Clinical Study Protocol	
EudraCT No.	2020-000133-41
Investigational Medicinal Product	GS-248
Sponsor study code	GS-1002
Protocol Version and Date	Final version v1.0; 29JAN2020

An open, one-sequence, three-period study in healthy subjects to evaluate pharmacokinetics and food effect after oral single dosing of two different solid formulations of GS-248

Phase	I
Indication	Digital ulcers, systemic sclerosis
Test product and dose	GS-248
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1 STUDY SYNOPSIS

Study title An open, one-sequence, three-period study in healthy subjects to evaluate pharmacokinetics and food effect after oral single dosing of two different solid formulations of GS-248	
Study code GS-1002	**EudraCT No** 2020-000133-41
Planned study period Q2 2020	**Phase of development** I
Principle Investigator Helena Litorp, MD, PhD CTC Clinical Trial Consultants AB Uppsala University Hospital, Entrance 85, 2nd level SE-751 85 Uppsala, Sweden	
Study design This is a Phase I, open, one-sequence, three-period study in healthy volunteers to evaluate pharmacokinetics (PK), safety and tolerability of two different solid formulation of GS-248, and the food effect on PK and safety of one of these two formulations.	
Objectives Primary objectives: • To evaluate the PK of two different solid formulations of oral GS-248 in healthy subjects. • To evaluate the effect of food on PK of one of the two formulations of GS-248. Secondary objectives: • To evaluate the safety and tolerability of two different solid formulations of oral GS-248 in healthy subjects. • To evaluate the safety and tolerability of one of the two formulations of oral GS-248 given after a standardised high-fat high-calorie breakfast.	
Endpoints Primary endpoints: • The PK parameters of a single dose of two different formulations of GS-248 in fasting conditions. The PK parameters to be assessed include, but are not limited to, maximum plasma concentration (C_{max}), time to C_{max} (T_{max}),area under the curve from timepoint 0 to the last measured timepoint ($AUC_{0\text{-}last}$), AUC from timepoint 0 to infinity ($AUC_{0\text{-}inf}$), plasma half-life associated with the terminal elimination phase ($T_{½(z)}$), volume of distribution associated with the terminal elimination phase following non-intravenous administration (V_z/F), and total clearance of the drug from plasma following non-intravenous administration (CL/F). • The relative bioavailability of GS-248 after a single dose of Formulation A versus Formulation B, and of one of the two formulations in fed versus fasting conditions. • The PK parameters of a single dose of one of the two formulations of GS-248 in fed conditions.	

Secondary endpoints:

- Frequency, intensity and seriousness of adverse events (AEs).
- Clinically significant changes in:
  - Physical examination
  - Vital signs
  - Body temperature
  - Resting 12-lead electrocardiogram (ECG)
  - Safety laboratory parameters

Number of subjects planned

Approximately 20 healthy subjects will be screened to achieve a total of 14 dosed subjects, and at least 12 evaluable subjects.

Diagnosis and main eligibility criteria

- Healthy male or female subject, aged ≥ 18 and ≤70 years.
- Subject 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.
- Willing to use sufficient contraception as defined in this clinical study protocol (CSP).
- Females must not be pregnant, breast feeding or plan to be pregnant until 2 weeks after the end-of-study visit.
- Regular use of corticosteroids (inhaled and systemic), Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), aspirin or cyclooxygenase inhibitors (coxibs), antacids, proton pump inhibitors (PPIs), or any other medication that changes gastric pH within 14 days of study drug administration.

Methodology

The study is divided in two parts. Part I will evaluate PK, safety and tolerability of a single oral dose of two different formulations of GS-248 in fasting conditions. Part II will evaluate PK, safety and tolerability of one of the two different formulations of GS-248 in fed conditions.

Subjects are expected to participate in both Part I and Part II and will come to the clinic for a total of 7 visits. Screening (Visit 1) will take place from Day -28 to Day -1 and will include an eligibility check and a general health assessment.

In Part I of the study, a single oral dose of GS-248 in two different solid formulations will be administered to 14 healthy subjects. All subjects will first receive Formulation A (a lipid-based formulation in a capsule) and then Formulation B (a dry powder in a capsule). A wash-out period of at least 4 days will be applied between the IMP administrations. Both doses contain 120 mg GS-248. For Part I, subjects will come to the clinic for 4 visits. At Visit 2, subjects will be admitted to the clinic on the afternoon/evening of Day -1 and will remain at the clinic until Day 2 (24 h post dose) for single dose administration of Formulation A and PK and safety assessments. The subjects must fast for at least 10 hours 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. Vital signs and ECG will be checked at regular intervals. The subjects will return to the clinic on Day 3 (Visit 3) at 48 h post dose for PK blood sampling and safety assessments. Safety assessments include AE reporting, physical examination, ECG, vital signs, body temperature, and blood sampling for analysis of safety laboratory parameters.

Visit 4 will be similar to Visit 2, at which subjects will stay overnight at the clinic from Day -1 to Day 2 for single dose administration of Formulation B and PK and safety assessments. Visit 5 will be

similar to Visit 3, at which subjects return to the clinic on Day 3 for PK blood sampling and safety assessments. After evaluation of the PK profiles of Formulation A and B in Part I of the study, one formulation will be selected to be given following intake of a standardised breakfast in Part II of the study. Subjects will return to the clinic for a second dose of the selected formulation (Visit 6, similar to Visit 2), yet now in fed conditions. The assessments during fed conditions will be the same as during fasting conditions except that the subjects will consume a high-fat high-calorie breakfast 30 minutes prior to IMP administration. At 48 h post dose, subjects will return to the clinic for PK blood sampling and final end-of-study safety assessments (Visit 7).
Investigational Medicinal Product, dosage and mode of administration GS-248 is provided in two different solid formulations for oral administration: • Formulation A: a lipid-based formulation in size 1 capsules • Formulation B: dry powder in size 1 capsules Subjects will receive a single dose of each formulation during Part I, and a single dose of one of the two formulations during Part II. Each single dose consists of 3 capsules of 40 mg GS-248, constituting a total of 120 mg GS-248 per IMP administration.
Duration of treatment Subjects will receive in total 3 single doses of GS-248, with a wash-out period of at least 4 days in between each IMP administration.
Duration of each subject's involvement in the study Each subject is expected to participate in both Part I and Part II of the study, which will take approximately 8 weeks including a screening period of up to 4 weeks.
Pharmacokinetic assessments Blood sampling for bioanalysis and subsequent determination of GS-248 PK parameters.
Safety assessments AE reporting, resting 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.
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 database lock. PK and safety data will be summarised by descriptive statistics as appropriate.
Study reporting After completion of the study, an International Council for Harmonisation (ICH) E3 compliant clinical study report (CSR) will be prepared.

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or term	Explanation
AA	Arachidonic acid
ADL	Activities of daily living
AE	Adverse event
ADR	Adverse drug reaction
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
$AUC_{0\text{-inf}}$	Area under the curve from timepoint 0 to infinity
$AUC_{0\text{-last}}$	Area under the curve from timepoint 0 to the last measured timepoint
BMI	Body mass index
bpm	Beats per minute
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
CL/F	Total clearance of the drug from plasma following non-intravenous administration
COX	Cyclooxygenase
Coxib	Cyclooxygenase inhibitor
CRP	C-reactive protein
CS	Clinically significant
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
CV	Coefficient of variation
CYP	Cytochrome P450
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
EMA	European Medicines Agency
EUSTAR	European Scleroderma Trials and Research group
FDA	U.S. Food and Drug Administration
FIH	First-in-human
FSH	Follicle stimulating hormone
GCP	Good clinical practice
GDPR	General data protection regulation
GMP	Good manufacturing practice
h	hour
Hb	Haemoglobin
HBsAg	Hepatitis B surface antigen
HCG	Human chorionic gonadotropin
HCVAb	Hepatitis C virus antibodies
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IMP	Investigational medicinal product
ISF	Investigator site file
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LPS	Lipopolysaccharide
MAD	Multiple ascending dose
MEC	Molar extinction coefficient
MedDRA	Medical dictionary for regulatory activities
mmHg	Millimetre of mercury (unit for pressure)
MPA	Medical products agency
MTD	Maximum tolerated dose
mPGES-1	Microsomal Prostaglandin E synthase-1
NCA	Non-compartmental analysis
NCS	Not clinically significant
NOAEL	No observed adverse effect level

NSAID	Non-steroidal anti-inflammatory drug
PDE-5	Phosphodiesterase type 5
PG	Prostaglandin
PGE_2	Prostaglandin E2
PGH_2	Prostaglandin H2
PGI_2	Prostaglandin I2 (prostacyclin)
pKa	Negative base-10 logarithm of the acid dissociation constant (Ka) of a solution.
PK	Pharmacokinetic
PII	Personally identifiable information
pH	'Potential of hydrogen', a measure of acidity or alkalinity of a solution
p.o.	per os (orally)
PPI	Proton pump inhibitor
PT	Preferred term
QC	Quality control
RBC	Red blood cell count
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
$T_{½(z)}$	Plasma half-life associated with the terminal elimination phase
ULN	Upper limit of normal
UVA	Ultraviolet A
UVB	Ultraviolet B

V_z/F	Volume of distribution associated with the terminal elimination phase following non-intravenous administration
WBC	White blood cell count
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 11.4.1.13.

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

Table 4.1-1 Medical emergency contacts

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

5 INVESTIGATOR AND STUDY ADMINISTRATIVE STRUCTURE

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Laboratory (Bioanalysis)	Lablytica Life Science AB Virdings allé 18 SE-754 50 Uppsala, Sweden
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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

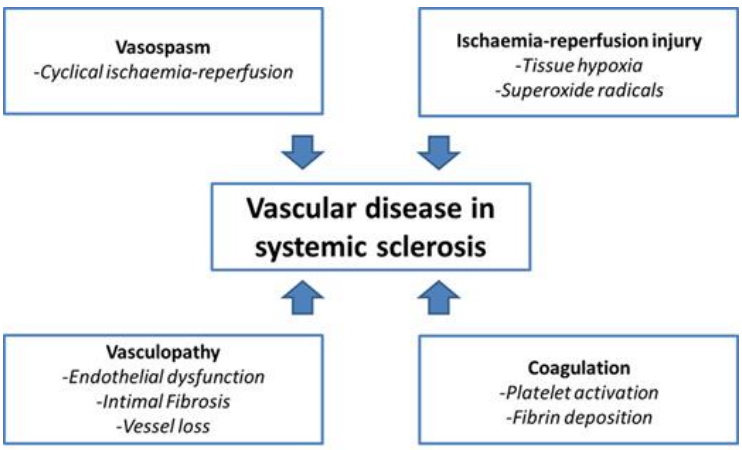
6.1.1 *Systemic sclerosis*

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). 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 [4]



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 European Scleroderma Trials and Research group (EUSTAR) database,

including 9182 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 on average 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 common and disabling manifestations 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]. DUs 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].

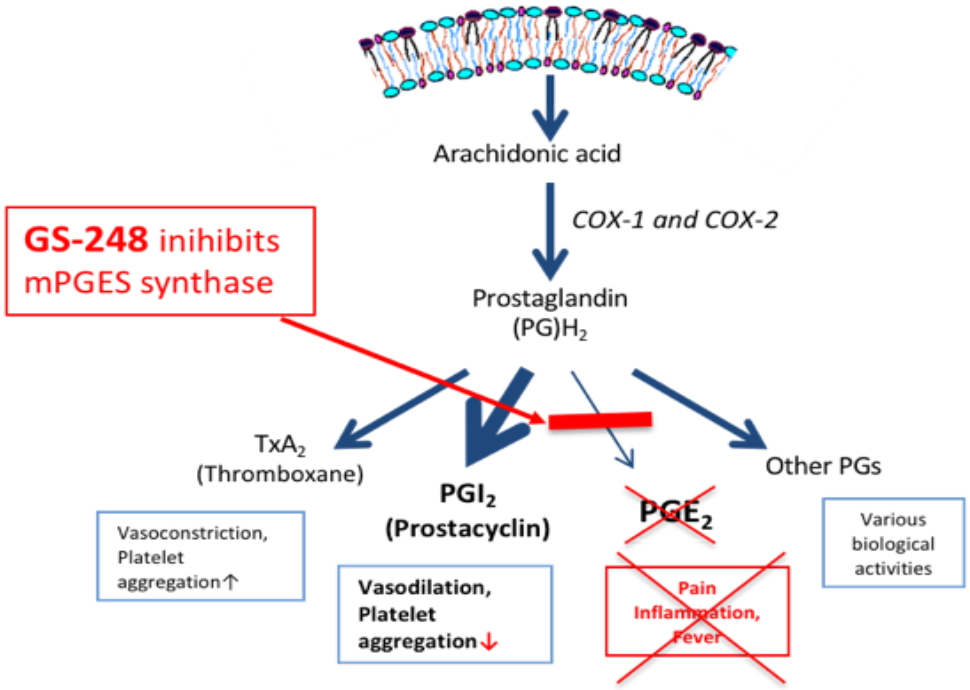
6.1.3 *Investigational medicinal product characteristics*

The IMP, GS-248, is under development for the treatment of DUs. 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-dependent.

6.1.4 *Mechanism of action of the investigational medicinal product*

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 6.1-2).

Figure 6.1-2 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 cyclooxygenase inhibitors (coxibs), which target the upstream cyclooxygenases (COX-1 and COX-2, respectively) for general inhibition of prostanoid production (Figure 6.1-2). 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 vasodilation 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, so as to elicit a vasodilatory and platelet inhibitory effect through increasing prostacyclin (PGI_2) production.

6.1.5 *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 µM. In a human whole blood assay (*ex vivo* measurements of mPGES-1 activity in lipopolysaccharide (LPS)-stimulated whole blood), 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 (LPS)-induced hyperalgesia in a dose dependent manner with maximal effect at 30 mg/kg per os (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 ($T_{½(z)}$) 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 area under the curve from timepoint 0 to the last timepoint ($AUC_{0\text{-}last}$). 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 cytochrome P450 (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 (they 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.

6.1.6 *Clinical experience*

A phase 1 first-in-human (FIH) study (GS-1001) has been performed in which GS-248 was dosed as an oral solution in fasting conditions. Of this study, the clinical phase has been completed (both the single ascending dose [SAD] and multiple ascending dose [MAD] part) and the clinical study report (CSR) is under development.

During the SAD part of this study, 6 cohorts of 8 subjects each were randomised to GS-248 and placebo at a 3:1 ratio, resulting in a total of 36 subjects being exposed to GS-248. Data from this part of the study indicate that GS-248 administered orally as single doses (1 mg to 300 mg) in healthy volunteers was safe and well tolerated as assessed by reported adverse events (AEs), vital signs, electrocardiograms (ECGs), physical examinations and safety laboratory parameters. No SAEs, no discontinuations due to AEs, and no other noteworthy safety or tolerability findings were reported at any dose level.

PK analysis demonstrated that GS-248 was rapidly absorbed and reached a maximum plasma concentration between 1 and 2.5 hours after single dose administration. The plasma concentration profiles exhibited a multi-exponential decline and the shape of the curves appeared to be similar between the different dose groups. The apparent total clearance of the drug from plasma following non-intravenous administration (CL/F) and apparent volume of distribution associated with the terminal elimination phase following non-intravenous administration (V_z/F) were both high. The terminal half-life was estimated to approximately 10 hours. GS-248 exhibited a large variability in exposure and dose proportionality was indicated.

6.2 Study rationale

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

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 pharmacokinetics (PK), safety and tolerability following a single dose of GS-248 in two different oral solid formulations in capsules to healthy subjects.

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

6.3 Risk/benefit assessment

The healthy volunteers in this study will, except for thorough health examinations, have no medical benefit from participation and their safety and wellbeing are of utmost importance. The FIH study with GS-248, in which the SAD part with doses of 1-300 mg is finalised and did not reveal any noteworthy safety or tolerability findings at any dose level. The current study concerns a single dose of 120 mg in two different formulations, which is well beneath the maximum dose level studied in the FIH study. Adverse drug reactions (ADRs) are therefore not expected.

In a pre-clinical study, 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.

Subjects will remain in the research clinic for approximately 24 h after the single dose and will be closely monitored by medical staff. In addition, subjects will return to the clinic at approximately 48 h post dose for safety check-up.

Overdosing is not likely to occur since all IMP will be administered by site personnel under medical surveillance. In cases of accidental overdose, standard supportive measures should be adopted as required. For further information regarding overdosing, refer to Section 11.4.1.17.

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. CTC has been regularly inspected by the Swedish Medical Products Agency (MPA) and is authorised to conduct early phase studies.

Besides the risks related to the IMP 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, the combined safety data from the pre-clinical studies and the FIH study have not revealed any safety issues that would outweigh the expected benefits of the study. 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 considered 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.

More detailed information about the known and expected benefits and risks and reasonably expected ADRs of GS-248 is found in the current version of the IB.

7 STUDY OBJECTIVES AND ENDPOINTS

7.1 Primary objective

- To evaluate the PK of two different solid formulations of oral GS-248 in healthy subjects.
- To evaluate the effect of food on the PK of one of the two formulations of oral GS-248.

7.1.1 *Primary endpoints*

- The PK parameters of a single dose of two different formulations of GS 248 in fasting conditions. The PK parameters to be assessed include, but are not limited to, maximum plasma concentration (C_{max}), time to C_{max} (T_{max}),area under the curve from timepoint 0 to the last measured timepoint ($AUC_{0\text{-}last}$), AUC from timepoint 0 to infinity ($AUC_{0\text{-}inf}$), plasma half-life associated with the terminal elimination phase ($T_{½(z)}$), volume of distribution associated with the terminal elimination phase following non intravenous administration (V_z/F), and total clearance of the drug from plasma following non-intravenous administration (CL/F).The relative bioavailability of GS-248 after a single dose of Formulation A versus Formulation B, and of one of the two formulations in fed versus fasting conditions.
- The PK parameters of a single dose of one of the two formulations of GS-248 in fed conditions.

7.2 Secondary objective

- To evaluate the safety and tolerability of two different solid formulations of oral GS-248 in healthy subjects.
- To evaluate the safety and tolerability of one of the two formulations of oral GS-248 given after a standardised high-fat high-calorie breakfast.

7.2.1 *Secondary endpoints*

- Frequency, intensity and seriousness of AEs.
- Clinically significant changes in:
    - Physical examination
    - Vital signs
    - Body temperature
    - Resting 12-lead ECG
    - Safety laboratory parameters

8 STUDY DESIGN

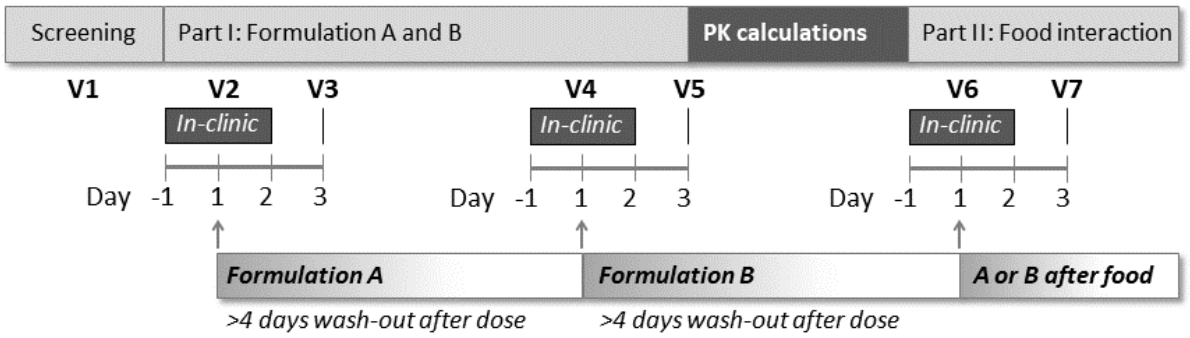
8.1 Overall study design and schedule of events

This is a Phase I, open, one-sequence, three-period study in healthy volunteers to evaluate the PK, safety and tolerability of two formulations of GS-248. The study is divided in two parts. Part I will evaluate PK, safety and tolerability of a single oral dose of two different formulations of GS-248 in fasting conditions (Section 8.1.1). Part II will evaluate PK, safety and tolerability of one of the two different formulations of GS-248 in fed conditions (Section 8.1.2).

Subjects are expected to participate in both Part I and Part II and will come to the clinic for a total of 7 visits. Screening (Visit 1) will take place from Day -28 to Day -1 and will include an eligibility check and a general health assessment, see Table 8.1-1 for details. Each subject is expected to participate in the study for approximately 8 weeks including a screening period of up to 4 weeks.

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

Figure 8.1-1 Study flow chart



8.1.1 *Part I: Two formulations of GS-248 in fasting conditions*

In Part I of the study, a single oral dose of GS-248 in two different solid formulations will be administered to 14 healthy subjects. All subjects will first receive Formulation A (a lipid-based formulation in a capsule) and then Formulation B (a dry powder in a capsule, see Section 10.1). A wash-out period of at least 4 days will be applied between the IMP administrations. Both doses contain 120 mg GS-248. The rationale for the dose is detailed in Section 8.3.

For Part I, subjects will come to the clinic for 4 visits. At Visit 2, subjects will be admitted to the clinic on the afternoon/evening of Day -1 and will remain at the clinic until Day 2 (24 h post dose) for single dose administration of Formulation A and PK and safety assessments. The subjects must fast for at least 10 hours 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 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. The subjects will return to the clinic on Day 3 (Visit 3) at 48 h post dose for PK blood sampling and safety assessments, as outlined in Table 8.1-1. Safety assessments include AE reporting, physical

examination, ECG, vital signs, body temperature, and blood sampling for analysis of safety laboratory parameters.

Visit 4 will be similar to Visit 2, at which subjects will stay overnight at the clinic from Day -1 to Day 2 for single dose administration of Formulation B and PK blood sampling and safety assessments. Visit 5 will be similar to Visit 3, at which subjects return to the clinic on Day 3 for PK blood sampling and safety assessments.

The schedule of events for Part I is shown in Table 8.1-1 and detailed for visit 2-7 in Table 8.1-2.

Study assessments are described in Section 11.

8.1.2 *Part II: Food interaction*

After evaluation of the PK profiles of Formulation A and B in Part I of the study, one formulation will be selected to be given following intake of a standardised breakfast in Part II of the study. In this part, any potential food interaction with GS-248 will be investigated.

After evaluation of the PK results from Part I, subjects will return to the clinic for a second dose of the selected formulation (Visit 6, similar to Visit 2), yet this time in fed conditions. The assessments during fed conditions will be the same as during fasting conditions (see Section 8.1.1), except for the fact that the subjects will consume a high-fat high-calorie breakfast 30 minutes prior to IMP administration as detailed in Section 10.5.

At 48 h post dose, subjects will return to the clinic for PK blood sampling and final end-of-study safety assessments (Visit 7).

The schedule of events for Part II is shown in Table 8.1-1 and detailed for visit 2-7 in Table 8.1-2.

Study assessments are described in Section 11.

Table 8.1-1 Schedule of events

Visit	**Refer to CSP section**	**Screening**	**Part I**						**Part II**	
			Formulation A		**Wash-out >4 days**	**Formulation B**		**Wash-out and PK calc >14 days**	**Formulation A or B fed**	
		Visit 1	**Visit 2[1]**	**Visit 3[1]**		**Visit 4[1]**	**Visit 5[1]**		**Visit 6[1]**	**Visit 7[1]**
			In-clinic			In-clinic			In-clinic	
Assessment		Day -28 to -1	Day -1 to 2	Day 3		Day -1 to 2	Day 3		Day -1 to 2	Day 3
Informed Consent	14.3	X								
Inclusion/exclusion criteria	9.4, 9.5	X	X[2]							
Demographics	11.2.3	X								
Medical/surgical history	11.2.5	X								
HIV, hepatitis B and C	11.2.7	X								
Alcohol breath test	11.2.10	X	X			X			X	
Weight/height (BMI)	11.2.4	X								X[3]
Pregnancy Test[4]	11.2.8	X	X			X			X	X
Urine Drug Screen[5]	11.2.9	X[5]	X	X		X	X		X	X
Physical Examination	11.4.2	X	X[6]			X[6]			X[6]	X
Laboratory Safety	11.4.6	X	X	X		X	X		X	X
Vital Signs	11.4.3	X	X	X		X	X		X	X
Body temperature	11.4.4		X	X		X	X		X	X
12-lead ECG	11.4.5	X	X	X		X	X		X	X
Baseline symptoms	11.2.11	X	X							
IMP administration	10.5		X			X			X	
PK blood sampling[7]	11.3.1		X	X		X	X		X	X
Breakfast (standardised)	10.5								X	
Other meals (standardised)[8]			X			X			X	
Prior/concomitant med.	11.2.6	---------- X ----------								
AEs[9]	11.4.1		---------- X ----------							

CSP = Clinical study protocol, HIV= human immunodeficiency virus, BMI = body mass index

1. Details in separate schedule (Table 8.1-2).
2. Eligibility check before IMP administration.
3. Only weight assessments.
4. Females only. At screening visit: plasma/serum tests; at other visits: urine test.
5. Drug tests may also be performed at 1 to 2 additional random occasions during the study.
6. Brief physical examination only
7. Timing of PK blood sampling is outlined in Table 8.1-2.
8. At visit 2, 4 and 6, standardised meals are served as outlined in Table 8.1-2.
9. From first administration of IMP.

Table 8.1-2 Detailed schedule of events for visit 2-7

Visit	**Refer to CSP section**		**Visit 2, 4, 6**														**Visit 3, 5, 7**
		Day -1	Day 1													Day 2	Day 3
Assessment	**Time[1]**		Pre-dose	00:00	00:15	00:30	01:00	01:30	02:00	03:00	04:00	06:00	08:00	12:00	16:00	24:00	48:00
Inclusion/exclusion criteria	9.4, 9.5		X[2]														
Alcohol breath test	11.2.10	X															
Weight/height (BMI)	11.2.4																X[3,4]
Pregnancy Test[5]	11.2.8	X															X[4]
Urine Drug Screen[6]	11.2.9	X															X
Physical Examination	11.4.2	X[7]															X[4]
Laboratory Safety	11.4.6	X															X
Vital Signs	11.4.3	X							X				X			X	X
Body temperature	11.4.4	X							X				X			X	X
12-lead ECG	11.4.5	X							X				X			X	X
Baseline symptoms	11.2.11	X[2]	X[2]														
IMP administration	10.5			X													
PK blood sampling[8]	11.3.1		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Breakfast (standardised)[9]	10.5		X[9]														
Other meals (standardised)[10]			X														
Prior/concomitant med.	11.2.6	---------- X ----------															
AEs	11.4.1			---------- X ----------													

1. Time is denoted in hh:mm. Time points reflect time in hours and minutes after IMP administration.

2. Only at Visit 2.
3. Only weight assessments.
4. Only at Visit 7 (end-of-study visit) or after early withdrawal.
5. Females only. Urine test.
6. Drug tests may also be performed at 1 to 2 additional random occasions during the study.
7. Brief physical examination only, may be performed on Day -1 or Day 1 pre-dose.
8. Actual time for PK sampling must not deviate more than ±10% from the planned time. The pre-dose sample may be taken within 60 minutes prior to dose. Refer to Section 11.3.1 for more information about timing of PK samples.
9. Standardised breakfast only at Visit 6, not at Visit 2 and 4. Breakfast should be served 30 min before IMP administration.
10. Standardised lunch, snack, dinner and evening snack at approximately 4, 7, 9 and 11 hours post breakfast.

8.2 Rationale for study design

The European Medicines Agency (EMA) guideline on strategies to identify and mitigate risks for FIH and early clinical trials with IMPs (EMEA/CHMP/SWP/28367/07 Rev. 1) has been considered.

The design of the study is based on the aim to study PK, safety and tolerability of two formulations of GS-248 in a limited number of healthy volunteers. The time points for PK blood sampling have been selected based on data obtained from pre-clinical studies and the FIH study (GS-1001).

A one-sequence design was chosen for the food interaction part of the study to yield a more efficient comparison of treatments than a parallel study design, *i.e.*, fewer subjects might be required since each subject will serve as his own control. To avoid carryover effects, a washout period of at least 4 days has been incorporated between the three treatment administrations. Interim analysis of the FIH study (GS-1001) revealed that none of the subjects receiving multiple doses of 180 mg GS-248 had plasma levels over 5% of C_{max} at 48 h after the last dose, which indicates that a 4-day wash-out period should be sufficient.

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 9.6.1, should be used during the study.

GS-248 is a low solubility compound with pH-dependent solubility. A high pH may decrease absorption and thus exposure. For this reason, use of antacids, proton pump inhibitors (PPIs) or any medication that changes gastric pH is not allowed from 14 days prior to IMP administration and until the end-of-study visit.

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 dose

A dose of 120 mg is selected to mimic the planned phase IIa study. Provisional data from the FIH phase I study (GS-1001) suggest that a dose of 120 mg is safe and tolerable.

8.4 Selection of formulation

After completion of Part I, PK data will be evaluated to determine which of the two formulations is to be used in Part II, the food interaction part. The selection will be based on PK parameters, *e.g.*, projected AUC and plasma level at the end of dosing intervals in repeated dose scenarios.

9 STUDY POPULATION

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

9.1 Recruitment

The subjects will be recruited from CTC's database of healthy volunteers and from advertising in media (including social media).

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 screen 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.

If a subject cannot receive the planned dose of IMP within four weeks after screening (*i.e.*, the time interval between signing informed consent until dose administration) the subject should be rescreened and assigned a new screening number before proceeding in the study.

9.3 Number of subjects

Approximately 20 healthy subjects will be screened to achieve a total of 14 dosed subjects, and at least 12 evaluable subjects. In the event of early withdrawals, subjects may be replaced.

9.4 Inclusion criteria

For inclusion in the study, subjects must fulfil the following criteria:

1. Willing and able to give written informed consent for participation in the study.
2. Healthy male or female subject aged ≥ 18 and ≤70 years.
3. Body Mass Index (BMI) ≥ 19.0 and ≤ 30.0 kg/m^2.
4. Clinically normal medical history, physical findings, vital signs, ECG and laboratory values at the time of screening, as judged by the Investigator.
5. Women of child bearing potential (WOCBP) must practice abstinence from heterosexual intercourse (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 [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. Female subjects must refrain from donating eggs from the date of dosing until 3 months after dosing with the IMP. Their male partner must agree to use a condom during the same time frame if he has not undergone vasectomy.

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 simultaneous blood sample with simultaneous detection of follicle stimulating hormone [FSH] 25-140 IE/L).

Male subjects must be willing to use condom, be vasectomised or practice abstinence from heterosexual intercourse (only allowed when this is the preferred and usual lifestyle of the subject) to prevent pregnancy and drug exposure of a partner. Male subjects must 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).

9.5 Exclusion criteria

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

1. Known allergy to GS-248.
2. Females who are breast feeding or who plan to become pregnant until 2 weeks after the end-of-study visit.
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. Regular use of corticosteroids (inhaled and systemic), NSAIDs, aspirin or coxibs, antacids, PPIs, or any other medication that changes gastric pH within 14 days of study drug administration.
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. Presence of inherited or acquired disorders of platelet function, bleeding or coagulation, as judged by the investigator.
7. History or presence of any clinically significant disease or disorder which, in the opinion of the Investigator, may either put the subject at risk because of participation in the study, or influence the results or the subject's ability to participate in the study.

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. Positive test for serum hepatitis B surface antigen (HBsAg), hepatitis C virus antibodies (HCVAb) or 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. Positive test for drugs of abuse or alcohol at screening or on admission to the unit prior to administration of the IMP.
12. Participation in other interventional studies within 3 months prior to administration of study drug.
13. Consumption of grapefruit, grapefruit juice, other grapefruit-containing products, or Seville oranges within 14 days of first IMP 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.
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, 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 three 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 and prior to IMP administration.
21. Plasma donation within one month of screening or blood donation (or corresponding blood loss) during three months prior to screening.
22. Investigator considers the subject unlikely to comply with study procedures, restrictions and requirements.
23. Estimated glomerular filtration rate (eGFR) < 50 mL/min/1.73 m^2 (determined by the revised Lund-Malmö GFR estimating equation).
24. Subjects with swallowing disorders, which may affect the subject´s capability to swallow the IMP.
25. Subjects who are vegetarian or for other reasons cannot eat the high-fat high-calorie breakfast.

9.6 Restrictions during the study

The subjects must be willing to comply to the following restrictions during the entire study duration *i.e.*, from screening to the end-of-study visit.

9.6.1 *General restrictions*

- Contraception Requirements:

  The male subjects are expected to use condom to prevent pregnancy and drug exposure of a partner and refrain from donating sperm from the date of first dosing until three months after last dosing of the IMP. Female partners of child-bearing potential are expected to use contraceptive methods with a failure rate of < 1% to prevent pregnancy (for details, refer to inclusion criterion No 5) during the same period.

  Female subjects of child-bearing potential must use effective contraception (defined in inclusion criterion No 5) or practice abstinence during the study and for 30 days after IMP administration. Female subjects must refrain from donating eggs from the date of dosing until 3 months after dosing with the IMP. Their male partner must agree to use a condom during the same time frame if he has not undergone vasectomy.

- Meals and Dietary Restrictions:

  Part I: Subjects should be fasting overnight (10 hours) before IMP administration and until 4 hours post dose. IMP will be swallowed together with 240 mL tap water.

  Part II: IMP will be administered within 30 minutes after intake of a standardised breakfast and swallowed together with 240 mL tap water.

  For details on IMP administration in the fasted and fed state, refer to Section 10.5.

  Part I and Part II: Standardised meals will be served while the study subjects are in the research clinic. Lunch will be served 4 hours post dose. Snack, dinner and evening snack will be served approximately 7, 9 and 11 hours post dose, respectively. Water is allowed ad libitum at the clinic except one hour before dose and one hour after dose on dosing days.

  Standardised meals: A menu option (decided by CTC) will be offered while the study subjects are in the research clinic. The meal selection is standardised in the sense that the nutritional content of the meals should be similar at each time point of each treatment day.

- Alcohol: Consumption of alcohol is not allowed within 48 hours prior to the screening visit and prior to and during all subsequent clinic visits, including the end-of-study visit.

- Drugs of abuse: Use of drugs of abuse is not allowed during the study from screening to the end-of-study visit. In addition to the urine drug testing described in Table 8.1-1, additional random testing can be performed at the clinic visits.

- Caffeine: Consumption of up to 5 cups of coffee (or equivalent) per day will be allowed from 48 h before each visit and during each visit.
- Xanthine or taurine containing products/beverages: Energy drinks (e.g. Red bull) are not allowed during the study from 48 h prior to first IMP administration until the end-of-study visit.
- Nicotine: Smoking or use of nicotine-containing products is not allowed during the study from screening until the end-of-study visit.
- Grapefruit and grapefruit containing products: Consumption of grapefruit and/or grapefruit-containing products, Seville oranges is not allowed during the study from screening until the end-of-study visit.
- Blood donation: The subjects must not donate blood or plasma during the study from first IMP administration until three months after the end-of-study visit.
- Participation in other clinical studies: Study subjects are not allowed to participate in any other interventional clinical study during the study period.
- Sun protection: Protection from the sun is required from day of IMP administration (Day 1) until 48 h post dose (Day 3) in each sequence. Study subjects are required to follow the recommendations given by Centres for Disease Control and Prevention (CDC, see [15]):
  - 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.
- Exercise: Subjects will abstain from strenuous exercise for 72 h before each blood collection for clinical laboratory tests.

9.6.2 *Prior and concomitant therapy*

Prohibited medication

Regular use of corticosteroids (inhaled and systemic), NSAIDs, aspirin, coxibs, antacids, PPIs or any other medication that changes gastric pH is prohibited from 14 days prior to first IMP administration until the end-of-study visit.

Use of corticosteroids (inhaled and systemic), NSAIDs, aspirin, coxibs, antacids, PPIs or any other medication that changes gastric pH, any other prescribed or non-prescribed medication, herbal remedies, vitamin supplements and minerals is prohibited from the first IMP administration until the end-of study visit, except as detailed below.

Allowed medication

- Paracetamol in doses up to 2000 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.
- Contraceptives.

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.

9.7 Screen failures

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

Subjects who do not meet the criteria for participation in this study may be rescreened.

Re-screening can be performed once if any of the following were reasons for screening failure or not-dosing (as judged by the Investigator):

- Practical reasons.
- Non-significant medical conditions (e.g. influenza, nasopharyngitis).
- 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.

9.8 Subject withdrawal

9.8.1 *General withdrawal criteria*

Subjects 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 may be discontinued from the study at any time at the discretion of the Investigator.

Reasons for discontinuation include:

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

- Pregnancy
- Death
- Meeting of an exclusion criterion during the study, which, in the opinion of the Investigator, may pose a risk for the subject

9.8.2 *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 msec
- Change from baseline: 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 value of the three ECGs used to determine whether the subject should be discontinued from the study.

9.8.3 *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 U.S. Food and Drug Administration (FDA) Guidance on Drug-Induced Liver Injury [16], 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.

9.8.4 *Procedures for discontinuation of a subject 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. Any ongoing AEs will be followed as described in Section 11.4.1.15. The following end-of-study safety assessments need to be performed in case of early withdrawal of a subject: weight, pregnancy test (females only), physical examination, laboratory safety, vital signs, 12-lead ECG.

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

9.8.5 *Subject replacement*

Subjects who are prematurely withdrawn from the study may be replaced during the course of the study.

10 TREATMENTS

10.1 Identity of investigational medicinal products

GS-248 is a selective inhibitor of mPGES-1, developed for the treatment of DUs secondary to SSc.

GS-248 is provided in two different solid formulations:

- Formulation A: a lipid-based formulation in size 1 capsules
- Formulation B: dry powder in size 1 capsules

Each capsule contains 40 mg GS-248.

Each single dose consists of 3 capsules, constituting a total of 120 mg GS-248 per IMP administration.

10.2 Manufacturing, packaging and labelling and release

GS-248 is manufactured, packaged, labelled and released by RISE, Research Institutes of Sweden, Södertälje, Sweden. Labels will comply with applicable Good Manufacturing Practice (GMP) requirements [17]. The IMP will be shipped to the research clinic (CTC) in bottles.

10.3 Conditions for storage

The IMP can be stored in room temperature (15-25^{o}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).

10.4 Preparation and accountability

The IMP will be administered by site personnel, *i.e.,* a registered nurse. The IMP, 3 capsules of 40 mg GS-248 (a total of 120 mg), will be given to the subject directly from the package. Two nurses/site staff will be present at IMP administration, one that provides the IMP to the subject, one that checks the procedure.

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, prepared for and used by each subject and study medication returned or destroyed at the end of the study. Any discrepancies between prepared and returned IMP must be explained and documented. Products deliberately and/or accidentally destroyed by the site or the subject must be accounted for.

10.5 Treatment administration

Part I - fasting conditions

Following an overnight fast of at least 10 hours, subjects will be administered the IMP (3 capsules containing 40 mg GS-248 each, constituting a total of 120 mg GS-248 per IMP administration) with 240 mL water. No food is allowed for at least 4 h post dose. Water, but no other drinks, is allowed as desired except for 1 h before and 1 h after IMP administration.

Part II - fed conditions

Following an overnight fast of at least 10 h, subjects will start a high-fat high-calorie breakfast 30 min prior to administration of the IMP (for details on the breakfast, see below). The subjects should eat this meal in 30 min or less, however, the IMP should be administered 30 min after start of the meal. The IMP (3 capsules) will be administered with 240 mL water. No food is allowed for at least 4 h post dose. Water, but no other drinks, is allowed as desired except for 1 h before and 1h after IMP administration (with the exception of the milk that is included in the breakfast, see below).

The high-fat, high-caloric breakfast will consist of the following (or equivalent): 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces hash brown potatoes (113 g) and 8 ounces (ca 240 mL) milk 3%. Substitutions in this meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity. The test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively.

10.6 Continuation of treatment with investigational medicinal product

This is a Phase I study in healthy volunteers who will have no medical benefit from the treatment and thus there will be no treatment with GS-248 after end of study participation.

10.7 Treatment compliance

All IMP will be administered at the research clinic under medical supervision to ensure compliance.

10.8 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 (Table 8.1-1 and Table 8.1-2).

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

1. Blood samples for PK
2. Resting 12-lead ECG
3. Vital signs
4. Safety laboratory samples

Time points for PK blood sampling, safety laboratory samples, 12-lead ECG and vital signs are outlined in Table 8.1-1 and Table 8.1-2.

Actual time for PK sampling and other assessments must not deviate more than ±10% from the planned time.

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 IMP administration. The criteria are specified in Sections 9.4 and 9.5.

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. BMI will be calculated in one decimal from the height and weight recorded.

For timing of the assessments, refer to Table 8.1-1 and Table 8.1-2.

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.

11.2.6 *Prior and concomitant medication*

Prior medications taken during the past two weeks will be obtained by subject interview in order to verify that the eligibility criteria are met (see also Section 9.6.2).

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, 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 screening until the last end-of-study visit must be documented appropriately in the subject's eCRF. Relevant information (*i.e.* name of medication, dose, unit, frequency, dose form, route, 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 HBsAg, HCVAb, and HIV prior to inclusion into the study. Any positive result will exclude the subject from participating in the study.

11.2.8 *Pregnancy test*

All females will do a pregnancy test at screening (blood/serum) and at visits specified in Table 8.1-1 and Table 8.1-2 (urine dipstick).

11.2.9 *Urine drug screen*

Urine will be screened for drugs of abuse at time points outlined in the schedule of events (Table 8.1-1 and Table 8.1-2) using the Alere™ Drug Screen Test Panel. Additional random tests can be performed during the study period.

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 and Table 8.1-2). 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 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

11.3.1 *Pharmacokinetic sampling and analysis*

Venous blood samples (approximately 4 mL) for the determination of plasma concentrations of GS-248 after administration of the IMP, will be collected through an indwelling venous catheter or by venepuncture at the pre-specified time-points (Table 8.1-2). Actual time for PK sampling must not deviate more than ±10% from the planned time.

Pre-dose sampling may be performed within 60 minutes prior to dosing.

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. 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 Lablytica Life Science AB, Uppsala, Sweden, by means of a validated bioanalytical method. The details of the analytical method used will be described in a separate bioanalytical report. For details on the PK parameters to be determined, refer to Section 17.5.1.

11.4 Assessments related to secondary endpoints

11.4.1 *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 the CTC standard operating procedures (SOPs) regarding emergencies and Phase I studies.

11.4.1.1 Definition of adverse event

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

11.4.1.2 Definition of serious adverse event

An SAE is any AE which:

- results in death
- is life-threatening (this refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might had led to death if the reaction was more severe)
- requires in-patient hospitalisation or prolongation of existing hospitalisation

- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (IME) (this refers to a reaction that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent any of the other outcomes defined above)

Examples of IMEs 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 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.

11.4.1.3 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.

11.4.1.4 Definition of serious adverse drug reaction

The term Serious Adverse Drug Reaction (SADR) is to be used whenever either the Investigator or Sponsor or designee assessed the SAE as at least possibly related to the IMP.

11.4.1.5 Definition of suspected unexpected serious adverse reaction

A suspected unexpected serious adverse reaction (SUSAR) is any SADR whose nature or intensity is not consistent with the current Reference Safety Information (RSI) in the IB or summary of product characteristics (SmPC) and therefore is assessed as unexpected.

11.4.1.6 Time period and frequency for collecting adverse events

All AEs (including SAEs) will be collected from the start of IMP administration until the end-of-study visit.

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

At the end-of-study visit, information on new AEs or SAEs, if any, and stop dates for ongoing events must be recorded as applicable.

Investigators are not obliged 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.

11.4.1.7 Assessment of intensity

The grading of the intensity of AEs will follow the common terminology criteria for adverse events (CTCAE) v5.0 [18]. 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 eCRF:

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 being bedridden.*

11.4.1.8 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.

11.4.1.9 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 has recovered completely, and no symptoms remain.
Recovering/resolving	The subject's condition is improving, but symptoms still remain.

Recovered/resolved with sequelae	The subject has recovered, but some symptoms remain (for example, the subject had a stroke and is functioning normally but has some motor impairment).
Not recovered/not resolved	The subject's condition has not improved and the symptoms are unchanged (for example, an atrial fibrillation has become chronic).
Fatal	
Unknown	

11.4.1.10 Reporting of action taken with study treatment

The Investigator must report the action taken with study treatment using the definitions below and record it on the AE Log of the eCRF:

Dose increased

Dose not changed

Dose rate reduced

Dose reduced

Drug interrupted

Drug withdrawn

Not applicable

Unknown

11.4.1.11 Collecting adverse events

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

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

11.4.1.12 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.

11.4.1.13 Reporting of serious adverse events

SAE reporting should be performed by the Investigator within 24 hours 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 within 24 hours of awareness.

If the SAE report in the eCRF is updated, a new e-mail alert will be sent.

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 manual completion of the paper SAE Form, provided in the Investigator Site File (ISF). The completed, signed and dated paper SAE Form should, within 24 hours, 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 competent authority (CA) and independent ethics committee (IEC) in accordance with local regulations.

11.4.1.14 Reporting of SUSARs to EudraVigilance, local CA and IEC

The term SADR is used whenever either the Investigator or Medical Monitor deems a SAE as possibly or probably related to IMP. If an SADR is assessed as unexpected by the Medical Monitor, 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 becomes aware of an SAE. 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 subjects.

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

11.4.1.15 Treatment and follow-up of adverse events

Subjects 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 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.

11.4.1.16 Procedures in case of pregnancy

In case of pregnancy or suspicion of possible pregnancy of a female subject, the study treatment of that subject 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 abortion, induced abortion, normal birth or congenital abnormality) must be followed up and documented even after the subject was discontinued from the study. The outcome of all pregnancies of a female partner to a male subject must also be followed up and documented, yet the male subject does not need to be discontinued from the study.

All events of congenital abnormalities/birth defects are SAEs. Spontaneous abortions 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.

11.4.1.17 Treatment of overdose

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

Over-dosing is not likely to occur in this study since all IMP will be administered by site personnel under medical surveillance. In cases of accidental overdose, standard supportive measures should be adopted as required.

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 medical records.

No known antidote is available.

11.4.2 ***Physical examination***

11.4.2.1 Full 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.

The result of the examination will be documented in the eCRF as normal, abnormal not clinically significant (NCS) or abnormal clinically significant (CS). Post-dose physical examination judged as abnormal CS will be reported as AE.

For timing of the assessments, refer to Table 8.1-1 and Table 8.1-2.

11.4.2.2 Brief physical examination

A 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 NCS or abnormal CS. Post-dose physical examination judged as abnormal CS will be reported as AE.

For timing of the assessments, refer to Table 8.1-1 and Table 8.1-2.

11.4.3 ***Vital signs***

Systolic and diastolic blood pressure (BP) and pulse will be measured in supine position after 10 minutes of rest.

Vital signs will be judged as normal, abnormal NCS or abnormal CS. The assessment will be recorded in the eCRF. Post-dose vital signs judged as abnormal CS will be reported as AEs.

For timing of the assessments, refer to Table 8.1-1 and Table 8.1-2.

11.4.4 ***Body temperature***

Body temperature will be measured orally using a digital thermometer, and will be judged as normal, abnormal NCS or abnormal CS.

For timing of the assessments, refer to Table 8.1-1 and Table 8.1-2.

11.4.5 *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 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 in the eCRF as NCS or CS. Abnormal post-dose findings assessed by the Investigator as CS will be reported as AEs.

For timing of the assessments, refer to Table 8.1-1 and Table 8.1-2.

11.4.6 *Laboratory safety assessments*

Blood samples for analysis of clinical chemistry and haematology 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.

Urine analysis will be performed at the research clinic using dip sticks. The assessments will be performed at visits specified in Table 8.1-1.

Urine pregnancy tests will be performed at visits specified in Table 8.1-1.

The safety laboratory parameters are defined in Table 11.4-1 and will be assessed at timepoints detailed in Table 8.1-1.

Safety laboratory parameters will be judged as normal, abnormal NCS or abnormal CS.

Abnormal values assessed by the Investigator as CS 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 11.4-1 Safety laboratory parameters

Category	Parameter
Clinical chemistry	Alanine aminotransferase (ALT)
	Albumin
	Alkaline phosphatase (ALP)
	Aspartate aminotransferase (AST)
	Bilirubin (total and conjugated)
	C-reactive protein (CRP)
	Calcium
	Creatinine
	Cystatin C
	Glucose
	Potassium
	Sodium
	Urea
Haematology	Haematocrit
	Haemoglobin (Hb)
	Platelet count
	Red blood cell (RBC) count
	White blood cell (WBC) count with differential count
Urinalysis (dip stick)	Bilirubin
	Erythrocytes
	Glucose
	Ketones
	Leucocytes
	Nitrite
	pH
	Protein
	Specific gravity
	Urobilinogen
FSH-test[2]	FSH
Pregnancy test[3]	Serum pregnancy test at screening
	Urine pregnancy test

[1] At screening only
[2] At screening, post-menopausal females only.
[3] Females only.

11.5 Appropriateness of measurements

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

12 PROCEDURES FOR BIOLOGICAL SAMPLES

12.1 Sample collection

The sample collection procedure for PK analysis is described in Section 11.3.1.

Safety laboratory samples are collected according to standard procedures.

12.2 Volume of blood

The estimated volume of blood to be collected from each subject during the study will be approximately 300 mL in Part I and Part II together. The anticipated volume of blood samples collected during the study from each subject will not exceed 450 mL (*i.e.*, less than 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 analyses of PK parameters will be stored at <-70°C until analysed. The samples will be disposed of after the CSR has been finalised.

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.

12.5 Withdrawal of informed consent for donated biological samples

If a subject 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 withdrawal of informed consent is notified immediately to Sponsor.
- Biological samples from the subject, 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 CSP 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 Council for Harmonisation (ICH) E6 R2.

Identified risks will be categorised separately from the CSP.

13.2 Quality assurance and quality control

The Sponsor is responsible for implementing and maintaining quality assurance (QA) and quality control (QC) 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 electronic data capture system and maintain SOPs for the whole life cycle of the system.

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

The Sponsor has delegated the responsibilities outlined above to CTC whilst maintaining overall study oversight.

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 [19] 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 subject information and ICF, any other written information to be provided to the subjects and any advertisements used for recruitment of subjects to applicable IEC for approval.

The Sponsor has delegated to CTC the responsibility to submit 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 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 information and consent

It is the responsibility of the Investigator or an authorised associate to give each potential study subject 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 may withdraw from participation at any time and for any reason, without any prejudice. All subjects will be given the opportunity to ask questions about the study and will be given sufficient time to consider participation before signing the ICF.

Before performing any study-related procedures the ICF must be signed and personally dated by the subject and by the Investigator. A copy of the subject information including the signed ICF will be provided to the subject.

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

The final approved version of the subject information and ICF must not be changed without approval from the Sponsor and the applicable IEC.

14.4 Subject information card

The subject will be provided with a Subject 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
- The name and phone number of the Investigator
- Name and address of the Sponsor

14.5 Subject 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 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. For further details on the subject information and ICF process, refer to Section 14.3.

The subject 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 Identification List which includes sufficient information to link records, i.e. the eCRF 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 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 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 enrolment 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 to whom study-specific duties are delegated.

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 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 at 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 enrolment, 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 medical history, that verifies the existence of the subject, the inclusion and exclusion criteria, and all records covering the subject'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 be enrolled.

15.5 Study timetable and end of study

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

A subject considered to have completed the study if he/she has completed all visits in the study including the End-of-Study visit.

The end of the clinical part of the study is defined as the last visit of the last subject participating in the study.

15.6 Termination of the study

The Investigator or the Sponsor may terminate this study prematurely for any reasonable cause. The IEC and CA should be informed promptly. Conditions that may warrant study termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study or potential study subjects; or
- A decision by the Sponsor to suspend or discontinue development of the IMP.
- If the CA obtains information that raises doubts about the safety or scientific validity of the clinical study, the CA can suspend or prohibit the study. Before the CA reaches its decision, it shall, except where there is imminent risk, ask the Sponsor and/or the Investigator for their opinion, to be delivered within one week (Directive 2001/20/EC, Article 12, Section 1).

If the study is prematurely terminated or suspended for any reason, the Investigator/institution should promptly inform the study subjects and should assure appropriate follow-up for the subjects.

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.

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 10 years after finalisation of the CSR. This includes any original

source documents related to the study, the Subject Identification List (providing the sole link between named subject source records and anonymous eCRF 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 TMF 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 ISF for archiving for 10 years after finalisation of the CSR.

The completed 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, 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 batch 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.

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 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 User ID and password; date and time stamps will be added automatically at time of electronic signature.

16.3 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 RBM plan. 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.

If corrections are needed, queries will be raised within the eCRF, either as a result of built-in edit checks or manually raised by the monitor. 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. The monitor will either approve the answer/correction or re-issue the query.

16.4 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.

16.5 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.

16.6 Medical coding

Medical coding will be performed by trained personnel at CTC. AEs and medical/surgical history verbatim terms will be 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 World Health Organisation (WHO) Anatomic Therapeutic Chemical (ATC) classification system. All coding will be approved by Sponsor prior to database lock.

16.7 Database lock

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

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 signed and approved prior to 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 last data collection point prior to each administration of IMP.

All hypothesis testing will use a significance level of 5%.

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.

Approximately 14 subjects will be dosed to achieve a total of at least 12 evaluable subjects that completed the study. Subjects will be evaluable for safety analysis after receiving 1 dose of the study drug.

17.3 Analysis data sets

17.3.1 *Safety analysis set*

The Safety Analysis Set will consist of all subjects who received at least one dose of the IMP.

17.3.2 *PK analysis set - formulation:*

The PK analysis set – formulation will consist of all subjects who received a single dose of both Formulation A and Formulation B, from whom PK blood samples were collected after IMP dosing, and for whom there were no AEs or protocol deviations judged to affect the analysis of the data.

17.3.3 ***PK analysis set – food interaction:***

The PK analysis set – food interaction will consist of all subjects who received all three IMP doses, from whom PK blood samples were collected after IMP dosing, and for whom there were no AEs or protocol deviations judged to affect the analysis of the data.

17.4 Description of study population

17.4.1 ***Demographics and baseline characteristics***

Descriptive statistics for demographics, weight and height will be presented.

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

Medical/surgical history will be presented by system organ class (SOC) and preferred term (PT). Prior/concomitant medications will be presented by ATC level 1, 3 and 5 as applicable.

All data will be listed by subject.

17.4.3 ***Treatment compliance***

The number of subjects treated in each treatment period and their individual dose will be listed.

17.5 Analysis of primary endpoints

17.5.1 ***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 NCA using the software Phoenix WinNonlin® version 8.1 or later (Certara, U.S.A.).

The NCA PK parameters to be assessed include, but are not limited to:

- $AUC_{0\text{-}inf}$
- $AUC_{0\text{-}last}$
- C_{max}
- T_{max}
- $T_{½(z)}$
- CL/F
- V_z/F
- Relative bioavailability for Formulation A versus B and for one of the two formulations in fed versus fasting conditions.
- Comparisons of all relevant PK parameters (*e.g.,* AUC, T_{max}, C_{max}) for Formulation A versus B and for one of the two formulations in fed versus fasting conditions.

Summary statistics for the PK parameters will be presented with number of measurements, arithmetic mean, SD, CV, median, minimum, maximum, geometric mean, geometric CV%, except for T_{max} for which only median, minimum and maximum will be presented.

The relative bioavailability of GS-248 will be analysed with a 90% confidence interval for the ratio of Formulation A and B, and for the ratio of the selected formulation in fed and fasting conditions using a mixed model approach with treatment, period and subject in the model.

Further details will be specified in the SAP.

All data will be listed by subject.

17.6 Analysis of secondary endpoints

17.6.1 *Adverse events*

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

Incidence of AEs and SAEs will be summarised by SOC and PT.

All AE data will be listed subject and include the verbatim term entered by the Investigator.

17.6.2 *Physical examination*

Clinically significant and non-clinically significant abnormal findings will be specified and presented by subject and summarised.

Changes over time will be presented using shift tables, if considered applicable.

All data will be listed by subject.

17.6.3 *Vital signs*

Vital signs (systolic/diastolic BP, pulse) will be summarised. Data will be presented with absolute and percent change from baseline at each visit. Clinical evaluation of vital signs will be summarised in frequency tables.

All data will be listed by subject.

17.6.4 *Body temperature*

Body temperature will be summarised. Data will be presented with absolute and percent change from baseline at each visit.

All data will be listed by subject.

17.6.5 *Resting 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 using frequency tables.

Changes over time will be presented using shift tables, if considered applicable.

All data will be listed by subject.

17.6.6 *Laboratory safety assessments*

Safety laboratory data will be summarised 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 subject.

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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

Name	Signature	Date
Helena Litorp		29 JAN 2020

CTC Uppsala
Site

19.2 Signature page (approval of the clinical study protocol)

Sponsor signatories

GÖRAN TORNLING		29JAN2020
Name	*Signature*	*Date*
Name	*Signature*	*Date*