Clinical trial results:
A Phase II, randomised, multi-centre 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)

Summary

EudraCT number	2020-002081-13
Trial protocol	GB NL BE PL
Global end of trial date	15 June 2022

Results information

Result version number	v1 (current)
This version publication date	05 May 2023
First version publication date	05 May 2023

Trial information

Trial identification

Sponsor protocol code	GS-2001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04744207
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gesynta Pharma AB
Sponsor organisation address	Wallingatan-24, Stockholm, Sweden, SE-111 24
Public contact	Clinical Information Point, Gesynta Pharma AB, ClinicalInformation@gesynta.se
Scientific contact	Clinical Information Point, Gesynta Pharma AB, ClinicalInformation@gesynta.se

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 October 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 June 2022
Global end of trial reached?	Yes
Global end of trial date	15 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the safety and efficacy of GS-248 versus placebo on RP in subjects with SSc.

Protection of trial subjects:

The first IMP administration was taken at the study site, under the supervision of the study staff. Patients were closely followed with regular safety blood samples taken, patients were asked about any adverse events at each visit and IMP accountability was checked at each visit.

Background therapy:

Subjects were permitted the following background vasodilatory treatment; Ca-blockers or PDE-5 inhibitors.

Evidence for comparator:

Not applicable

Actual start date of recruitment	29 December 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	Poland: 43
Country: Number of subjects enrolled	United Kingdom: 37
Country: Number of subjects enrolled	Belgium: 5
Worldwide total number of subjects	94
EEA total number of subjects	57

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	83
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In addition to fulfilling all eligibility criteria, subjects must fulfil the following criteria to be randomised:
• ≥7 RP attacks during the last week of the run-in period as captured in the eDiary, with no more than 2 days without RP attacks.
• Compliance with the eDiary during the 7 most recent days prior to baseline (Visit 2), excluding the vi

Pre-assignment

Screening details:

The run-in period was 14-21 days prior to Day 1, Baseline visit (the first dose of IMP).

Pre-assignment period milestones

Number of subjects started	94
Number of subjects completed	69

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 2
Reason: Number of subjects	Violated inclusion/exclusion: 23

Period 1

Period 1 title	Treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	GS-248

Arm description:

Allocated to receive active treatment, GS-248

Arm type	Experimental
Investigational medicinal product name	GS-248
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

GS-248, supplied as 40mg capsules. Each single dose consisted of 3 capsules constituting a total of 120mg.
The initial dose of IMP (120 mg once daily) was taken at the study site at Visit 2 under supervision of the investigator or qualified staff. Subsequent doses of IMP were self-administered by the subject, taken orally, once daily. The final dose of IMP was taken at the study site (Visit 4).

The IMP was administered with water, in the morning with food.

Arm title	Placebo

Arm description:

Placebo arm

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo, supplied as capsules identical to GS-248.
The initial dose of placebo (3 capsules) was taken at the study site at Visit 2 under supervision of the investigator or qualified staff. Subsequent doses of placebo were self-administered by the subject, taken orally, once daily. The final dose of placebo was taken at the study site (Visit 4).
The placebo was administered with water, in the morning with food.

Number of subjects in period 1[1]	GS-248	Placebo
Started	33	36
Completed	30	34
Not completed	3	2
Consent withdrawn by subject	2	-
Adverse event, non-fatal	1	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of patients enrolled worldwide is all patients who signed the ICF but the number of subjects in the baseline period is those who completed the pre-assignment period and were randomised.

Period 2

Period 2 title	Follow-Up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	GS-248

Arm description:

Follow-up of those allocated to receive active treatment, GS-248

Arm type	Experimental
Investigational medicinal product name	GS-248
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Not applicable, no treatment was received during follow-up period

Arm title	Placebo

Arm description:	
Follow-up of those randomised to placebo arm	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Not applicable as no treatment received during follow-up period.

Number of subjects in period 2	GS-248	Placebo
Started	30	34
Completed	30	34

Baseline characteristics

Reporting groups	
Reporting group title	GS-248
Reporting group description:	
Allocated to receive active treatment, GS-248	
Reporting group title	Placebo
Reporting group description:	
Placebo arm	

Reporting group values	GS-248	Placebo	Total
Number of subjects	33	36	69
Age categorical			
Units: Subjects			
Adults (18-64 years)	30	32	62
From 65-84 years	3	4	7
Age continuous			
Patients were aged between 18 and 75 years			
Units: years			
arithmetic mean	49.0	50.6	
standard deviation	± 10.6	± 10.6	-
Gender categorical			
Units: Subjects			
Female	27	33	60
Male	6	3	9
Subjects per stratum (background vasodilatory treatment)			
Subjects were stratified for background vasodilatory treatment (Ca- blockers, PDE-5 inhibitors or no vasodilatory treatment.			
Units: Subjects			
Ca-blockers	18	19	37
PDE-5 inhibitors	9	10	19
No vasodilatory treatment	6	7	13

Subject analysis sets	
Subject analysis set title	FAS - GS-248
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set (FAS) consisted of all subjects that were randomised to receive GS-248 and received at least one dose	
Subject analysis set title	PPS - GS-248
Subject analysis set type	Per protocol
Subject analysis set description:	
The Per Protocol Set (PPS) encompassed all subjects randomized to receive GS-248 of the FAS who had no major protocol deviations that affected the evaluation of the effect of GS-248 on the primary endpoint as determined during the blinded data review meeting (BDRM).	
Subject analysis set title	SAS - GS-248
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set (SAS) consisted of all subjects who were randomised to receive GS-248 and administered GS-248 at least once

Subject analysis set title	FAS - placebo
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) consisted of all subjects that were randomised to receive placebo and received at least one dose.

Subject analysis set title	PPS - placebo
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol Set (PPS) encompassed all subjects randomized to receive placebo of the FAS who had no major protocol deviations that affected the evaluation of the effect of placebo on the primary endpoint as determined during the blinded data review meeting (BDRM).

Subject analysis set title	SAS - placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set (SAS) consisted of all subjects who were randomised to receive placebo and administered the placebo at least once

Reporting group values	FAS - GS-248	PPS - GS-248	SAS - GS-248
Number of subjects	33	29	33
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years			
Age continuous			
Patients were aged between 18 and 75 years			
Units: years			
arithmetic mean	49.0	48.9	49.0
standard deviation	± 10.6	± 10.6	± 10.6
Gender categorical Units: Subjects			
Female	27	24	27
Male	6	5	6
Subjects per stratum (background vasodilatory treatment)			
Subjects were stratified for background vasodilatory treatment (Ca- blockers, PDE-5 inhibitors or no vasodilatory treatment.			
Units: Subjects			
Ca-blockers	18	16	18
PDE-5 inhibitors	9	7	9
No vasodilatory treatment	6	6	6

Reporting group values	FAS - placebo	PPS - placebo	SAS - placebo
Number of subjects	36	32	36
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years			
Age continuous			
Patients were aged between 18 and 75 years			
Units: years			

arithmetic mean	50.6	50.1	50.6
standard deviation	± 10.6	± 10.6	± 10.6

Gender categorical Units: Subjects			
Female	33	29	33
Male	3	3	3
Subjects per stratum (background vasodilatory treatment)			
Subjects were stratified for background vasodilatory treatment (Ca- blockers, PDE-5 inhibitors or no vasodilatory treatment.			
Units: Subjects			
Ca-blockers	19	18	19
PDE-5 inhibitors	10	8	10
No vasodilatory treatment	7	6	7

End points

End points reporting groups

Reporting group title	GS-248
Reporting group description:	
Allocated to receive active treatment, GS-248	
Reporting group title	Placebo
Reporting group description:	
Placebo arm	
Reporting group title	GS-248
Reporting group description:	
Follow-up of those allocated to receive active treatment, GS-248	
Reporting group title	Placebo
Reporting group description:	
Follow-up of those randomised to placebo arm	
Subject analysis set title	FAS - GS-248
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set (FAS) consisted of all subjects that were randomised to receive GS-248 and received at least one dose	
Subject analysis set title	PPS - GS-248
Subject analysis set type	Per protocol
Subject analysis set description:	
The Per Protocol Set (PPS) encompassed all subjects randomized to receive GS-248 of the FAS who had no major protocol deviations that affected the evaluation of the effect of GS-248 on the primary endpoint as determined during the blinded data review meeting (BDRM).	
Subject analysis set title	SAS - GS-248
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Analysis Set (SAS) consisted of all subjects who were randomised to receive GS-248 and administered GS-248 at least once	
Subject analysis set title	FAS - placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set (FAS) consisted of all subjects that were randomised to receive placebo and received at least one dose.	
Subject analysis set title	PPS - placebo
Subject analysis set type	Per protocol
Subject analysis set description:	
The Per Protocol Set (PPS) encompassed all subjects randomized to receive placebo of the FAS who had no major protocol deviations that affected the evaluation of the effect of placebo on the primary endpoint as determined during the blinded data review meeting (BDRM).	
Subject analysis set title	SAS - placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Analysis Set (SAS) consisted of all subjects who were randomised to receive placebo and administered the placebo at least once	

Primary: Mean change from baseline to week 4 in the number of RP attacks per week.

End point title	Mean change from baseline to week 4 in the number of RP attacks per week.

End point description:

End point type	Primary

End point timeframe:

From baseline to week 4, i.e. the 7 most recent days prior to Visit 2 and Visit 4 respectively.

End point values	FAS - GS-248	PPS - GS-248	FAS - placebo	PPS - placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	29	33	30
Units: number of attacks				
arithmetic mean (standard deviation)	-3.3 (± 4.7)	-3.1 (± 4.6)	-4.4 (± 7.4)	-4.5 (± 7.8)

Statistical analyses

Statistical analysis title	Primary endpoint analysis

Statistical analysis description:

ANCOVA model for change from baseline to visit 4 (week 4) including the stratification factor (vasodilatory treatment) and treatment as fixed factors and baseline levels as a covariate. The placebo multiple imputation (pMI) method was used for replacement of missing data.

Comparison groups	FAS - GS-248 v FAS - placebo
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Least square means estimate
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.48
upper limit	4.1
Variability estimate	Standard deviation
Dispersion value	0.628

Notes:

[1] - The primary objective was to be met if there was 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.

Secondary: Mean change from baseline to week 4 in the Raynaud's Condition Score

End point title	Mean change from baseline to week 4 in the Raynaud's Condition Score

End point description:

End point type	Secondary

End point timeframe:

From baseline to week 4, i.e. the 7 most recent days prior to Visit 2 and Visit 4 respectively.

End point values	FAS - GS-248	FAS - placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	29	33		
Units: score				
arithmetic mean (standard deviation)	-0.9 (± 1.3)	-1.0 (± 1.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline to week 4 in the cumulative duration of RP attacks.

End point title	Mean change from baseline to week 4 in the cumulative duration of RP attacks.

End point description:

End point type	Secondary

End point timeframe:

From baseline to week 4, i.e. the 7 most recent days prior to Visit 2 and Visit 4 respectively.

End point values	FAS - GS-248	FAS - placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	33		
Units: minutes				
arithmetic mean (standard deviation)	-84.9 (± 437.2)	-148.5 (± 249.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline to week 4 in pain experienced during RP attacks.

End point title	Mean change from baseline to week 4 in pain experienced during RP attacks.

End point description:

End point type	Secondary

End point timeframe:

From baseline to week 4, i.e. the 7 most recent days prior to Visit 2 and Visit 4 respectively.

End point values	FAS - GS-248	FAS - placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	29	32		
Units: numeric rating scale				
arithmetic mean (standard deviation)	-0.62 (± 1.0)	-0.66 (± 1.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline to week 4 in the mean duration of RP attacks

End point title	Mean change from baseline to week 4 in the mean duration of RP attacks

End point description:

End point type	Secondary

End point timeframe:

From baseline to week 4, i.e. the 7 most recent days prior to Visit 2 and Visit 4 respectively.

End point values	FAS - GS-248	FAS - placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	33		
Units: minutes				
arithmetic mean (standard deviation)	4.5 (± 37.6)	-3.5 (± 11.3)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All SAEs and AEs were to be collected from the signing of the ICF until the follow-up visit (Visit 5)

Adverse event reporting additional description:

An AE that occurs from first IMP dose until 7 days after last IMP dose was considered a Treatment Emergent AE regardless of the assessed relationship to the IMP. All other AEs reported after signed ICF but outside of the period specified above were considered non-treatment emergent.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	GS-248

Reporting group description:

Actually received GS-248 during the study

Reporting group title	Placebo

Reporting group description:

Actually received placebo during study

Serious adverse events	GS-248	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Injury, poisoning and procedural complications			
Thermal burn			
subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	GS-248	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 33 (30.30%)	9 / 36 (25.00%)	
Investigations			
White blood cell count decreased			
subjects affected / exposed	0 / 33 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 33 (18.18%)	4 / 36 (11.11%)	
occurrences (all)	18	5	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 33 (6.06%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	2 / 33 (6.06%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 33 (0.00%)	3 / 36 (8.33%)	
occurrences (all)	0	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 July 2020	The protocol has been updated to reflect following changes and for some minor administrative and clarification changes, including to the exclusion criteria. Secondary efficacy endpoints were updated: - 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 from baseline to week 4 in recovery of peripheral blood flow after cold challenge - Number of countries was updated for the conduct of the study. - Study assessment was updated to include PK sampling - Removed the inclusion criteria related to finger temperature - Exclusion Criterion for Cold Challenge was added - Definition of Prolonged QTcF interval was updated
01 September 2020	The protocol has been updated following requests from the MHRA and for some minor administrative changes WOCBP and Highly Effective Contraception was updated based on the request from MHRA WOCBP given home pregnancy test to be used 35-40 days after their last dose of IMP (Visit 4).
25 March 2021	The protocol has been updated to reflect following changes and for some minor administrative and clarification changes, including to the exclusion criteria. - Visit 4, End of Treatment Visit, occurred on Day 28 (-2/+1 days), which was the day subjects took their final dose of IMP, to be administered at the study site - Mean change in recovery of peripheral blood flow after cold challenge from pre-IMP to post-IMP administration at Visit 2. - A COVID-19 vaccination considered a permitted concomitant medication and is therefore not contraindicated for use with GS-248.
10 December 2021	The protocol has been updated to reflect emerging data on GS-248 interaction with moderate and strong CYP3A4 inhibitors resulting in an additional exclusion criterion and addition of prohibited concomitant medications. Changes in the descriptions of analyses populations as well as some minor administrative updates have also been made. A safety measure added relating to results from a drug-drug interaction (DDI) clinical study with GS-248.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
20 April 2021	Subject recruitment was temporarily interrupted during summer months to protect data integrity and minimize influence of warmer weather on the efficacy outcome variables. No subjects were enrolled in the study between 20-April-2021 and 22-September-2021.	22 September 2021

Notes:

Limitations and caveats

None reported