dyscrasias, convulsions that do not result in hospitalisation, development of drug dependency, and drug abuse.

Planned hospitalisations or surgical interventions for a condition that existed before the subject/patient signed the ICF and that did not change in intensity are not SAEs.

If there is any doubt as to whether an AE meets the definition of an SAE, a conservative viewpoint must be taken, and the AE must be reported as an SAE.

11.3.1.3 Definition of adverse drug reaction

The term ADR is to be used whenever either the Investigator or Sponsor or designee assessed the AE as at least possibly related to the IMP.

11.3.1.4 Definition of serious adverse drug reaction

The term SADR is to be used whenever either the Investigator or Sponsor or designee assessed the SAE as possibly or probably related to the IMP.

11.3.1.5 Definition of suspected unexpected serious adverse reaction

A SUSAR is any SADR whose nature or intensity is not consistent with the current version of the IB.

11.3.1.6 Time period and frequency for collecting adverse events

Part I, II and IV: All AEs (including SAEs) will be collected from the start of IMP administration until the end-of-study visit of each part.

Part III: SAEs will be collected from the time of signing the informed consent whereas AEs will be collected from the start of IMP administration. Both AEs and SAEs will be collected until the end-of-study visit.

Any AE with start date on the day IMP administration must be recorded with start time.

At the end-of-study visit, new information regarding AEs or SAEs, if any, including status of ongoing events must be recorded as applicable.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

11.3.1.7 Assessment of intensity

The grading of the intensity of AEs will follow the CTCAE v5.0 [1]. Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline.

The Investigator must assess the intensity of an AE using the following definitions, and record it on the AE Log in the CRF:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self- care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

**Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.*

***Self- care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.*

11.3.1.8 Assessment of causal relationship

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:

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).

An AE is considered causally related to the use of the IMP when the causality assessment is probable or possible.

11.3.1.9 Assessment of outcome

The Investigator must assess the outcome of an AE using the definitions below and record it on the AE Log of the eCRF:

Recovered/resolved	The subject/patient has recovered completely, and no symptoms remain.
Recovering/resolving	The subject's/patient's condition is improving, but symptoms still remain.
Recovered/resolved with sequelae	The subject/patient has recovered, but some symptoms remain (for example, the subject/patient had a stroke and is functioning normally but has some motor impairment).
Not recovered/not resolved	The subject's/patient's condition has not improved and the symptoms are unchanged (for example, an atrial fibrillation has become chronic).
Fatal	
Unknown	

11.3.1.10 Collecting adverse events

AEs identified using any of the following methods will be recorded:

- AEs spontaneously reported by the subject/patient
- AEs observed by the Investigator or medical personnel
- AEs elicited based on non-leading questions from the Investigator or medical personnel

11.3.1.11 Recording adverse events

AEs must be recorded in the AE Log of the eCRF. The investigator must provide information on the AE, preferably with a diagnosis or at least with signs and symptoms; start and stop dates, start and stop time; intensity; causal relationship to IMP; action taken, and outcome.

If the AE is serious, this must be indicated in the eCRF.

AEs, including out-of-range clinically significant clinical safety laboratory values, must be recorded individually, except when considered manifestations of the same medical condition or disease state; in such cases, they must be recorded under a single diagnosis.

11.3.1.12 Reporting of serious adverse events

SAE reporting should be performed by the Investigator within 24 h of awareness via the eCRF. All available information regarding the SAE should be entered in the AE Log for the specific subject. By saving the event as "serious" in the eCRF and once the Investigator has signed-off of the event, an e-mail alert is automatically sent to predefined recipients to highlight that an SAE has been registered. The same information is automatically sent to sae@ctc-ab.se.

The SAE report is reviewed by a designated person at CTC's Pharmacovigilance (CTC PV) department to ensure that the report is valid and correct. For fatal or life-threatening SAEs where important or relevant information is missing, immediate follow-up is undertaken and queries to the site are raised. Investigators or other site personnel should inform CTC PV of any follow-up information on a previously reported SAE immediately but no later than the end of the next business day of when he or she becomes aware of it.

If the SAE report in eCRF is updated, a new e-mail alert is sent to the predefined recipients.

If any additional documentation is required (e.g. autopsy report), CTC PV will request this information from the study site.

In case the eCRF cannot be accessed, the SAE should be reported by manually completing the paper SAE Form, provided in the Investigator Site File (ISF). The completed, signed and dated paper SAE Form should, within 24 h, be scanned and e-mailed to:

Medical monitor: Cornelia Lif-Tiberg
E-mail: cornelia-lif-tiberg@ctc-ab.se

Sponsor's medically representative: Göran Tornling
E-mail: goran.tornling@gesynta.se and sae@gesynta.se

A copy of the paper SAE form must also be e-mailed to CTC at: sae@ctc-ab.se.

The study site should notify the site monitor via phone or e-mail about the submission of the SAE report. As soon as the site personnel have access to the eCRF, the SAE should be reported electronically as well.

The Sponsor or delegate will assume responsibility for reporting SAEs to the CA and IEC in accordance with local regulations.

11.3.1.13 Reporting of SUSARs to EudraVigilance, CA and IEC

The term SADR is used whenever either the Investigator or medical monitor deems a blinded SAE as possibly or probably related to IMP. If an SADR is assessed as unexpected by the medical monitor, it is a potential SUSAR and under such circumstances an EudraVigilance reporter will be unblinded. In case the subject had received active treatment, the event is regarded as a SUSAR and the certified EudraVigilance reporter will report the SUSAR to the CA, via the EudraVigilance database, and to the IEC in accordance with local regulations and CTC SOPs within the following timelines:

- 7 calendar days if fatal or life-threatening (follow-up information within an additional 8 days)
- 15 calendar days if non-fatal and non-life-threatening (follow-up information as soon as possible)

The clock for expedited initial reporting (Day 0) starts as soon as the Sponsor has received the information containing the minimum reporting criteria. The date should be documented on an acknowledgement receipt.

The medical monitor is responsible for medical review of the SAE narrative in the Council for International Organisations of Medical Sciences (CIOMS) for (or equivalent) prior to expedited reporting.

The Sponsor or delegate is responsible for informing the Investigators concerned of relevant information about SUSARs that could adversely affect the safety of patients.

The Sponsor or delegate is responsible for once a year throughout the clinical study (or on request), submit a safety report to the CA and the IEC taking into account all new available safety information received during the reporting period.

11.3.1.14 Treatment and follow-up of adverse events

Subjects/patients with AEs that occur during the study must be treated according to daily clinical practice at the discretion of the Investigator.

AEs must be followed up until resolution or to the end-of-study visit, whichever comes first. At the end-of-study visit, information on new AEs, if any, and stop dates for previously reported AEs must be recorded (if known). AEs assessed as stable by the Investigator at the end-of-study visit will not have to be followed up until resolution.

It is the responsibility of the Investigator to follow up on all SAEs until the subject/patient has recovered, stabilised, or recovered with sequelae, and to report to the Sponsor all relevant new information using the same procedures and timelines as those for the initial report. Relevant information includes discharge summaries, autopsy reports, and medical consultation.

11.3.1.15 Treatment of overdose

An overdose is a dose in excess of the dose specified for each cohort in this CSP.

Overdosing of GS-248 is not likely to occur in this study since all IMP will be administered by site personnel under medical surveillance. Overdosing of celecoxib may occur during the period when subjects self-administer celecoxib at home. In the event of suspected overdose, appropriate supportive medical care should be provided. Reactions will be treated symptomatically.

An overdose should be documented as follows:

- An overdose with associated AE is recorded as the AE diagnosis/symptoms in the AE Log of the eCRF.
- An overdose without associated symptoms is only reported in the subject's/patient's medical records.

No known antidote is available.

11.3.1.16 Procedures in case of pregnancy

In case of pregnancy or suspicion of possible pregnancy of any female subjects or female partners of male subjects, the study treatment must be stopped immediately, and the subject discontinued from participation in the study. Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP may have interfered with the effectiveness of the contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even after the subject was discontinued from the study.

All events of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as AEs. All outcomes of pregnancy must be reported to the Sponsor and the Principal Investigator on the pregnancy outcomes report form.

11.3.2 ***Physical examination***

A complete physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities.

Short version of physical examination will include an assessment of selected body systems at the judgement of the Investigator but will at least include cardiovascular, lung and abdomen. The result of the examination will be documented in the eCRF as normal/abnormal.

For timing of assessments, refer to Table 8.1-1 to Table 8.1-7.

11.3.3 ***Vital signs and body temperature***

All parts: Systolic and diastolic blood pressure and pulse will be measured in supine position after 10 minutes of rest. Body temperature will be measured orally using a digital thermometer.

Abnormal post-dose findings assessed by the Investigator as clinically significant will be reported as AEs.

For timing of assessments, refer to Table 8.1-1 to Table 8.1-7.

11.3.4 *Resting 12-lead ECG*

Single 12-lead ECG will be recorded in supine position after 10 minutes of rest using an ECG machine. HR and PQ/PR, QRS, QT and QTcF intervals will be recorded.

Safety ECGs will be reviewed and interpreted on-site by the Investigator.

Any abnormalities will be specified and documented as clinically significant or not clinically significant. Abnormal post-dose findings assessed by the Investigator as clinically significant will be reported as AEs.

For timing of assessments, refer to Table 8.1-1 to Table 8.1-7.

11.3.5 *Telemetry*

Ambulatory ECG telemetry will be used for cardiac surveillance up to 24 h after IMP administration in the Part I of the study.

Telemetry will be reviewed on-site by the Investigator. Any abnormalities will be specified and documented as clinically significant or not clinically significant. Abnormal post-dose findings assessed by the Investigator as clinically significant will be reported as AEs.

11.3.6 *Clinical laboratory profile*

Blood samples for analysis of clinical chemistry, haematology and coagulation parameters will be collected through venepuncture or an indwelling venous catheter and sent to the certified clinical chemistry laboratory at Uppsala University Hospital and analysed by routine analytical methods at visits specified in Table 8.1-1 to Table 8.1-7..

Urinalysis will be performed at the research clinic using dip sticks.

Serum/urine pregnancy tests will be performed at visits specified in Table 8.1-1 to Table 8.1-7.

The safety laboratory parameters are defined in Table 11.3-1.

Abnormal values assessed by the Investigator as clinically significant will be reported as AEs. If an abnormal value is associated with corresponding clinical signs or symptoms, the sign/symptom should be reported as the AE.

Table 11.3-1 Safety laboratory parameters Part I, II and III

Category	Parameter
Clinical chemistry	Alanine aminotransferase (ALT)
	Albumin
	Alkaline phosphatase (ALP)
	Aspartate aminotransferase (AST)
	Bilirubin (total and conjugated)
	Calcium, total
	Creatinine
	Estimated glomerular filtration rate (eGFR) calculated according to the revised Lund-Malmö GFR estimating equation
	Cholesterol
	C-reactive protein (CRP)
	Cystatin C
	Gamma Glutamyl Transferase (gGT)
	Glucose
	Lactate dehydrogenase (LD)
	Osmolality
	Phosphate
	Potassium
	Sodium
	Urea nitrogen
Haematology	Erythrocyte count
	Haematocrit (Erythrocyte volume fraction)
	Haemoglobin (Hb)
	Leucocyte count
	Leucocyte differential, absolute count (lymphocytes, monocytes, neutrophil-, eosinophil-, and basophil-granulocytes)
	Mean Corpuscular Volume (MCV)
	Platelet count (Thrombocyte particle concentration [TPC])
Coagulation	Activated Partial Thromboplastin Time (APTT)
	Prothrombin Complex International Normalised Ratio
Urinalysis (dip stick)	Bilirubin
	Erythrocytes
	Glucose
	Ketone
	Leucocytes
	Nitrite
	pH
	Protein
	Specific gravity
	Urobilinogen
Urine creatinine[1]	
Hormone analysis (at screening only)	Thyroid Stimulating hormone (TSH)

Category	Parameter
FSH-test (at screening, postmenopausal females only)	FSH
	Oestradiol
Pregnancy test	Serum pregnancy test at screening, urine pregnancy test at other
	visits

1. Part II and III. Urine creatinine is not regarded as a safety parameter but is taken in order to normalise the PD urine analysis.

Table 11.3-2 Safety laboratory parameters Part IV

Category	Parameter
Clinical chemistry	ALT
	Albumin
	ALP
	AST
	Bilirubin (total and conjugated)
	Creatinine
	eGFR calculated according to the revised Lund-Malmö GFR estimating equation
	CRP
	gGT
	LD
Haematology	Erythrocyte count
	Haematocrit (Erythrocyte volume fraction)
	Hb
	Leucocyte count
	MCV
	Platelet count (TPC)
Urinalysis (dip stick)	Bilirubin
	Erythrocytes
	Glucose
	Ketone
	Leucocytes
	Nitrite
	pH
	Protein
	Specific gravity
	Urobilinogen
Urine creatinine[1]	
Hormone analysis (at screening only)	TSH
FSH-test (at screening, postmenopausal females only)	FSH
	Oestradiol
Pregnancy test	Serum pregnancy test at screening, urine pregnancy test at other
	visits

1. Urine creatinine is not regarded as a safety parameter but is taken in order to normalise the PD urine analysis

11.4 Assessments related to secondary endpoints: pharmacokinetics and pharmacodynamics

11.4.1 *Pharmacokinetic sampling and analysis*

Blood samples for PK analysis will be drawn in Part I (SAD), Part II (MAD) and Part III (SSc patients).

Venous blood samples (approximately 5 mL) for the determination of plasma concentrations of GS-248 will be collected through venepuncture or an indwelling venous catheter at the pre-specified time-points (Part I, SAD: Table 8.1-1 and Table 8.1-2, Part II, MAD: Table 8.1-3 Table 8.1-4, and Part III, SSc patients: Table 8.1-5 and Table 8.1-6). Actual time for PK blood sampling must not deviate more than ±10% from the planned time except as detailed below.

Pre-dose PK sampling before the first dose may be performed within 60 minutes prior to dosing.

Pre-dose PK sampling on Day 8, Day 9 and Day 10 in Part II (MAD) and Part III (SSc patients) must be performed immediately before dosing (within 5 minutes).

The 24 h sample to be taken on Day 2 in Part I (SAD) must be taken within 10 minutes of the nominal time for the dosage interval.

The 24 h samples to be taken pre-dose on Day 2 and on Day 11, respectively, in Part II (MAD) and Part III (SSc patients) must be taken within 10 minutes of the nominal time for the dosage interval.

The date and time of collection of each sample will be recorded in the eCRF.

The collected blood samples will be centrifuged to separate plasma, which will be divided into aliquots after centrifugation for PK analysis, MIST (Part II) and further metabolite analysis (Part I and II). Further collection and handling details will be specified in a separate laboratory manual.

Samples for determination of plasma concentrations of GS-248 will be analysed by Recipharm, Uppsala, Sweden by means of a validated bioanalytical method. The details of the analytical method used will be described in a separate bioanalytical report. Both the bioanalytical laboratory and the pharmacokineticist will be blinded to treatment. For details on the PK parameters to be determined, refer to Section 17.6.1.

Samples for determination of GS-248 metabolites will be analysed under a separate protocol, see Section 11.5.4.

11.5 Assessments related to exploratory endpoints

11.5.1 *Blood sampling for ex-vivo whole blood assay (WBA)*

Blood samples (approximately 3 mL) to determine mPGES activity (PGE_2 levels) will be drawn in Part I (SAD, from cohort 3 and onwards), Part II (MAD), Part III (SSc patients) and in Part IV (celecoxib) at visits and time points detailed in Table 8.1-1 to Table 8.1-7.

The date and time of collection of each sample will be recorded in the eCRF. Collection and handling details will be specified in a separate laboratory manual.

Samples for determination of PGE_2 levels, will be analysed by means of a validated method. The details of the analytical method used will be described in a separate bioanalytical report.

Both the bioanalytical laboratory and the evaluator will be blinded to treatment.

11.5.2 *Urine sampling for analysis of AA metabolites, GS-248 metabolites and future biomarker analysis*

Urine collection for exploratory analysis of AA metabolites and for future biomarker analysis will be performed in Part II (MAD), Part III (SSc patients) and in Part IV (celecoxib) whereas urine collection for future exploratory analysis of GS-248 metabolites will be performed in Part II (MAD) only.

Urine will be collected at visits and time intervals presented in Table 8.1-3 (Part II, MAD), Table 8.1-5 (Part III, SSc patients) and Table 8.1-7 (Part IV, celecoxib). The volume of urine will be determined by total weight and documented in the eCRF. The date and time interval of each collection (start and stop time) will be recorded in the eCRF.

Three urine aliquots (5 mL) from each collection interval will be transferred to pre-labelled polypropylene cryotubes and will thereafter immediately be frozen at -70°C. Urine samples for future analysis will be stored for retention in a biobank, see Section 12.3.

Details on sample collection and handling will be provided in a separate laboratory manual.

11.5.3 *Blood sampling for ADMA analysis*

Blood collection for exploratory analysis of ADMA in plasma will be performed in Part II (MAD), Part III (SSc patients) and in Part IV (celecoxib).

Blood will be collected at visits presented in Table 8.1-3 (Part II, MAD), Table 8.1-5 (Part III, SSc patients) and Table 8.1-7 (Part IV, celecoxib). The date and time of collection of each sample will be recorded in the eCRF.

Venous blood samples (approximately 5 mL) will be collected through venepuncture or an indwelling venous catheter. The separated plasma from each blood sample will be divided into aliquots and frozen at -70°C within 1 h after centrifugation.

Collection and handling details will be provided in a separate laboratory manual.

11.5.4 *Blood sampling for GS-248 metabolites (including MIST)*

Blood sampling for future analysis of GS-248 metabolites will be performed in Part I and Part II. The collection and handling of these samples are described in Section 11.4.1 since the samples constitute an aliquot of the plasma generated from each PK sample. Metabolite sampling will be performed at visits presented in Table 8.1-1 (Part I, SAD) Table 8.1-3 (Part II, MAD).

The results will be analysed under a separate protocol and reported separately.

11.5.5 *Blood sampling for future biomarker analysis*

Blood sampling for future exploratory analysis of biomarkers e.g. inflammatory biomarkers will be performed in all parts. Blood will be collected at visits presented in Table 8.1-1 (Part I,

SAD) Table 8.1-3 (Part II, MAD), Table 8.1-5 (Part III, SSc patients) and Table 8.1-7 (Part IV, celecoxib). The date and time of collection of each sample will be recorded in the eCRF.

Venous blood samples (approximately 5 mL) analysis will be collected through venepuncture or an indwelling venous catheter. The separated plasma from each blood sample will be divided into aliquots after centrifugation. Collection and handling details will be provided in a separate laboratory manual.

Plasma samples for future analysis will be stored for retention in a biobank, see Section 12.3.

11.5.6 *Open question, Raynaud's (Part III only)*

On Day 11, approximately 24 h post last dose in Part III of the study, an open question will be raised to each participating patient:

"Did you experience any change in your Raynaud's status during the treatment period (Y/N)?"

If the answer was yes, the patient will be asked to specify the change. The response to both questions will be documented in the eCRF.

11.6 Appropriateness of measurements

The stopping rules for dose escalation used (see Section 8.3.7) follows the recommendations and grading system of CTCAE v4.03 [1] but also take into account the recommendations published by Sibille et al 2010 [20], which is an adaptation to FIH studies of the grading systems previously proposed by NCI [1], WHO [21], NIH [22] and FDA [23].

All other methods used for safety assessments are commonly used in standard medical care and in Phase I clinical studies. Non-compartmental analysis of PK parameters is also standard for Phase I clinical studies.

12 PROCEDURES FOR BIOLOGICAL SAMPLES

12.1 Sample collection

The sample collection procedures for PK, PD and metabolite analysis are briefly described in Section 11.4.1 and are detailed in a separate laboratory manual.

Safety laboratory samples will be collected according to standard procedures.

12.2 Volume of blood

The estimated volume of blood to be collected from each subject/patient during the study will be approximately 150 mL in Part I, 300 mL in Part II and III and 130 mL in in Part IV, which is less than 450 mL, i.e. the volume drawn during a regular blood donation.

12.3 Handling, storage and destruction of laboratory samples

All biological samples will be registered in a biobank at CTC (893).

Any remains from the safety laboratory samples will be disposed of after analyses.

The samples for analysis of GS-248 plasma concentration, WBA and ADMA in plasma and AA metabolites in urine will be stored at -70°C until analysed. The samples will be disposed of once the exploratory analyses have been documented in addendum to the CSR. The samples will not be retained for longer than 15 years after study completion.

Bulk urine samples will be discarded immediately after collection of aliquots for analysis (including future analysis).

Exploratory GS-248 metabolite samples may be retained for up to 15 years after study completion for future analysis. Exploratory plasma and urine samples for potential future biomarker analysis may also be retained for up to 15 years after study completion.

12.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

CTC keeps full traceability of collected biological samples from the subjects while in storage at the research clinic until shipment and keeps documentation of receipt of arrival.

The sample receiver (the analytical laboratory) keeps full traceability of the samples while in their storage and during use until used or disposed of.

The Sponsor keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers. The Sponsor has delegated to CTC the responsibility to monitor study sites and to audit any external laboratory provider.

Remaining samples collected for analysis of GS-248 plasma concentrations and exploratory biological samples will be transferred to Gesynta AB or designee at an agreed timepoint and stored for up to 15 years after study completion.

12.5 Withdrawal of informed consent for donated biological samples

If a subject/patient withdraws consent to the use of biological samples donated, the samples will be disposed of /destroyed, if not already analysed and documented.

The Principal Investigator will ensure that:

- Subject/patient withdrawal of informed consent is notified immediately to Sponsor.
- Biological samples from the subject/patient, if stored at the research clinic, are immediately identified, disposed of/destroyed and the action is documented.

The Sponsor has to ensure that the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed or returned to the research clinic and the action is documented.

13 QUALITY MANAGEMENT, QUALITY ASSURANCE AND QUALITY CONTROL

13.1 Quality management: critical process, system and data identification

During protocol development, the sponsor will identify those processes, systems (facilities, computerised systems) and data that are critical to ensure human subject protection and the reliability of trial results according to applicable SOPs and International conference on Harmonisation (ICH) E6 R2.

Identified risks will be categorised separately from the CSP and will be discussed/addressed between CTC and the Sponsor. Specific mitigation and contingency plans will be put into place.

13.2 Quality assurance and quality control

The Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs with regards to management of identified risks, CSP compliance, good clinical practice (GCP) compliance and applicable regulatory requirements.

The Sponsor is responsible for securing agreements with involved subcontractors and to perform regular subcontractor oversight to ensure CSP compliance, GCP compliance and compliance with applicable regulatory requirements.

The Sponsor is responsible for implementing a risk-based validated EDC system and maintain SOPs for the whole life- cycle of the system.

The Sponsor has delegated the responsibilities mentioned above whilst maintaining overall study oversight.

Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

14 ETHICAL AND REGULATORY REQUIREMENTS

14.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki [27] and are consistent with ICH/ GCP E6 (R2), EU Clinical Trials Directive, and applicable local regulatory requirements.

14.2 Ethics and regulatory review

The Principal Investigator is responsible for submission of the CSP, the patient information and ICF, any other written information to be provided to the subjects/patients and any advertisements used for recruitment of subjects/patients to applicable IEC for approval.

The Sponsor has delegated to CTC the responsibility for submission of study documents to the applicable CA according to local regulatory requirements.

Approval must be obtained in writing from both IEC and CA before the first subject/patient can be recruited.

The Sponsor will provide the CA, IEC and Principal Investigators with safety updates/reports according to local requirements. Progress reports and notifications of SUSARs will be provided to the IEC according to local regulations and guidelines.

14.3 Subject/Patient information and consent

It is the responsibility of the Investigator or an authorised associate to give each potential study subject/patient adequate verbal and written information before any study specific assessments are performed.

The information will include the objectives and the procedures of the study as well as any risks or inconvenience involved. It will be emphasised that participation in the study is voluntary and that the subject/patient may withdraw from participation at any time and for any reason, without any prejudice. All subjects/patients will be given the opportunity to ask questions about the study and will be given sufficient time to consider participation before signing the ICF.

The informed consent must be signed by the subject and by the person who conducted the informed consent discussion before any study-related information is recorded or procedures performed. A copy of the subject/patient information including the signed ICF will be provided to the subject/patient.

Documentation of the discussion and the date of informed consent must be recorded in the source documentation and in the CRF. The subject/patient information sheet and the signed ICF should be filed by the Investigator for possible future audits and/or inspections.

The final approved versions (one per part) of the subject/patient information and ICF must not be changed without approval from the Sponsor and the applicable IEC.

14.4 Subject/Patient information card

The subject/patient will be provided with a Subject/Patient information card including the following information:

- That he/she is participating in a clinical study
- Subject study ID
- That he/she is treated with the IMP/celecoxib
- The name and phone number of the Investigator
- Name and address of the Sponsor

14.5 Subject/Patient data protection

The ICF includes information that data will be recorded, collected and processed and may be transferred to European Economic Area (EEA) or non-EEA countries. In accordance with the

European Union Data Protection Directive (95/46/EC) and General Data Protection Regulation (GDPR), the data will not identify any persons taking part in the study.

The potential study subject/patient (or the subject's/patient's legally acceptable representative and/or witness, as applicable) should be informed that by signing the ICF he/she approves that authorised representatives from Sponsor and CTC, the concerned IEC and CA have direct access to his/her medical records for verification of clinical study procedures. This agreement is to be substantiated in a separate document, according to local requirements.

The subject/patient has the right to request access to his/her personal data and the right to request rectification of any data that is not correct and/or complete in accordance with the European Union Data Protection Directive (95/46/EC) and the request will be raised to the Principal Investigator.

The Investigator must file a Subject/Patient Identification List which includes sufficient information to link records, i.e. the CRF and clinical records. This list should be preserved for possible future inspections/audits but must not be made available to the Sponsor except for monitoring or auditing purposes.

Personal data that are collected in the study such as health information and ethnicity are considered as sensitive personal data. This data will be pseudoanonymised, i.e. personally identifiable information (PII) will be removed and replaced by a unique subject ID and will be processed by the Sponsor and other involved parties during the study. After the study end, only anonymised data, i.e. aggregated data sets, can be used.

For this study, the Sponsor Gesynta AB is the data controller of all data processed during the study (e.g. trial master file [TMF], study reports) and CTC AB is the data processor. Any subcontractors used in the study are also data processors.

For data that are processed at the clinic(s) (e.g. medical records and ISF), CTC AB is the data controller.

14.6 Changes to the approved clinical study protocol

Any proposed change to the approved Final CSP (including appendices) will be documented in a written and numbered clinical protocol amendment. All substantial amendments to the protocol must be approved by the appropriate IEC and/or CA before implementation according to applicable regulations.

14.7 Audits and inspections

Authorised representatives of Sponsor, a CA, or an IEC may perform audits or inspections at the research clinic, including source data verification (SDV). The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, ICH-GCP guidelines and any

applicable regulatory requirements. The Investigator will contact the Sponsor immediately if contacted by a CA about an inspection at the centre.

14.8 Insurance

Subjects/patients will be covered under Gesynta Pharma AB's liability insurance policy through the Swedish Pharmaceutical Insurance (Läkemedelsförsäkringen). The certificate of insurance and an information leaflet containing essential information about the insurance coverage can be provided upon request. The participating subjects/patients are also protected in accordance with national regulations, as applicable. CTC has a company insurance covering services performed by CTC.

15 STUDY MANAGEMENT

15.1 Training of study site personnel

Before screening of the first study subject a Sponsor representative or delegate will perform a study initiation visit at the research clinic. The requirements of the CSP and related documents will be reviewed and discussed and the investigational staff will be trained in any study specific procedures and system(s) utilised.

It is the responsibility of the Investigator to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study and have a detailed knowledge of and training in the procedures that are to be executed by them. Any new information of relevance to the performance of this study must be forwarded to the staff involved in a timely manner.

The Investigator will keep a list of all personnel involved in the study together with their function and study related duties delegated. A Curriculum Vitae will be available for all staff delegated study-specific duties.

15.2 Clinical monitoring

The Sponsor is responsible for securing agreement from all involved parties to ensure direct access to all study related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

As defined in the risk-based monitoring (RBM) plan, approved by the sponsor and provided separately, the responsible Monitor will periodically visit the study site at times agreed upon by the Investigator and the Monitor. At the time of each monitoring visit, the role of the Monitor is (but not limited to) to:

- provide information and support to the investigational team.
- confirm that facilities and resources remain acceptable.
- confirm that the investigational team is adhering to the CSP, applicable SOPs, guidelines, manuals and regulatory requirements.
- verify that data are being accurately and timely recorded in the CRFs and that IMP accountability checks are being performed.

- verify that data in the eCRF are consistent with the clinical records (SDV) in accordance with the RBM plan.
- verify that the correct informed consent procedure has been adhered to for participating subjects.
- ensure that withdrawal of informed consent to the use of the subject's/patient's biological samples will be reported and biological samples are identified and disposed of/destructed accordingly, and that this action is documented and reported to the subject.
- verify that AEs are recorded and reported in a timely manner and according to the CSP.
- raise and escalate any serious quality issues, serious GCP breach and any data privacy breach to the Sponsor.

Centralised monitoring will also be performed continuously by study team members ay CTC in accordance with the RBM plan.

When the study has been completed and all queries have been resolved and the database has been locked, the Monitor will perform a close-out visit.

15.3 Source data documents

A separate Origin of Source Data List will be generated for each site before start of screening, specifying the location of the source of derived information appearing in the CRF. This document must be signed by the Principal Investigator and the Monitor to confirm agreement before start of recruitment.

Source documents are all documents used by the Investigator or hospital that relate to the subject's/patient's medical history, that verifies the existence of the subject, the inclusion and exclusion criteria, and all records covering the subject's/patient's participation in the trial. They include laboratory notes, memoranda, material dispensing records, subject files, etc. The eCRF may constitute source data if clearly defined in the Origin of Source Data List.

The Investigator should guarantee access to source documents to the Monitor, CAs and the IECs, if required.

15.4 Study agreements

The Principal Investigator must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study.

Agreements between Sponsor and CTC must be in place before any study-related procedures can take place, or subjects/patients be enrolled.

15.5 Study timetable and end of study

The study is expected to start in Q2, 2019 and to be completed by Q2, 2020.

A subject/patient is considered to have completed the study if he/she has completed all visits in the study including the last scheduled procedure at the end-of-study visit of each part.

The end of the study is defined as the date of last scheduled visit/procedure shown in the Schedules of Events (Table 8.1-1 to Table 8.1-7) for the last subject/patient in study.

15.6 Termination of the of the study

The Sponsor reserves the right to discontinue the study at any time but intends only to exercise this right for valid scientific or administrative reasons.

After such a decision, the Investigator must inform all participating subjects/patients and perform relevant assessments, preferably according to the scheme for the final assessments. All delivered and unused study products and other study materials must be returned and all eCRFs completed as far as possible.

15.7 Reporting and publication

15.7.1 *Clinical study report*

A summarising report must be submitted to the applicable CA and IEC within 12 months after completion of the study (in accordance with LVFS 2011:19, Chapter 9).

A CSR, in compliance with ICH E3, describing the conduct of the study, any statistical analyses performed and the results obtained, will be prepared by CTC AB. The report will be reviewed and approved by, as a minimum, the Principal Investigator, the Statistician and the Sponsor. The study results will be reported in the EudraCT database per applicable regulations within 12 months after completion of the study.

The data obtained from any exploratory analyses may be reported separately from the CSR.

15.7.2 *Annual safety report*

If the study duration exceeds one year, the Sponsor must submit development safety update report (DSUR) to the CA and to the IEC. The report shall summarise all pertinent safety information collected during the reporting period and contain an update of the risk-benefit evaluation if there has been any change since the approval of the clinical study.

15.7.3 *Confidentiality and ownership of study data*

Any confidential information relating to the IMP or the study, including any data and results from the study, will be the exclusive property of the Sponsor. The Investigator and any other persons involved in the study are responsible for protecting the confidentiality of this proprietary information belonging to the Sponsor.

15.7.4 *Publication*

The results from this study may be submitted for publication at the discretion of the Sponsor.

15.8 Archiving

The Principal Investigator is responsible for maintaining essential documents, (as defined in ICH E6 GCP, Section 8) for 15 years after finalisation of the CSR. This includes any original

source documents related to the study, the Patient/Subject Identification List (providing the sole link between named subject/patient source records and anonymous CRF data), the original signed ICFs and detailed records of disposition of IMP.

It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

The Sponsor will archive the Trial Master File in accordance with ICH E6 GCP, Section 8 and applicable regulatory requirements.

The data from the eCRFs will be sent to the Sponsor and a copy will be sent to the clinic and filed in the Investigator Study File for archiving for 15 years after finalisation of the CSR.

The completed original eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorised representatives of appropriate Health/Regulatory Authorities, without written permission from the Sponsor.

16 DATA MANAGEMENT

The data management routines include procedures for handling of the eCRF, database set-up and management, data entry and verification, data validation, quality control (QC) of the database, and documentation of the performed activities including information of discrepancies in the process. The database, data entry screens, and program will be designed in accordance with the CSP.

Data validation/data cleaning procedures are designed to assure validity and accuracy of clinical data. These procedures consist of computerised online edit checks identifying e.g. data values that are outside the allowed range and SAS-programmed offline checks on data exports. All study-specific and standard data validation programming will be tested in a separate testing environment prior to use on production data.

Detailed information on data management will be described in a study-specific Data Management Plan (DMP).

16.1 The web-based eCRF

Clinical data will be entered into a 21 CFR Part 11-compliant eCRF (Viedoc™) provided by PCG Solutions AB. The eCRF includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents or at bedside (if the eCRF data constitutes source data). Source data are to be defined at the site before inclusion of the first subject (Section 15.3).

Authorised site personnel designated by the Investigator will complete data collection. Appropriate training and security measures will be completed with the Investigator and all authorised trial site personnel prior to the trial being initiated and any data being entered into the system for any study subject/patient.

16.2 The entering of data into the eCRF

All entries, corrections, and alterations are to be made by the Investigator or designee. Neither the Monitor nor any other study team member besides site staff can enter data in the eCRF. All data should be entered in English. The eCRFs should be completed as soon as possible during or after the subject's/patient's visit. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable or unknown, the Investigator or assigned clinical staff should record such information in the eCRF. The Investigator will be required to electronically sign off the clinical data. This will be performed by means of the Investigator's unique UserID and password; date and time stamps will be added automatically at time of electronic signature.

16.3 Electronic patient reported outcome

The subjects in Part IV (celecoxib) of the study will record data (celecoxib intake twice daily and AEs) using a web-based electronic patient reported outcomes (ePRO) system (ViedocMe™) linked to the eCRF. The ePRO system includes password protection and internal quality checks. Mobile phone text reminders can be sent to the subject through the ePRO. All data registered in ViedocMe are stored together with the eCRF data.

16.4 The query process

The Monitor will review the eCRFs and evaluate them for completeness and consistency. Data in the eCRF will be compared with the respective source documents to ensure that there are no discrepancies for critical data as described in the risk-based monitoring plan.

If corrections are needed, queries will be raised within the eCRF. An appropriate member of the site staff will answer the queries in the eCRF either by correcting the data or by entering a response to the query.

16.5 Audit trail

All entries in the eCRF will be fully recorded in a protected audit trail. Once clinical data have been saved, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who made the change, together with time and date will be logged.

16.6 External data

External data consists of data that are not recorded in the eCRF. Data may be received in electronic format or as a paper printout. Key variables are defined in order to uniquely identify each sample record. File and data formats are agreed with the external data provider.

16.7 Medical coding

Medical coding will be performed by trained personnel at CTC. AEs and medical/surgical history verbatim terms are coded using the Medical Dictionary of Regulatory Activities

(MedDRA; latest version available at start of coding). Prior and concomitant medications will be coded according to the WHO Anatomic Therapeutic Chemical (ATC) classification system. All coding will be approved by Sponsor prior to database locks.

16.8 Database lock

When all data have been entered and discrepancies solved, clean file will be declared, the database will be locked, the code will be broken and the data will be analysed.

There will be two database locks (DBLs), one following completion of Part I, II and IV and one following completion of Part III.

One ICH-E3 compliant CSR will be written following the final DBL.

17 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The principal features of the statistical analysis to be performed are described in this section. A more technical and detailed elaboration of the principal features will be presented in a separate Statistical Analysis Plan (SAP), which will be prepared and signed prior to the first database lock.

Analyses of the primary and secondary endpoints will be performed by CTC.

17.1 General

Continuous data will be presented in terms of evaluable and missing observations, arithmetic mean, standard deviation (SD), median, minimum and maximum value. In addition, for the parameters AUC and C_{max} the geometric mean and coefficient of variation (CV) will be presented.

Categorical data will be presented as counts and percentages. When applicable, summary data will be presented by treatment, and by assessment time. Individual subject data will be listed by subject number, treatment, and, where applicable, by assessment time.

All descriptive summaries and statistical analyses will be performed using SAS Version 9.4 or later (SAS Institute, Inc., Cary, NC).

Baseline will be defined as the visit with last data collection point prior to the first administration of IMP.

No imputation of missing data will be performed.

17.2 Determination of sample size

No formal sample size calculation has been performed for this study. The proposed sample size is considered sufficient to provide adequate information for the study objectives.

17.3 Analysis data sets

17.3.1 *Safety analysis set*

The safety analysis set of each part will consist of all subjects/patients who have been randomised and received at least one dose of IMP.

17.3.2 *Full analysis set*

The Full Analysis Set (FAS) of each part will consist of all subjects/patients who have been randomised and received at least one dose of IMP and who has at least one post-baseline assessment of efficacy data.

17.3.3 *Per protocol set*

The Per Protocol Set (PPS) of each part will consist of all subjects who have been randomised and completed the study without any major protocol deviations that are judged to compromise the analysis of the data. All protocol violations will be judged as major or minor prior to database lock.

17.3.4 *PK analysis set*

The PK analysis set will consist of all subjects who received at least one dose of the study drug and provided evaluable plasma concentration data and who have no AEs or protocol deviations judged to affect the PK analysis.

17.4 Description of study population

17.4.1 *Demographics and baseline characteristics*

Descriptive statistics for demographics, weight and height will be presented by part, treatment and cohort/dose group.

17.4.2 *Medical/surgical history and prior/concomitant medication*

Medical/surgical history and prior/concomitant medications will be presented by part, treatment, cohort/dose group and overall using descriptive statistics and listings.

17.4.3 *Treatment compliance*

The number of subjects/patients treated in each cohort and part and their individual dose will be listed.

17.5 Analysis of primary endpoints

17.5.1 *Adverse events*

An overview of all AEs, including SAEs, intensity, relationship to IMP, and deaths will be presented by SOC and preferred term (PT).

Incidence of AEs and SAEs will be summarised by SOC and PT by part, treatment, cohort/dose group and overall.

All AE data will be listed by part, cohort, treatment and subject/patient and include the verbatim term entered by the Investigator.

17.5.2 *Physical examination*

Clinically significant and non-clinically significant abnormal findings will be specified and presented by subject/patient and summarised by part, treatment and cohort/dose group.

Changes over time will be presented using shift tables.

All data will be listed by part, cohort, treatment and subject/patient.

17.5.3 *Vital signs and body temperature*

Vital signs (systolic/diastolic blood pressure and pulse) and body temperature will be summarised by part, treatment and cohort/dose group. Data will be presented with absolute and percent change from baseline at each visit.

All data will be listed by part, cohort, treatment and subject/patient.

17.5.4 *12-lead ECG*

All ECGs will be categorised as ”normal”, ”abnormal, not clinically significant”, or ”abnormal, clinically significant” (as judged by the Investigator) and summarised by part, treatment and cohort/dose group using frequency tables.

Changes over time will be presented using shift tables.

All data will be listed by part, cohort, treatment and subject/patient.

17.5.5 *Safety laboratory analyses*

Safety laboratory data will be summarised by part, treatment and cohort/dose group with absolute and percent change from baseline at each visit.

Abnormal, clinically significant values will be summarised separately if considered appropriate.

All data will be listed by part, cohort, treatment and subject/patient.

17.6 Analysis of secondary endpoints

17.6.1 *Analysis of pharmacokinetics*

The PK analysis will be based on the PK analysis set and performed by CTC. The PK parameters will be calculated by non-compartmental analysis (NCA) using the software Phoenix WinNonlin® version 6.3 or later (Pharsight Corporation, U.S.A.).

The following non-compartmental PK parameters will be assessed in Part I (SAD):

- AUC_{0-t},
- $AUC_{0-\infty}$,
- $T_{½}$,
- T_{max},
- C_{max},
- Dose proportionality after a single dose based on AUC and C_{max}
- V_z/F
- CL/F

The following non-compartmental PK parameters will be assessed after the first dose interval in Part II (MAD) and Part III (SSc patients):

- AUC_{0-t}
- $T_{½}$
- T_{max}
- C_{max}
- Dose proportionality after the first dose interval based on AUC and C_{max}

The following non-compartmental PK parameters will be assessed after the last dose interval in Part II (MAD) and Part III (SSc patients):

- AUC_{0-t}
- AUC_{ss}
- $T_{½}$
- T_{max}
- C_{max}
- C_{trough} from the 2 doses preceding the last dose
- Dose proportionality after the last dose interval based on AUC_{ss} and C_{max}
- V_z/F
- CL/F
- Accumulation ratio

Summary statistics for the PK parameters will be presented by part, treatment and cohort with number of measurements, arithmetic mean, SD, CV, median, minimum, maximum, geometric mean, geometric CV%. Additional PK parameters may be determined if deemed appropriate.

All data will be listed by part, cohort, treatment and subject/patient.

17.7 Analysis of exploratory endpoints

17.7.1 *Analysis of mPGES-1 activity (PGE_2 levels) levels using whole blood assay*

PGE_2 levels will be summarised by part, treatment and cohort with absolute and percent change from baseline at each visit.

All data will be listed by part, cohort, treatment and subject/patient.

17.7.2 *ADMA and AA metabolites in plasma and urine*

Each parameter will be summarised by part, treatment and cohort with absolute and percent change from baseline at each visit.

All data will be listed by part, cohort, treatment and subject/patient.

17.7.3 *Metabolites in safety testing (MIST)*

Details will be specified elsewhere.

17.7.4 *Future exploratory analyses of biomarkers and GS-248 metabolites*

Details will be specified elsewhere.

17.7.5 *Raynaud's questioning*

Data will be listed by treatment and patient.

18 REFERENCES

1. Allanore Y, Simms R, Distler O, Trojanowska M, Pope J, Denton CP, Varga J. Systemic sclerosis. Nature Reviews Disease Primers. 1:15002, 2015
2. Ruaro B, Sulli A, Smith V, Pizzorni C, Paolino S, Alessandri E, Cutolo M. Microvascular damage evaluation in systemic sclerosis: the role of nailfold videocapillaroscopy and laser techniques. Reumatismo, 2017; 69 (4): 147-155
3. Aïssou L, Meune C, Avouac J, Meunier M, Elhaï M, Sorbets E, André Kahan A, Allanore Y. Small, medium but not large arteries are involved in digital ulcers associated with systemic sclerosis. Joint Bone Spine 83:444-447 2016
4. Hughes M & Herrick AL. Digital ulcers in systemic sclerosis. Rheumatology 2017;56:14-25
5. Wilkinson JD, Leggett SA, Marjanovic EJ et al. A multicenter study of the validity and reliability of responses to hand cold challenge as measured by laser speckle contrast imaging and thermography; Outcome measures for systemic sclerosis–related Raynaud's phenomenon. Arthritis & Rheumatology. 70(6):903-911, 2018 Jun.
6. Farnebo S, Zettersten EK, Samuelsson A, Tesselaar E and Sjöberg F (2011). Assessment of Flood Flow Changes in Human Skin by Microdialysis Urea Clearance. Microcirculation 18(3), 198–204 2011
7. Elhai M, Avouac J, Walker UA et al. A gender gap in primary and secondary heart dysfunctions in systemic sclerosis: a EUSTAR prospective study. Ann Rheum Dis 2016;75:163–169
8. Meier FM, Frommer KW, Dinser R et al. Update on the profile of the EUSTAR cohort: an analysis of the EULAR Scleroderma Trials and Research group database. Ann Rheum Dis 2012; 71: 1355–1360
9. Hughes M, Snapir A, Wilkinson J, Snapir D, Wigley FM, Herrick AL. Prediction and impact of attacks of Raynaud's phenomenon, as judged by patient perception. Rheumatology (Oxford) 2015;54: 1443-7.
10. Merkel PA, Herlyn K, Martin RW et al. Measuring Disease Activity and Functional Status in Patients With Scleroderma and Raynaud's Phenomenon. Arthritis & Rheumatism 46, 2410–2420, 2002
11. Sunderkötter C, Herrgott I, Brückner C et al. Comparison of patients with and without digital ulcers in systemic sclerosis: detection of possible risk factors. British Journal of Dermatology 2009 160:835–843
12. Matucci-Cerinic M, Krieg T, Guillevin L, Schwierin B, Rosenberg D, Cornelisse P, Denton CP. Elucidating the burden of recurrent and chronic digital ulcers in systemic sclerosis: long-term results from the DUO Registry. Ann Rheum Dis 2016; 75: 1770–1776
13. Herrick AL. Evidence-based management of Raynaud's phenomenon. Ther Adv Musculoskel Dis 2017, Vol. 9(12) 317–329
14. Samuelsson, B., R. Morgenstern, and P.J. Jakobsson, Membrane prostaglandin E synthase-1: A novel therapeutic target. Pharmacological Reviews, 2007. 59(3): p. 207-224.
15. Jin Y, Smith CL, Hu L, Campanale KM, Stoltz R, Huffman Jr LG, McNearney TA, Yang XY, Ackermann BL, Dean R, Regev A and Landschultz W. Pharmacodynamic comparison of LY3023703, a novel microsomal prostaglandin E Synthase 1 inhibitor, with celecoxib: Clin Pharmacol Ther 2016;99:274-84
16. Norman BH, Fisher MJ, Schiffler MA, Kuklish SL, Hughes NE, Czeskis BA, Cassidy KC, Abraham TL, Alberts JJ,and Luffer-Atlas D.J. Identification and Mitigation of Reactive Metabolites of 2-Aminoimidazole-Containing Microsomal Prostaglandin E Synthase-1

Inhibitors Terminated Due to Clinical Drug-Induced Liver Injury. J Med Chem; 2018; 61: 2041−2051

17. https://www.fda.gov/downloads/Drugs/Guidances/UCM078932.pdf)
18. Trebino CE, Stock JL, Gibbons CP, Naiman BM, Wachtmann TS, Umland JP, Pandher K, Lapointe J-M, Saha S, Roach ML, Carter D, Thomas NA, Durtschi BA, McNeish JD, Hambor JE, Jakobsson P-J, Carty TJ, Perez JR and Audoly LP. Impaired inflammatory and pain responses in mice lacking an inducible prostaglandin E synthase. PNAS 2203; 100(15): 9044-9049.
19. National Cancer Institute Cancer Therapy Evaluation Program. Common terminology criteria for adverse events, CTCAE v5.0 (2017).
20. M Sibille *et al.* A safety grading scale to support dose escalation and define stopping rules for healthy subject first-entry-into-man studies, British Journal of Clinical Pharmacology, 70:5, 736-748, (2010).
21. WHO Recommendations for grading of acute and subacute toxicity: reporting the results of cancer treatment. Cancer, 47:207-214 (1981).
22. NIH. Division of AIDS table for grading the severity of adult and paediatric adverse events (2004).
23. FDA. Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials (2007).
24. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum 65: 2737–47 (2013).
25. FDA Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation (2009).
26. EudraLex VOLUME 4, Good manufacturing practices, ANNEX 13, Manufacture of investigational medicinal, products, February 2010, section 26.
27. Declaration of Helsinki: http://www.up.ac.za/media/shared/Legacy/sitefiles/file/45/2875/declarationofhelsinki_fortaleza_brazil2013.pdf

19 SIGNATURES

19.1 Principal Investigator statement

I have read and understood this CSP and agree to conduct the study accordingly and to comply with the investigator obligations stated in this CSP, GCP and applicable regulatory requirements.

Principal Investigator

Folke Sjöberg, MD, PhD, Professor		29 MAY 2019
Name	Signature	Date

CTC Clinical Trial Consultants AB

Site

19.2 Signature page (approval of the clinical study protocol)

Sponsor signatory

Göran Tornling, MD, PhD, MSc Gesynta Pharma AB Name	Signature	29 MAY 2019 Date