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

Statistical Analysis Plan (SAP)

Sponsor:	Gesynta Pharma AB
Study Title:	A Phase II, randomized, multi-center, placebo-controlled, double-blind study to investigate the safety of GS-248, and efficacy on Raynaud's phenomenon (RP) and peripheral vascular blood flow, in subjects with systemic sclerosis (SSc)
Protocol Version/Date:	Final v5.0, 10-December-2021
SAP Version/Date:	Final Blinded SAP GS-2001 V2.0, 19-Jul-2022
Supersedes SAP Version:	Final 1.0
Appendices (external documents):	1. List of Tables, Listing, Figures (TLFs)

Approval

The Trial Statistician hereby confirms that the SAP was prepared in conformance with the procedures and principles set forth in the indicated protocol version and all established relevant guidelines.

Name **Affiliation, Function**	**Signature:**	**Date:**
Gonnie van Osta, Consultant/Ergomed Trial Statistician	DocuSigned by: Gonnie van Osta Signer Name: Gonnie van Osta Signing Reason: I approve this document Signing Time: 20-Jul-2022 | 10:42:34 AM BST ACA3E26607C74B70B98B7C4824F60601	

By signing hereafter, I confirm that this Statistical Analysis Plan adequately describes the statistical analyses to be performed in the context of this study.

Name **Affiliation, Function**	**Signature:**	**Date:**
Jan Kowalski, Gesynta Pharma AB	DocuSigned by: Signer Name: Jan Kowalski Signing Reason: Jag godkänner dokumentet Signing Time: 20-Jul-2022 | 2:46:22 PM BST 0180BFBDA70F495CB54A3CD001BB97E5	

Revision history

SAP Version	Version date	Reason(s) for change
0.1	23-Mar-2021	1st draft for sponsor review
0.2	7-Aug-2021	2nd draft for sponsor review
0.3	30-Sept-2021	3rd draft after discussion with sponsor
0.4	11-Oct-2021	4th version for sponsor review
0.5	15-Oct-2021	5th version for sponsor review
1.0	18-Oct-2021	Final version for sponsor sign-off
1.1	8-Jul-2022	Draft updated SAP prior to unblinding
2.0	19-Jul-2022	Final SAP prior to unblinding

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
ANCOVA	Analysis of Covariance
ASRAP	Assessment of Scleroderma-associated Raynaud's Phenomenon
ATC	Anatomic, Therapeutic, Chemical (Classification System for Drugs)
AUC	Area under the Curve
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
DDD	Distal Dorsal Difference
DMP	Data Management Plan
DRM	Data Review Meeting
DVP	Data Validation Plan
ECG	Electrocardiogram
FACS	Fluorescence-activated cell sorting
FAS	Full Analysis Set
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
LN	Natural Log
LSmeans	Least Squares Means
MCP	Multiple Comparisons Procedure
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	Missing not at random
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per-protocol
PPS	Per-protocol Set
PT	Preferred Term
RCS	Raynaud's Condition Score
RP	Raynaud's Phenomenon
SAE	Serious Adverse Event
SAS	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis Software Package
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SP	Statistical Programmer
SSC	Systemic sclerosis
TEAE	Treatment Emergent Adverse Event

TLFs	Tables, Listings, Figures
TS	Trial Statistician

Statistical Analysis Plan	Version 2.0		Page 8 of 9
Sponsor	Gesynta Pharma AB	Protocol No	GS-2001

1 STUDY INFORMATION

1.1 Primary objective

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

1.2 Secondary objective

Table 1.1: Study Objectives and Endpoints

Objectives	Endpoints
Secondary:	***Secondary:*** • Mean change from baseline to week 4 in peripheral blood flow prior to

Objectives	Endpoints
To determine the efficacy of GS-248 on peripheral vascular blood flow in subjects with SSc and RP.	cold challenge and IMP administration. • Mean change in peripheral blood flow from pre-IMP to post-IMP administration at Visit 2. • Mean change in recovery of peripheral blood flow after cold challenge from pre-IMP to post-IMP administration at Visit 2. • Mean change from baseline to week 4 in recovery of peripheral blood flow after cold challenge.

1.3 Exploratory objective

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

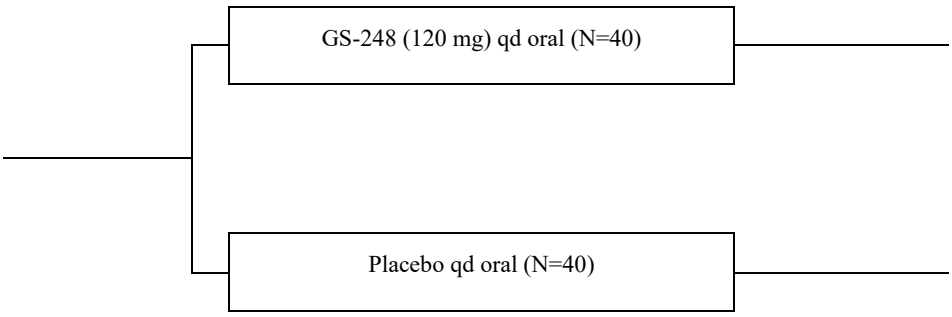
1.4 Study design

This is a randomised, double-blind, placebo-controlled study conducted in multiple sites in 4 countries in Europe. Approximately 80 subjects will be randomised in a 1:1 allocation to receive either GS-248 (120 mg) or placebo daily, stratified to any of the 3 strata of background

vasodilatory treatment (Ca-blockers, PDE-5 inhibitors or no background vasodilatory treatment), with approximately 40 subjects in each treatment group.

The study will comprise a run-in/enrolment period, a treatment period, and a follow-up period, with a total of 5 study visits.

Figure 1



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

Study assessments of thermography and pharmacodynamics will be conducted at preselected sites based on availability of technology.

The flowchart/schedule of events (several pages) can be found in Appendix 2-4 of the protocol.

1.5 Planned sample size

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

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

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

2 GENERAL INFORMATION

2.1 Background details

All study data will be transferred to a SAS database (version 9.4 or later) for statistical analysis purposes. Data will be imported from a Data Capture System Viedoc and External Data Vendors Lablytica Life Science, University of Manchester, Dr Del Galdo at Chapel Allerton Hospital and Medicover via validated SAS programs.

The SAP will be finalized before database lock and unblinding after agreement with the Sponsor on subject disposition and coding.

2.2 Deviations from the trial protocol with regard to statistical analyses

The following deviations from the protocol were identified as being important for the statistical analysis:

Definition of FAS population was changed to include all randomised and treated subjects. And the requirement to have eligible data at visit 4 was removed.

> Original text in protocol v4.0: The Full Analysis Set (FAS) includes all subjects who were randomized, received at least one dose of IMP and have evaluable data on the primary endpoint at visit 4.
>
> The revised definition in the SAP: The Full Analysis Set (FAS), consists of all subjects that were randomised and received at least one dose of IMP.

Definition of PK Analysis Set (PKAS) was changed to include GS-248 treated patients only:

> Original text in protocol v4.0: The PK Analysis Set (PKAS) consists of all subjects who received at least one dose of IMP within 30 hours before a blood sample for GS-248 bioanalysis was taken.
>
> The revised definition in the SAP: The PK Analysis Set (PKAS) consists of all subjects who received at least one dose of GS-248 within 30 hours before a blood sample for GS-248 bioanalysis was taken.

2.3 Individual protocol deviations

In the course of the study, all protocol deviations will be collected, and during a Blind Data Review Meeting (BDRM) with the sponsor, protocol deviations and the consequences regarding the analysis populations and statistical analysis will be assessed.

The following protocol deviations may affect the evaluation of subject data and will be considered for exclusion from the Per-Protocol analysis:

- Violation of inclusion/exclusion criteria
- Not receiving the medication to which the subject was randomized
- Use of prohibited concomitant medication
- Non-compliance with protocol procedures
- Less than 80% compliance with IMP intake

Any subjects or data values excluded from analysis will be identified, along with their reason for exclusion. A complete listing of documented and derived protocol deviations and the judgment for assessment of subject disposition (i.e. analysis population membership) will be signed before database lock.

3 ANALYSIS POPULATIONS

3.1 Screened Set

The Screened Set consists of all subjects that were screened for the study by signing the Informed Consent Document. Non-randomized subjects in the screened set, will be considered screening failures.

3.2 Randomized Set

The Randomized Set includes all subjects who were randomized.

3.3 Full Analysis Set

The Full Analysis Set (FAS) includes all subjects who were randomized and received at least one dose of the IMP.

3.4 Per-protocol Set

The Per-Protocol Set (PPS) includes all subjects of the FAS who had no major protocol deviations in a way that might affect the evaluation of the effect of the study drug(s) on the primary endpoint as determined during the BDRM.

3.5 Safety Analysis Set

The Safety Analysis Set (SAS) consists of all subjects who administered the IMP at least once.

3.6 PK Analysis Set

The PK Analysis Set (PKAS) consists of all subjects who received at least one dose of GS-248 within 30 hours before a blood sample for GS-248 bioanalysis was taken.

4 STATISTICAL ANALYSES

If not stated otherwise the following standard types of descriptive analyses will be presented:

- Descriptive statistics for continuous data
  Number of subjects, mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum.
- Descriptive statistics for categorical data
  Percentage bases (denominators) will be identified in the table title or footnote (i.e. all subjects at risk, all non-missing cases, all cases).
- Inferential statistics
  Unless otherwise stated, all statistical tests will be performed two-sided and at a type I error probability of α=0.05.
  Unless otherwise stated, all confidence intervals (CIs) will be derived two-sided and at a confidence probability of 1-α=0.95.

For exploratory endpoints nominal p-values for comparison between treatments using a will be presented.

- Listings
  All recorded data will be listed by subject ID, treatment group and stratification group.

4.1 Conventions

4.1.1 Baseline definition

The last non-missing measurement prior to first dose will serve as baseline for calculating changes from baseline. In practical terms this means that the general approach will use visit 2 data as the defined baseline and if that is missing, the visit 1 data will be used. For some data, e.g demographics, there is only a screening visit and this will be defined as the baseline visit in this case. Unscheduled visits will not be used as baseline visits.

4.1.2 Missing data

For the analyses of the primary endpoint and the key secondary endpoints on the FAS, missing data will be replaced using the placebo multiple imputation, (pMI) method. Details are described in the primary efficacy endpoint section. All other analyses will be performed on observed data only.

4.1.3 Study day definition

Study day will be calculated relative to the date of randomization i.e.

If Assessment date < Randomisation Date then;
Study day = Assessment Date – Randomisation Date

Else if Assessment date >= Randomisation Date then;
Study day= Assessment Date – Randomisation Date +1

4.1.4 Completion of study definition

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

4.1.5 End of Study definition

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

4.1.6 Window date

The Window date in Diary information is the actual date of the event

4.2 Demographic and other background data

Demographic, baseline and disease specific subject characteristics will be summarized in frequency or sampling statistics tables for the FAS and PP population. Tables will be split by treatment group and will show pooled groups as well.
The following variables will be summarized:

Demographics

- Age
- Sex
- Weight
- Height
- BMI (calculated)
- Country
- Centre
- Race
- Females only: childbearing potential (Yes/No)

Disease specific subject characteristics measured at screening/baseline only

- Stratification factors i.e. Background vasodilatory treatment
- Baseline Nailfold capillaroscopy (interpretation of vasculopathy of 8 fingers, density, width and presence of giant capillaries)
- Thyroid hormones (free T3/T4, tot T4, TSH)
- SSc-related antibodies

4.3 Disposition

The disposition of subjects, presenting the number of subjects, number and reasons for discontinuations will be tabulated by visit, treatment and overall, for the Screened set. A CONSORT flow diagram on subject disposition, will be created in the CSR.

The number and percentage of subjects completing study visits and either completing or discontinuing the study, showing the reason for terminations will be presented by treatment for the FAS and PP set.

By subject listings of disposition details for discontinued subjects and subjects completing the study will be provided. In addition, a by-subject listing of the randomisation scheme and codes will be provided.

Screen failure data will be listed.

4.4 Analysis Sets

The number/percentage of subjects in the various analysis sets will be presented by treatment, for the Randomized Set. Frequencies of different reasons for exclusions from the FAS and PP set will be presented for the Randomized set.

Analyses on the FAS population will be done according to the ‘as randomized’ principle, i.e., according to the treatment group subjects were randomised to even if they may have got incorrect treatment.
Analyses on the SAS and PK set will be done according to the ‘as treated’ principle.

A listing displaying the analysis set information (including reasons for exclusion from each analysis population) on a per subject level will be created, based on the outcome of the BDRM.

4.5 IMP exposure, compliance

The IMP extent of exposure (in days) will be derived as follows:

Duration of exposure (days)=Date of last dose-Date of first dose+1

Exposure duration is based on first and last IMP date, where the first IMP date was captured on Visit 2 Day 1 exposure eCRF page and last IMP intake was taken from discontinuation page (for early discontinuations) or Visit 4 exposure eCRF page.

Number of IMP intake days is defined as the number of days IMP was taken as recorded in the diary and eCRF. When diary information indicated two replies on IMP intake on a same window date (see definition of window date in section 4.1.6) the last information was used to determine IMP intake on that day.

IMP Compliance will be calculated as the ratio of the number of IMP intake days and the IMP extent of exposure (number of days IMP should have been taken).

Compliance with IMP is defined as IMP compliance ≥80%
Non-compliance with IMP is defined as IMP compliance <80%.

A summary of the IMP extent of exposure and cumulative exposure over time, Number of IMP intake days, IMP compliance, compliance/non-compliance will be presented per treatment group for the FAS.

A by subject listing of IMP intake, IMP extent of exposure, Number of IMP intake days, cumulative exposure and IMP compliance will be provided.

4.6 Medical history, physical examination

Medical history will be coded with the latest available version but not older than 23.1 Medical Dictionary for Regulatory Activities (MedDRA) and summarized by System Organ Class, Preferred Term, treatment group with counts and percentages for the FAS. A subject will only be counted once in a System Organ Class and a System Organ Class/Preferred Term combination.

All medical history and physical examination (full and abbreviated (digital ulcer statement)) data will be listed.

4.7 Prior and concomitant medication

Any medication taken at time of screening and all new medications taken by the subject during the study period are defined as ‘Concomitant’. Any changes of medications during the study period will also be recorded.

Prior and concomitant medications will be coded using the WHO Drug Global thesaurus in the version current at the time of study start. Coding will be performed by the CRO and agreed upon with the sponsor before data base lock. (cf. DMP). Prior and concomitant medication tables will show the frequencies of subjects by WHO Drug Global preferred term.

All details of concomitant medications will also be listed including the route, dose, frequency, start and stop date and indication.

Prior and concomitant medications will be analysed based on two periods:

1) Prior medications: medications that the subject started to take prior to Visit 1
2) Concomitant medications: medications that the subject take anytime on or after Visit 1 up to Visit 5

Where dates are missing or partially missing medications will be assumed to be concomitant unless there is clear evidence (through comparison of partial dates) to suggest that the medication started and stopped prior to Visit 1 or started after Visit 5.

The following summaries will be provided:

- A summary of the number and percentage of subjects who used any prior medication by ATC (level 3) and PT, by treatment group and overall
- A summary of prohibited concomitant medications during study period, ATC (level 3) and PT, by treatment group and overall
- A summary of all allowed concomitant medications during study period, ATC (level 3) and PT, by treatment group and overall

The identification of prohibited concomitant medications will be conducted as part of the medical review.

Multiple records for a subject in the same ATC level 3 category and PT will be counted only once in each summary.

5 EFFICACY

5.1 Primary endpoint: Mean change from baseline to week 4 in number of Raynaud's Phenomenon (RP) attacks

5.1.1 Diary: Number of RP attacks

RP attacks in the daily diary
RP attacks are captured in the diary. For each RP attack the date, start time, stop time and the experienced pain (scale of 0 (No pain) to 10 (worst imaginable pain)) is captured. If an RP attack continues into the next day, the RP attack is counted on the date the attack started.

In addition to the daily entry of RP attacks in the diary, the diary is organized in such a way that patients are asked, through the previous attack details form, whether they had any RP attacks on the previous day:

- Did you have any attacks yesterday (CEPERF=Yes/No)
- Did you record them all in the diary (CECONF=Yes/No)

The replies to these questions are used for the interpretation of the RP attacks recorded in the diary in the following way:

If the patient answers (CEPERF=No) or the patient answers (CEPERF=Yes and CECONF=Yes), it is assumed that RP attacks on the previous day are recorded as instructed.

If the patient confirms both questions (CEPERF=Yes and CECONF=Yes), it is assumed that RP attacks on the previous day are recorded as instructed.

If the patient answers CEPERF=Yes and CECONF=No, and any RP attacks are recorded on the previous day, it is assumed that RP attacks on the previous day are recorded as instructed.

If the patient answers CEPERF=Yes and CECONF=No, and no RP attacks are recorded on the previous day, it is assumed the RP attacks on the previous day are confirmed missing.

Missing value imputation to come to number of RP attacks in the 7 days preceding a visit
For each day, starting during the baseline diary week, the number of recorded RP attacks as defined above and the number of days with confirmed RP attack information, are counted.

For the baseline week and for week 4 the number of daily attacks in the 7 most recent days before a visit (Day 1 and Day 28 (-2/+1)), will be derived by calculating the mean number of daily RP attacks on the days with RP attack information in the 7 most recent days and subsequently imputing this mean on the days with confirmed missing RP attack information in the 7 most recent days in the following way:

1) Summing the number of confirmed RP attacks in the 7 most recent days before a visit (total number of confirmed RP attacks)
2) Dividing this sum by the number of days with confirmed RP attack information in the 7 most recent days before a visit (=mean daily number of confirmed RP attacks)
3) Multiplying this mean number of daily attacks with 7.

This derivation results in the number of RP attacks in a week.

5.1.2 Derivation of the mean change from baseline to week 4 number of RP attacks
The primary endpoint for this study is the mean change from baseline to week 4 in the number of Raynaud's Phenomenon attacks per week as derived in 5.1.1 i.e., number of RP attacks in week 4 minus the number of RP attacks during the baseline week, where a decrease change in the number of RP attacks at week 4 compared to baseline indicates an improvement compared to baseline

5.1.3 Missing value imputation of primary endpoint
Missing value imputation for the primary endpoint, i.e. the number of RP attacks in a week prior to the week 4 visit (i.e for patients missing a week 4 diary due to early discontinuation or a lost diary) will be done as follows:

Placebo multiple imputation assumes that the statistical behaviour of drug- and placebo-treated patients after discontinuing study medication becomes that of placebo-treated patients. Multiple imputations (MIs) are used to replace missing change from baseline at week 4 outcomes for drug- and placebo-treated patients who discontinued utilizing multiple draws from the posterior predictive distribution estimated from the placebo arm, based on the ANCOVA

(Analysis of Covariance) model including the stratification factor (vasodilatory treatment i.e., Ca-blockers, PDE-5 inhibitors, or no background vasodilatory treatment) and treatment as fixed factors and baseline levels as a covariate in the model.

The final inference on treatment difference is conducted from the multiple datasets using Rubin's combining rules as implement in SAS PROC MI ANALYSE. Thus, in the effectiveness context, pMI assumes no pharmacological benefit of the drug after dropout. In the efficacy context, pMI is a specific form of a missing-not-at-random (MNAR) analysis expected to yield a conservative estimate of efficacy.

This process will be performed for both the FAS and PP set.

5.1.4 Descriptive statistics

Descriptive statistics will be presented for the number of RP attacks by visit and mean change between visit 4 and baseline, using observed data only.
The analysis of the primary endpoint will be performed using analysis of covariance, ANCOVA), including the stratification factor (vasodilatory treatment i.e., Ca-blockers, PDE-5 inhibitors, or no background vasodilatory treatment) and treatment as fixed factors and baseline levels as a covariate in the model.

5.1.5 Statistical inference on Mean change in number of RP attacks

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

Mean change in the number of RP attacks from baseline to week 4 will be tested using the following:

$\mu 1$ = mean change in active treatment group
$\mu 2$ = mean change in placebo group

The following hypothesis is set for $\mu 1$ and $\mu 2$:

H_0 : $\mu 1 = \mu 2$
H_a : $\mu 1 \neq \mu 2$

The primary objective will be met if there is a p-value <0.05 with a numerical superior efficacy of the active group versus placebo with regard to the primary endpoint, i.e. the mean change (reduction) in RP attacks that is greater in the active group.

Results for the outcome of the primary endpoint will be presented for the least square means estimates and accompanying 95% CIs.

Analysis will be done on the FAS and PP population. The primary analysis population is the FAS.

5.1.6 Robustness

Residuals will be used to assess the adequacy of the ANCOVA model and to detect outliers and influential points.

As a exploratory analysis, analysis will be done on the observed cases only, i.e., with no imputation

5.2 Key Secondary endpoints

If the primary efficacy endpoint achieves superiority, $p<0.05$, formal statistical testing of the secondary efficacy endpoints will be performed using a closed testing procedure:

The overall type I family-wise error rate for testing the primary and the key secondary efficacy endpoints will be controlled at the 0.05 significance level using the following 2-family serial gatekeeping multiple comparisons procedure (MCP). Following this MCP, progression to the next family will only occur if the null hypothesis with-in the current family is rejected at a family-specific overall significance level. If the null hypothesis within a family is not rejected, the statistical tests corresponding to all subsequent families will be considered not statistically significant. All hypothesis tests will be 2-sided.

1. The first family will include the primary endpoint: The p-value for the null hypotheses must be less than 0.05 to be considered to have met the primary efficacy objective. If the primary efficacy null hypotheses is not rejected (i.e., p-value >0.05), all subsequent statistical tests, i.e. on key secondary and will not be considered statistically significant.

2. The second family will include the key secondary endpoints (see below) and they will be tested using an over-all type I error rate of 0.05 by means of a hierarchical procedure in order to control for multiplicity within this family. The hierarchical order to test the key secondary variables will be the following:

Due to the closed testing procedure, no correction for multiplicity is necessary. If superiority cannot be shown, the secondary endpoints will be presented using descriptive statistics, per treatment, and nominal p-values.

The secondary endpoints will be analysed using the following hierarchical test order:

1) Pain
2) Raynaud's Condition Score
3) Duration of RP attacks

5.2.1 Mean change from baseline to week 4 in pain experienced during RP attacks

For each RP attack the pain experienced during the RP attack is scored rating from 0 (No pain) to 10 (Worst imaginable pain).

For the baseline week and for week 4 the individual mean pain scores of the RP attacks in the 7 most recent days before a Visit (Visit 2 and Visit 4), will be derived by calculating the sum of individual pain scores of each RP attack in the 7 most recent days before the Visit divided by the number of RP attacks in the same period.

Change in mean daily pain will be calculated as the mean of the individual mean pain score at Visit 4 minus the individual mean pain score at Visit 2.

If there are no attacks in a week, the pain score has no eligible values and in the calculations, it will be set to missing.

The analysis of the mean daily pain experienced during RP attacks endpoint will be similar to the analysis of the primary endpoint

5.2.2 Mean change from baseline to week 4 in the Raynaud's Condition Score (RCS)

Each day, at bedtime the RCS, rating how much difficulty the subject had with their Raynaud's that day on a scale from 0 (No difficulty) to 10 (Extreme difficulty). Blinded diary data review showed that patients could enter more than 1 RCS score on a day. Daily RCS scores are identified in the diary database through the window date. If more than 1 RCS score was entered with the same window date, the last entry (identified either by the event time or by the visit, was used as the daily RCS score for that date. The other entry on that date is kept in the raw data-sets, but not used in the derivation of the daily RCS score.

Derivation of mean RCS score in 7 days preceding a visit
The mean RCS score in the 7 days preceding a visit is defined as the mean of the non-missing RCS scores of 7 most recent days prior to the visit.

Change in mean RCS score will be calculated as the mean of the individual mean RCS score at visit 4 minus the mean of the individual mean RCS score at baseline.

The analysis of the Raynaud's Condition Score endpoint will be similar to the analysis of the primary endpoint.

5.2.3 Mean change from baseline to week 4 in the cumulative and mean duration of RP attacks

For each RP attack the duration can be derived from the start and stop time points.

The cumulative RP attack duration is defined as follows:

1) Determine the sum of confirmed RP attacks duration on the 7 most recent days with confirmed RP attack information prior to a visit.
2) Determine the mean RP attack duration by dividing the sum of confirmed RP attack duration by the number of confirmed RP attacks.
3) Multiply the mean RP attack duration of confirmed RP attacks with the number of RP attacks (including imputations) as derived in 5.1.1 to come to the cumulative RP attack duration.

Blinded Diary review showed that for RP attack duration, some patients entered a stop date/time of an RP attack that was before the start date/time of the RP attack. For these entries the following rules will be applied:

- For the overlapping events – the latest entered event of the overlapping ones (using SEQ no. in the database) will be used. The other entry will not be used in any attack reporting (RPA, Pain, duration i.e. not be counted at all). The information will be kept in the raw data-sets.
- If stop time was before start time – duration will be set to missing, but attacks will as be counted as confirmed attacks in RPA and Pain derivations

- If recall period > 1 day this will be a minor protocol deviation, recalled data will not be excluded from the analysis.

Blinded review of the derived cumulative and mean RP attack duration as derived of the 7 most recent days prior to a visit showed that the derived values have a skewed distribution. For that reason, the evaluation of cumulative RP attack duration and mean RP attack duration will be done on natural log scale.

For each patient change in log-transformed cumulated RP attack duration and log-transformed mean RP attack duration will be derived as follows:

- Change =LN(cumulative RP attack duration prior to week 4 visit) – LN(cumulative RP attack duration prior to baseline visit)
- Change=LN(mean RP attack duration prior to week 4 visit) - LN(mean RP attack duration prior to baseline visit)

The analysis of the mean change in LN(cumulative duration of RP attacks) and mean change in LN (mean RP attack duration) will be similar to the analysis of the primary endpoint.

Descriptive statistics will be provided for the cumulative RP durations and mean RP attack durations on both the absolute and the log-transformed scales. After summarizing the log-transformed values, the back-transformed values of the descriptive statistics of the log-transformed values and of the descriptives of the changes on log-scale will be created for these parameters at baseline visit and week 4 visit.

5.3 Exploratory objectives and endpoints

5.3.1 Patient Global Impression of Change at week 4.

Patient Global Impression of Change at week 4 will be presented for the number and percentage of subjects providing the categorized week 4 responses for each treatment group.

The statistical analysis will consist of a Cochran-Mantel-Haenszel analysis comparing treatment groups adjusting for the stratification factor.

5.3.2 Physician Global Impression of Change at week 4.

Physician Global Impression of Change at week 4 will be presented for the number and percentage of subjects providing the categorized week 4 responses for each treatment group.

The statistical analysis will consist of a Cochran-Mantel-Haenszel analysis comparing treatment groups adjusting for the stratification factor.

5.3.3 Mean change in ASRAP Questionnaire score from baseline to week 4

The ASRAP questionnaire score (reporting on the past 7 days) results for each patient in the ASRAP total score, the sum of all items scores.

The analysis of the Mean ASRAP Questionnaire total score will be similar to the analysis of the primary efficacy endpoint using observed data.

Descriptive statistics of the observed cases and mean change from baseline will be created for the ASRAP Questionnaire total score at baseline, week 2, week 4 and at follow-up.

5.3.4 Mean change from baseline to week 4 in peripheral blood flow prior to cold challenge and IMP administration

The following parameters for peripheral blood flow prior to cold challenge are defined:

- Mean temperature of all eight fingers prior to cold challenge (MTEMPALL)
- Mean Distal Dorsal Difference (DDD) of all eight fingers prior to cold challenge (MDDDF)

Descriptive statistics of the observed cases and change from baseline will be created for these parameters at baseline (first assessment at visit 2, t<0) and week 4 (t=-5 min).

The analysis of the peripheral blood flow will be similar to the analysis of the primary efficacy endpoint using observed data.

5.3.5 Mean change in peripheral blood flow from pre-IMP to post-IMP administration at Visit 2

The following parameters for peripheral blood flow from pre-IMP to post-IMP administration are defined:

- Mean temperature of all eight finger after IMP administration but prior to cold challenge at visit 2 (MTEMPALL)
- Mean DDD of all eight fingers after IMP administration but prior to cold challenge at visit 2 (MDDDF)

Descriptive statistics of the observed cases and change from baseline will be created for these parameters at pre-IMP (Baseline, Session 1, t=80 to 120 min) and post-IMP (Session 2, t=0 to 150 min).

The analysis of the peripheral blood flow will be similar to the analysis of the primary efficacy endpoint using observed data.

5.3.6 Mean change in recovery of peripheral blood flow after cold challenge from pre-IMP to post-IMP administration at Visit 2

The following parameters for recovery of peripheral blood flow after cold challenge from pre-IMP to post-IMP administration are defined:

- Recovery of peripheral blood flow, in terms of mean LN(AUC temp at all eight fingers after cold challenge and after IMP administration) at Visit 2. (Session 2, LN(MAUC8))
- Mean LN(maximum temperature of all eight fingers after cold challenge and after IMP administration) at Visit 2. (Session 2, LN(MMAX8))

After summarizing the log-transformed values, the back-transformed values of the descriptive statistics of the log-transformed values and of the descriptives of the changes on log-scale will be created for these parameters at pre-IMP (Baseline, Session 1) and post-IMP (Session 2).

The analysis of the peripheral blood flow will be similar to the analysis of the primary efficacy endpoint using observed data.

5.3.7 Mean change from baseline to week 4 in recovery of peripheral blood flow after cold challenge.

The following parameters for recovery of peripheral blood flow after cold challenge are defined:

- Recovery of peripheral blood flow, in terms of mean LN(AUC temp all eight fingers after cold challenge) at visit 4.
- Mean LN(maximum temperature of all eight fingers after cold challenge) at Visit 4.

After summarizing the log-transformed values, the back-transformed values of the descriptive statistics of the log-transformed values and of the descriptives of the changes on log-scale will be created for these parameters at pre-IMP (Baseline, Session 1) and post-IMP (Visit 4).

The analysis of the peripheral blood flow will be similar to the analysis of the primary efficacy endpoint using observed data.

5.3.8 Mean change of maximum daily pain score for RP attacks

For each RP attack the pain experienced during the RP attack is scored rating from 0 (No pain) to 10 (Worst imaginable pain).

For the baseline week and for week 4 the mean maximum daily pain score over the 7 most recent days before a visit (Day 1 and Day 28 (-2/+1)), will be derived by calculating the mean maximum daily pain score on the days with RP attack information in the 7 most recent days.

Mean change of maximum daily pain scores between week 4 and baseline is derived as the mean of individual differences of week 4 maximum daily pain minus baseline maximum daily pain.

5.4 Subgroup analysis

Subgroups are defined by “use of background vasodilatory treatment” stratification factors:

- Ca-blockers
- PDE-5 inhibitors
- No background vasodilatory treatment

Descriptive statistics of primary and key secondary endpoints will be created for these 3 subgroups.

6 PHARMACOKINETIC ENDPOINTS ANALYSIS

The pharmacokinetic endpoints analysis of GS-248 will be described later in an amended version of the SAP.

7 PHARMACODYNAMIC ANALYSIS

7.1.1 Percentage change in PGE_2 level in whole blood ex vivo from baseline to week 4.

PGE_2 levels are measured in a subgroup at pre-selected sites. The endpoint is the percentage change from baseline at week 4.

No modelling will be done.

Descriptive statistics of the observed cases will be created for these parameters at baseline, week 4, change from baseline and percentage change from baseline at visit 4.

A by-treatment boxplot will be created for the percentage change from baseline at week 4.

7.1.2 Percentage change in levels of PGEM, PGIM and TXM (AA-metabolites) in urine from baseline to week 4.

Results for AA_metabolites will be corrected for urinary creatinine concentration in the following way:

Urinary creatinine is measured in mg/dL, this results in the following formula for the AA_metabolite in ng/mg:

AA_metabolite concentration in ng/mg=(100*AA-metabolite analyte concentration in ng/ml)/(Creatinine concentration in mg/dL).

The endpoint is the percentage change from baseline at week 4 of the AA_metabolite.

Descriptive statistics will be created for the observed cases of AA metabolites expressed in ng/mg) at baseline, week 4, change from baseline (in ng/mg) and for percentage change from baseline at week 4.

A by-treatment boxplot will be created for the percentage change from baseline at week 4.

7.1.3 Percentage change in levels of biomarkers in blood/plasma from baseline to week 4.

The following biomarkers for inflammation and endothelium dysfunction are predefined:

- hsCRP
- Endothelin-1
- sE-selectin
- xICAMI
- TNF
- IL-lb
- IL-4
- IL-6
- IL-10
- s-PECAMI CXCL-4

- CD40L
- von Willebrand factor

The endpoint for these parameters is the percentage change from baseline at week 4.

Descriptive statistics of will be created for the observed cases of biomarkers at baseline, week 4, change from baseline and for percentage change from baseline at week 4.

A by-treatment boxplot will be created for the percentage change from baseline at week 4.

7.1.4 Expression of platelet surface markers.

The FACS (Fluorescence-activated cell sorting) at pre-selected sites was cancelled by the sponsor. Available FACS data gathered prior to the cancellation will be listed.

7.1.5 Change in microvascular volume from baseline to week 4 (D-OCT)

Microvascular volume (plexus depth, vessel diameter, vessel density microvascular volume) is measured in a subgroup at one pre-selected site.

No modelling will be done.

Descriptive statistics of the observed cases will be created for the microvascular volume at baseline, visit 4 and change from baseline at week 4.

8 SAFETY

The Safety Analysis Set (SAS) will be used for the analysis of safety data.

8.1 Adverse events

All AEs occurring during the course of the study will be coded using the latest MedDRA coding dictionary at the time of DBL. All AEs (serious and non-serious) reported from the first day of study treatment up until and including 7 days after the last dose of study treatment will be considered treatment emergent AEs (TEAEs).

Where dates are missing or partially missing, AEs will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the AE started prior to the first dose of study treatment or more than 7 days after the last dose of study treatment.

Verbatim terms will be coded by Ergomed and all relevant codes will be stored in the database. It is assumed that for each change in intensity, relationship or seriousness of an AE a new entry of the AE was recorded in the data capture database; hence such cases will be analysed like different phases of the same AE.

Subjects experiencing more than one AE within a given SOC category will be counted only once when calculating the number and percentage of subjects experiencing that SOC (e.g., a subject that experiences both nausea and vomiting will only be counted once in such calculations for the SOC gastrointestinal disorders). Similarly, subjects experiencing the same AE

multiple times throughout the course of the trial will be counted only once when calculating the number and percentage of subjects experiencing that PT (e.g., a subject that experiences mild nausea in both the first and fourth treatment cycle will only be counted once in such calculations for mild nausea). If a PT is reported at more than one severity level for a given subject, the greatest severity will be presented in the summary table.

If the same PT is reported multiple times for a given subject, but with varying study drug relationship assignment, the worst-case attribution will be presented in the summary table.

An AE is considered drug-related if the relationship to study drug is classified as either 'Possible' or 'Probable'.

The following AE summaries will be provided:

- An AE overview table will be created displaying the number of TEAEs, number/percentage of subjects experiencing any TEAE, deaths, any SAE, any TEAEs causing discontinuation, any severe TEAE and any drug-related TEAE per treatment group.
- A summary of the number of events (TEAEs) by treatment group, SOC and PT
- A summary of the number and percentage of subjects reporting a TEAE by treatment group, SOC and PT
- A summary of the number of TEAEs by treatment group, intensity and PT
- A summary of the number and percentage of subjects reporting a TEAE by treatment group, intensity and PT
- A summary of the number and percentage of subjects reporting a TEAE by treatment group, relationship and PT
- A summary of the number of subjects reporting a TEAE with a frequency of ≥2% by treatment group and PT
- A summary of the number and percentage of subjects reporting a non-serious adverse event occuring in greater than 5% of subjects by treatment group, SOC and PT

TEAE summaries will be ordered in terms of international order of SOC, and alphabetically for PT within SOC.

For the summary of TEAE with a frequency of ≥2% TEAEs will be ordered by decreasing frequency.

For each subject and each AE, the worst intensity recorded will be attributed and used in the by-intensity summaries. Similarly, the worst relationship will be attributed and used in the by-relationship summaries.

All adverse events (i.e. TEAEs as well as non-treatment emergent events) will be listed in section 16.2 of the CSR. However, only TEAEs will be summarized in the tables.

AE listings will be presented by treatment group and will include: subject identifier, treatment, age, sex, race, AE (PT and verbatim term), study day of onset, duration, intensity, seriousness, action taken, relationship, outcome and concomitant medication given (incluing CM number).

8.2 Deaths, serious adverse events and other significant adverse events

TEAEs will be included in the summary tables below.

The following AE summaries will be provided on deaths, SAEs and other significant adverse events:

- A summary of the number and percentage of subjects reporting a TEAE with outcome of death by treatment group, SOC and PT
- A summary of key subject information for subjects reporting TEAE with outcome of death
- A summary of the number of SAEs reported by treatment group, SOC and PT
- A summary of the number and percentage of subjects reporting a SAE by treatment group, SOC and PT
- A summary of key subject information for subjects reporting a SAE
- A listing and summary of subjects reporting COVID-19 infection as recorded as an AE

Detailed listings of all fatal and other serious events will be provided (for section 14.3.2). Narratives will not be included in section 14.3.3 but will be provided by medical writing in section 12.3.2 of the CSR.

8.3 Vital signs

For the vital signs safety analysis, data from Visit 2 onwards will be used only.

Vital signs parameters (systolic/diastolic blood pressure, heart rate, body weight) will be assessed at each of the visits as per schedule of assessment.

The following summaries will be provided:

- A summary of the observed absolute values and change from baseline in each vital sign parameter by treatment group and time point.

Any clinically relevant vital signs measurement was to be recorded as an AE and will be presented with the AEs.

By-subject listings of vital signs (including screening data) will also be provided.

8.4 ECG

ECGs are scheduled at the following visits/time-points:

Visit/Time	ECG schedule
Visit 1/Screening	Triple ECG ECG result summary

Visit 2/Day 1, prior to dosing	Triple ECG ECG result summary
Visit 2/Day 1, 170 min post-IMP administration	Triple ECG ECG result summary
Visit 3/Day 15	Triple ECG ECG result summary
Visit 5/Follow-up (and/or early termination)	Triple ECG ECG result summary

For the ECG safety analysis, data from Visit 2 onwards will be used only.

The following ECG parameters are captured:

- RR interval
- PR interval
- QRS interval
- QT interval
- QTc interval
- QTcF interval
- Mean QTcF interval
- ECG normality/abnormality evaluation

8.4.1 Descriptive statistics

The triple ECG parameter results will be averaged per assessment (visit 2 (pre-dose, baseline), visit 2 (170 min post dose), 3 and 5).

For the derivation of change from baseline, the mean of the triple ECG pre-dose measurement on visit 2/Day 1 will be used as the baseline value.

The following summaries will be provided:

- Descriptive statistics of the mean absolute values and change from baseline of the mean values for each ECG parameter by treatment group and time point for visit 2 (pre-dose, baseline), visit 2 (post-dose), visit 3 and visit 5.

8.4.2 QTc prolongation

Evaluation of QTc prolongation will be based on the mean QTcF interval parameter as captured in the eCRF.
QTcF Frequencies will be calculated for following classified values and changes (according to ICH E14):

- Absolute values: $\leq$450 ms as normal, >450-480 ms, >480-500 ms, >500 ms
- Changes from baseline: decreases or increases $\leq$30 as normal, increases >30-60 ms, increases >60 ms.

8.4.3 ECG categorical data

For the evaluation of ECG categorical data the result at the visit 2, pre-dose will be used as the baseline value.

The 12-lead ECG categorical data, will be summarized by treatment group using a shift table from baseline to each subsequent assessment time point and categories of normal, abnormal NCS, and abnormal CS.

8.4.4 Listings

Screening ECG data will be included in the listings only.
By-subject listings of ECG results (original, mean of triple measurements and ECG abnormalities) will be provided.

8.5 Laboratory variables

The following routine laboratory safety data are collected through the Central Laboratory:

Clinical chemistry	Haematology	Urinalysis
Albumin Sodium Potassium Calcium, total Glucose C-reactive protein (P-CRP) Bilirubin, total Bilirubin - conjugated Uric acid ASAT ALAT Cholesterol Cystatin C Creatinine eGFR Osmolality Urea or BUN ALP GT LDH Electrophoresis pro-BNP	Haemoglobin Erythrocyte count Ery-Mean Corpuscular Volume Haematocrit (Erythrocyte volume fraction) Platelet count (Thrombocyte particle concentration) Leukocyte count (LPC) Leukocyte differential, absolute count (lymphocytes, monocytes, neutrophil-, eosinophil- and basophil- granulocytes)	pH Glucose Ketone Bilirubin Blood Creatinine WOCBP pregnancy test Drug screen

For the safety laboratory analysis, data from Visit 2 onwards will be used only.

8.5.1 **Continuous laboratory data:**

- Continuous data laboratory safety data (original values and change from baseline) will be summarized using descriptive statistics per visit and treatment group.
- Frequencies of high and low values with respect to the normal range will be displayed by visit and treatment group
- Shift tables comparing each post-baseline visit with baseline with respect to normal range will be displayed by treatment group.

- In addition, abnormal values outside reference ranges will be summarized in a listing per visit and per subject.

8.5.2 Qualitative laboratory data:

For qualitative laboratory safety data ordered frequency tables will be prepared per visit and treatment group.
Frequencies of shift comparing each post-baseline visit with baseline will be displayed by treatment group.

8.6 Interim analyses

There is no interim analysis planned for this study.

9 QUALITY CONTROL

The SAP was prepared by the TS. Particularly the TS has checked the consistency of the described methods and outputs with the actual version of the study protocol. In addition, a sponsor representative has reviewed the SAP before final approval.

Log files of all SAS® programs used in the analysis will be checked for errors, warnings and suspicious notes by the statistical programmer. All findings will be either eliminated or commented upon. The final version of each program will be stored along with its log file in the electronic archive.

All programs will be validated by the program author or an independent statistical programmer depending on the requested validation level selected in the List of TLFs form (FRM/BS/001.02) for a particular program.

The agreement of the program outputs with the SAP, their consistency and plausibility will be checked by the TS. Moreover, the TS will review the outputs regarding completeness, readability and comprehensibility.

The described process is associated with the 'normal' level of program validation. Additional levels of quality control can be specified in the List of TLFs (see Appendix, 1) for individual outputs.

10 DERIVATIONS AND TRANSFORMATIONS

10.1 Formulas for derived variables

Variable	Definition / Derivation
BMI	Weight [kg] / (height [m])**2

10.2 Transformations to be applied

Not applicable

11 REFERENCES

Not applicable.

12 STANDARDS USED IN PREPARATION OF STATISTICAL OUTPUTS

The below conventions will be followed as agreed with the Sponsor.

12.1 Programming

- One SAS program should create only one output.
- One output file can contain different output types (e.g. descriptive and inferential).
- Individual output files will be created in MS Word format (Rich Text Format, RTF).
- Once delivered to the client, numbering of TLFs will not be altered, unless agreed with the client

12.2 Layout

- TLFs will be produced in landscape format
- TLFs will have a minimum 2 cm on every side
- TLFs will be produced using the Courier New font, size 8
- Section numbering of TLFs will follow ICH E3 guideline.
- Numbering of TLFs will follow the convention XXX-YY, where XXX stands for a (sub-)section number of the ICH E3 guideline and YY represents the sequence number of the output within the section. A dash ('-') will always be used to separate section numbers from output sequence numbers
- Titles and footnotes for figures will also be in Courier New font, size 8.
- Tables and listings will be in black and white (no colour), figures may include only colour that can be distinguished when printed on a grey-scale printer
- Text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will be used sparingly in the TLFs
- The ANSI character set will be used in the TLFs. Certain subscripts and superscripts (e.g., m2, AUC_{norm}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, unless they are derived directly from the data

12.3 Headers, Titles and Footnotes

- All output will have the following header at the top left of each page showing the study ID, the date of output generation and an internal pagination, where Y stands for the total number of pages in the pertaining output.

Study ID — ERGOMED, YYYY-MM-DD
Study description — Page [X / Y]

- Also, all TLFs will have the following footer, identifying the generating SAS program (XXX.SAS), a reference to the relevant subject listing and the date of the data snapshot:

SAS program: <XXX>.sas — Ref. list X.X.X-YY — Data status: YYYY-MM-DD

- Each TLF will bear a title which is repeated on each page of the output.
- The title at the top of the page will be horizontally cantered in bold font.
- A blank line will separate the title from the body of the output.

- The title will consist of an Output number, a descriptive title and a description of the presented analysis set (if applicable).
- The title will have the following general appearance:

Table / Figure / List XX.X.X-YY
Descriptive Title line 1
Descriptive Title line 2
(All subjects in the FAS, N=nnn)

- Each new footnote should start on a new line, where possible.
- Preferably, footnotes should be left justified. When extending beyond a single line, a manual linefeed should be inserted to avoid meaning distortion.
- An automatic footnote '(continued)' will appear at the bottom of TLFs that extend over more than one page.

12.4General Conventions

- For measured variables column headers should include the unit in their description
    - The order of treatment arms in the TLFs will be consistent throughout the entire TLF presentation
- Alphanumeric values are preferably displayed left-justified;
- Dates are presented left-justified
- Integer numbers (e.g., counts) can be centered or right-aligned
- Numbers containing fractional portions will be decimal-aligned.
- Fractional numbers with absolute value less than 1 will carry a leading zero, i.e. 0.123 not .123.
- Units of measured or derived variables will be included where appropriate
- Unless otherwise warranted, the estimated mean, median and quartiles for a set of values will be displayed with 1 more significant digit than the original values, and standard deviations with 2 more significant digits. The minimum and maximum should report the same significant digits as the original values.
- P-values are output in the format: "0.xxxx", where xxxx is the value rounded to 4 decimal places. P-values less than 0.0001 will be presented as <0.0001.
- Precision of percentages displayed will depend on the total study size. For studies with less than 1000 subjects, values will be presented with one decimal place. For studies with more than 1000 subjects, values will be presented with two decimal places.
- Tabular display of data for medical history, prior/concomitant medications and all tabular displays of adverse event data are generally presented by body system, treatment class, or SOC according to the Internationally Agreed Sorting Order of the MedDRA, unless otherwise agreed.
- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis (sub-) population presented.
- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, an explanatory text will be added to clarify that multiple answers were possible.

- Missing values will be displayed either by a double-dash ("--") or as "NA" (='not available/applicable'), whichever is appropriate.
- Dates are displayed in according to ISO date/time format as YYYY-MM-DD, e.g. 2010 03 24. Missing dates may be represented as "NA", if not available/applicable.
- Clock times are displayed as HH:MM or HH:MM:SS based on 24-hour clock

APPENDICES

1. List of Tables, Listings, Figures

A complete List of tables, listings, figures (TLFs) will be given in a separate document which can be updated without updating the SAP. The List will serve as a reference for both the Sponsor, the TS and the SP and describes the entire set of statistical output to be produced. Therefore, this List will be versioned and approved by both Ergomed and Sponsor before commencing the statistical programming

2. List of Efficacy Endpoints

Below the Efficacy Endpoints are listed. No derivation details beyond what is in sections 5, 6 and 7 of this SAP are applicable.

Primary endpoint:

- Mean change from baseline to week 4 in number of Raynaud's Phenomenon (RP) attacks

Key Secondary endpoints

- Mean change from baseline to week 4 in pain experienced during RP attacks
- Mean change from baseline to week 4 in the Raynaud's Condition Score (RCS)
- Mean change from baseline to week 4 in the cumulative and mean duration of RP attacks

Exploratory objectives and endpoints

- Patient Global Impression of Change at week 4
- Physician Global Impression of Change at week 4
- Mean change in ASRAP Questionnaire score from baseline to week 4
- Mean change from baseline to week 4 in peripheral blood flow prior to cold challenge and IMP administration
- Mean change in peripheral blood flow from pre-IMP to post-IMP administration at Visit 2
- Mean change in recovery of peripheral blood flow after cold challenge from pre-IMP to post-IMP administration at Visit 2
- Mean change from baseline to week 4 in recovery of peripheral blood flow after cold challenge.

Pharmacokinetic Endpoints analysis

- GS-248 levels in plasma. And PK parameters as described in section 6.1

Pharmacodynamic analysis

- Percentage change in PGE2 level in whole blood ex vivo from baseline to week 4.
- Percentage change in levels of PGEM, PGIM and TXM (AA-metabolites) in urine from baseline to week 4.
- Percentage change in levels of biomarkers in blood/plasma from baseline to week 4.
- Change in microvascular volume from baseline to week 4 (D-OCT)