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)

Published: 17-08-2020
Last updated: 17-01-2025

Primary:To determine the safety and efficacy of GS-248 versus placebo on RP in subjects with SSc.Secondary:To determine the efficacy of GS-248 on peripheral vascular blood flow in subjects with SSc and RP.Exploratory:• To explore the...

Ethical review	Approved WMO
Status	Completed
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON52928

Source
ToetsingOnline

Brief title
GS-248 in subjects with RP

Condition

- Autoimmune disorders

Synonym
Raynaud□s phenomenon (RP)

Research involving

Human

Sponsors and support

Primary sponsor: Gesynta Pharma AB
Source(s) of monetary or material Support: Sponsor;Gesynta Pharma AB

Intervention

Keyword: GS-248, mPGES1 inhibittor, Raynaud□s phenomenon (RP)

Outcome measures

Primary outcome

Primary Efficacy:

Mean change from baseline to week 4 in the number of Raynaud*s Phenomenon

attacks per week.

Primary safety:

• Incidence of Adverse events.

• Incidence of Serious Adverse Events.

• Clinical laboratory and vital signs.

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.

Secondary outcome

Secondary:

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

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

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

• Mean change from baseline to week 4 in recovery of peripheral blood flow after cold challenge (see Appendix 5).

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

Exploratory:

• GS-248 levels in plasma.

• Change in PGE2 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.

Study description

Background summary

See protocol paragraph 1.

Study objective

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

Secondary:
To determine the efficacy of GS-248 on peripheral vascular blood flow in subjects with SSc and RP.

Exploratory:
• To explore the pharmacokinetics (PK) of GS-248.
• To explore the efficacy of GS-248 on PGE2 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).

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 once daily, stratified for use of background vasodilatory treatment (Ca-blockers, PDE-5 inhibitors, or no background vasodilatory treatment) with approximately 40 subjects in each treatment group.
The study will comprise an enrolment period, a treatment period, and a follow-up period, with a total of 5 study visits (see Overall Schedule of

Assessments, Appendix 2).

Run-in/Enrolment Period
At Visit 1 (Screening Visit) informed consent will be gained from each subject and eligibility for the study will be established. Eligibility screening will be conducted, including demographic data, subject medical history, a physical examination, and other procedures. In addition, blood and urine samples will be collected. Subjects will be issued with an eDiary to record information on a daily basis, including the number of Raynaud attacks and RCS (see Overall Schedule of Assessments, Appendix 2).
Some study assessments will only be conducted at pre-selected sites (see Overall Schedule of Assessments, Appendix 2).

Treatment Period
On Day 1 (Visit 2, Baseline Visit) eligible subjects will be randomised and receive their first dose of IMP under medical supervision at the study site. Study assessments including PK sampling and safety will be performed throughout this visit. In total, this visit will last for approximately 4 or 6 hours dependent on whether the subject is enrolled in the cold challenge assessment. Subjects will be permitted to leave the study clinic for short periods of time between assessments as feasible, but will be asked to remain on site. At the end of the visit, subjects will be dispensed sufficient amount of medication to last until the next study visit, scheduled for 14 (±2) days later.
Subjects will continue to fill in their eDiary throughout the Treatment Period.
On Day 15 (±2 days) subjects will return to the study site for Visit 3. Safety assessments, PK sampling and safety monitoring will be performed (see Overall Schedule of Assessments, Appendix 2). Treatment compliance will be checked, used bottle of IMP collected, and sufficient IMP for the remainder of the Treatment Period will be distributed. The visit will last approximately 1,5 hours.
Visit 4, End of Treatment Visit, will occur on Day 28 (-2/+1 days), which will be the day subjects take their final dose of IMP, to be administered at the study site.
This visit will last for up to 5 hours, and for subjects undergoing rich PK sampling, this visit will last for up to 9 hours. Additional safety monitoring assessments will be performed (see Overall Schedule of Assessments, Appendix 2).
The eDiary will be checked, and all IMP will be collected.
An ASRAP questionnaire will be completed by subjects, along with a Global Impression of Change, which is also completed by physicians.

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

hours.

Intervention

Subjects will be randomised in a 1:1 allocation to receive either GS-248 (120 mg) or placebo once daily, stratified for use of background vasodilatory treatment (Ca-blockers, PDE-5 inhibitors, or no background vasodilatory treatment).

The study consists of an inclusion period, a treatment period and a follow-up period, with a total of 5 study visits. The total treatment period can be up to 70 days.

Study burden and risks

The patient will be burdened with 5 visits to the hospital. The following quantities of blood (may) be taken:
- 130 ml from all participants
- 48 ml for subset analyses (including pharmacokinetics)

Contacts

Public
Gesynta Pharma AB

Wallingatan 24
Stockholm 111 24
SE
Scientific
Gesynta Pharma AB

Wallingatan 24
Stockholm 111 24
SE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Subjects must provide signed and dated written informed consent before the conduct of any study-specific procedures.
2. Male and female subjects aged 18-75 years inclusive.
3. SSc diagnosed according to European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) criteria (van den Hoogen F et al. 2013).
Subjects with signs of other autoimmune diseases (e.g. Sjögren*s syndrome, myositis, rheumatoid arthritis) could be included if SSc is the dominating phenotype.
4. Raynaud attacks typically >=7 times per week during the last 4 weeks prior to screening despite background medication (only allowed vasodilatory therapy is calcium channel blockers or PDE-5 inhibitors).
5. Women of childbearing potential (WOCBP) must be using a highly effective method of contraception to avoid pregnancy throughout the study and for 4 weeks after the last dose of IMP in such manner that the risk of pregnancy is minimised. (Clinical Trials Facilitation Group, 2014).
6. Women must not be pregnant or breastfeeding.
7. Male subjects to agree to use condom in combination with use of contraceptive methods with a failure rate of <1% to prevent pregnancy and drug exposure of a partner and refrain from donating sperm from the first date of dosing until 3 months after last dosing of the IMP.
8. Ability of subjects to participate fully in all aspects of this clinical trial.

Exclusion criteria

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

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

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

Randomization Criteria:
In addition to fulfilling all inclusion and exclusion criteria, subjects must fulfil the following criteria to be randomised:
1. >=7 RP attacks during the last week of the run-in period as captured in

the eDiary, with no more than 2 days without RP attacks.
2. Compliance with the eDiary during the 7 most recent days prior to baseline (Visit 2), excluding the visit day itself, defined as having submitted >=5 days of eDiary records (out of a possible 7 days) for RCS and RP during that period.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	16-02-2021
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO Date:	17-08-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-10-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO Date:	02-11-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-04-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-05-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-07-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-07-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-12-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	31-01-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2020-002081-13-NL
Other	http://www.clinicaltrialsregister.eu.
CCMO	NL74530.091.20

Study results

Date completed: 15-06-2022

Results posted: 15-03-2023

First publication
22-02-2023