Clinical Trial Protocol

Title:	**A Phase 2, single-center, randomised, double-blind, placebo-controlled, cross-over, cold challenge study investigating the effect of C21 on cold-induced vasoconstriction in subjects with Raynaud's Phenomenon (RP) secondary to systemic sclerosis (SSc)**
Short Title:	**Cold challenge with C21 in RP**
Sponsor:	**Vicore Pharma AB** **Kronhusgatan 11** **SE-411 05 Göteborg** **Sweden**
Trial ID:	**VP-C21-004**
NCT No.:	**NCT04388176**
EudraCT No.:	**2019-003203-35**
Investigational Medicinal Product:	**C21**
Indication:	**RP secondary to SSc**
Phase:	**2**
Version:	**4.0**
Date:	**22-OCT-2020**

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Sponsor's Approval of Clinical Trial Protocol

This trial will be conducted in compliance with the protocol, GCP, and applicable regulatory requirements.

Sponsor's Medical Expert:

Rohit Batta, MBBS MRCGP FFPM.,
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_____ Signature

_____ Date

Sponsor's Statistical Expert:

Thomas Bengtsson, M.Sc.,
StatMind AB

_____ Signature

_____ Date

Senior Director,
Head of Clinical Operations:

Anne Katrine Cohrt,
Vicore Pharma AB

_____ Signature

_____ Date

Signatory Investigator's Approval of Clinical Trial Protocol

This trial will be conducted in compliance with the protocol, GCP, and the applicable regulatory requirements.

I confirm, that I agree to conduct this study in compliance with the Declaration of Helsinki, the International Conference on Harmonisation (ICH) Guideline for GCP and applicable regulatory requirements.

Furthermore, I confirm that I have read and understood the present clinical trial protocol and agree to conduct the study in compliance with this. I fully understand that any changes from the protocol constitute a deviation which will be notified to the Sponsor.

Coordinating Investigator:

Ariane Herrick, MD, FRCP	Signature	Date

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1 PROTOCOL SUMMARY

Trial Title	A Phase 2, single-center, randomised, double-blind, placebo-controlled, cross-over study investigating the effect of C21 on cold-induced vasoconstriction in subjects with Raynaud's Phenomenon (RP) secondary to systemic sclerosis (SSc)
Trial ID	VP-C21-004
Trial Phase	2
Objectives	Primary To evaluate the effect of a single dose C21 200 mg o.d. on cold-induced vasoconstriction in subjects with Raynaud's Phenomenon (RP) secondary to systemic sclerosis (SSc). Secondary • To evaluate the safety of a single dose C21 200 mg o.d. in subjects with RP secondary to SSc. • To evaluate the effect of a single dose C21 200 mg o.d. on finger temperature in subjects with RP secondary to SSc Exploratory To evaluate the effect of a single dose C21 200 mg o.d. on relevant biomarkers.
Endpoints	Primary Area under the curve for rewarming of each finger after cold challenge (AUC) as measured by thermography. Secondary To evaluate the safety of a single dose C21 200 mg o.d. in subjects with RP secondary to SSc. To evaluate the effect of a single dose C21 200 mg o.d. on finger temperature in subjects with RP secondary to SSc. Exploratory • Change in hand temperature from intake of IMP to start of cold challenge • Nailfold capillaroscopy • Potential analyses of biomarkers related to endothelium and platelets
Trial Design	This is a randomised, double-blind, placebo-controlled, cross-over, cold challenge study The subjects will come to the clinic for four visits: • Visit 1: Screening • Visit 2: IMP administration and cold challenge (3-21 days after Visit 1) • Visit 3: IMP administration and cold challenge (3-7 days after Visit 2) • Visit 4: End of trial (3-15 days after Visit 3 or after withdrawal from trial)
Inclusion Criteria	1) Written informed consent must be obtained before any trial related procedures are performed 2) Subjects diagnosed with SSc according to European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) criteria [van den Hoogen et al 2013] 3) Age 19-75 years inclusive 4) RP secondary to SSc as determined by the investigator, and with a typical frequency of attacks during the winter months (November-March) of on average at least 5 per week
Exclusion Criteria	1) Smoking (including E-cigarettes) or use of nicotine replacement therapy for three months prior to Visit 1 and during the trial

	2) BMI >35 3) Mixed connective tissue disease or "overlap" (i.e. those who satisfy more than one set of ACR criteria for a rheumatic disease) 4) Concurrent serious medical condition with special attention to cardiac or ophthalmic conditions which in the opinion of the investigator makes the patient inappropriate for this study 5) Malignancy within the past 5 years with the exception of in situ removal of basal cell carcinoma and cervical intraepithelial neoplasia grade I 6) Planned major surgery within the duration of the study 7) Subjects who forsake any alcohol intake or have known uncontrolled allergic conditions or allergy/hypersensitivity to any components of the trial drug or placebo excipients (see Section 7.1) 8) Blood donation (or corresponding blood loss) within three months prior to Visit 1 9) Treatment with any of the medications listed below within 4 weeks prior to Visit 1: • Any dose-change or initiation of vasoactive substances), and not able or willing to withhold these medications for 3 days preceding Visit 2 and Visit 3, respectively • Iloprost • Any treatment with CYP3A4 inducers (e.g. rifampicin, phenytoin, St John's Wort) • Any treatment with CYP3A4 inhibitors (e.g. clarithromycin, ketoconazole, nefazodone, itraconazole, ritonavir) • Any treatment with medicines that are substrates of CYP1A2, CYP3A4 or CYP2C9 with a narrow therapeutic range • Any experimental drug • Any systemic immunosuppressive therapy other than: o Inhaled corticosteroids which can be used throughout the trial period oThe continuation of stable doses of ≤10 mg prednisolone o Mycophenolate mofetil (MMF) which must be withheld for 3 days preceding Visit 2 and Visit 3 10) Any of the following findings at the time of screening: • Finger temperature below 27°C after acclimatising at an ambient temperature of 23°C for a period of 20 minutes • Prolonged QTcF (>450 ms), cardiac arrhythmias or any clinically significant abnormalities in the resting ECG, as judged by the Investigator • Positive results for HBsAg, HCVAb or HIV 1+2 Ag/Ab • Positive serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) • Clinically significant abnormal laboratory value at Visit 1 indicating a potential risk for the subject if enrolled in the trial as evaluated by the Investigator 11) Pregnant or breast-feeding female subjects. 12) Female subjects of childbearing potential not willing to use contraceptive methods described in Section 5.3.1 13) Male subjects not willing to use contraceptive methods described in Section 5.3.1. 14)Participation in any other interventional trial during the trial period 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)

2 FLOW CHARTS

Table 1. Flow Chart for Trial Procedures

	Screening	Treatment	Treatment	End-of-Trial
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4***
Visit Window (days allowed from previous visit)		3–21 Days	3–7 Days	3–15 Days
Clinical assessments				
Informed consent	X			
In- & exclusion criteria	X			
Randomisation		X		
Withdrawal criteria		X	X	
Demographics	X			
Medical history & concomitant illness	X			
Weight, height and BMI	X			
Physical examination	X	X[1)]	X[1)]	X
Vital signs	X	X	X	X
Nailfold Capillaroscopy	X	X	X	
Thermal probe[2)]	X			
Modified Rodnan Skin Score	X			
Raynaud's Condition Score	X	X	X	
Thermography [3)]		X	X	
Cold challenge		X	X	
Concomitant medication	X	X	X	X
12-lead ECG	X			X
Holter ECG		X[4)]	X[4)]	
IMP administration [5)]		X	X[6)]	
Adverse events [7)]	X	X	X	X

* Visit 4: End-of-Trial Visit for all randomised subjects must be performed no later than 30 days after Visit 2 (randomisation). Visit 4 must also be performed if a randomised subject is withdrawn from the trial for any reason

1) Brief examination according to Investigator's judgement
2) Application of thermal probe for check of finger temperature not being below 27°C (exclusion criterion 10)
3) Please refer to Section 6.5.2 for details
4) Holter ECG from 30 mins prior to IMP administration and until 180 mins after
5) Withdrawal criteria must be checked prior to IMP administration (see Section 5.4)
6) Subjects will cross-over to opposite IMP (either C21 or placebo) compared to Visit 2
7) AEs will be reported from signing of informed consent until End of Trial participation (Visit 4)

Table 2. Laboratory Parameters

		Screening	Treatment	Treatment	End-of-
		Visit 1	Visit 2	Visit 3	Visit 4*
Time tolerance from previous visit			3–21 Days	3–7 Days	3–15 Days
Laboratory Assessments					
Haematology[1)]		X			X
Biochemistry[2)]		X			X
Urinanalysis[3)]		X			X
HIV and Hepatitis B/C[4)]		X			
Thyroid Stimulating hormone (TSH)		X			
Blood samples for potential analyses of exploratory biomarkers		X	X[5)]	X[5)]	X
Blood sample for potential analysis of exposure to C21			X[6)]	X[6)]	
Pregnancy tests (WOCBP)	beta-HCG for WOCBP. Follicular Stimulating Hormone (FSH), oestradiol for confirmation of WONCBP	X			X
	Urine dip-stick		X	X	

* Visit 4: End-of-Trial Visit for all randomised subjects.
Visit 4 must be performed if a randomized subject is withdrawn from trial treatment for any reason

1) Haemoglobin (Hb), haematocrit (Erythrocyte volume fraction), platelet count (Trombocyte particle concentration [TPC]), leucocyte count, Mean Corpuscular Volume (MCV)
2) Albumin, alanine transferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase Gamma (ALP), bilirubin, Blood Urea Nitrogen (BUN), calcium, creatinine, C-Reactive Protein (CRP), Gamma Glutamyl Transferase (gGT), glucose, Lactate dehydrogenase (LD), potassium, sodium
3) PH, glucose, protein/albumin and Hb
4) HBsAg, HCVAb and HIV 1+ 2 AgAb
5) Samples to be obtained before IMP administration, before cold challenge, immediately after cold challenge, 15 min after cold challenge
6) Samples to be collected 15 min after cold challenge

Table 3. Procedures and Assessments Visit 2 and Visit 3

Time	Procedure/Assessments (to be done in the following order)
≥ 20 min	• Subjects arrive at the department after overnight fasting (minimum 4 hours fasting - allowed to drink water and take usual medicine) and being requested to refrain from various activities (e.g. vigorous exercise, caffeine, and alcohol prior to any trial related assessments) see Section 5.4 • Withdrawal criteria controlled (see Section 5.4) • Pregnancy test (WOCBP) – urine dip stick • Brief physical examination according to Investigator's judgement • Randomisation (Visit 2 only) • Adverse Event questions reflecting the time from the previous visit • Concomitant medication • Raynaud's Condition Score • Capillaroscopy • Application of intravenous cannula for blood sampling (before IMP administration, before cold challenge, immediately after cold challenge, 15 minutes after cold challenge) • Application of Holter ECG from 30 mins prior to IMP administration until 180 min after
0 min	• Capillaroscopy immediately before IMP administration • IMP administration (definition of the time 0 min) • Thermography image every 10 minutes
40 min	• Last thermography image before cold challenge test • Capillaroscopy immediately before cold challenge test • Immersion of both hands up to the metacarpophalangeal joints for 1 minute into cooled water (15°C) • Thermography images every 15 sec for 15 min • Capillaroscopy after thermography measurements have been completed
120 min	• Meal
180 min	• Removal of Holter ECG • Questions on Adverse Events during the day • Discharge

3 BACKGROUND AND RATIONALE

3.1 Indication Raynaud's phenomenon in Systemic sclerosis

Systemic sclerosis (SSc) is an autoimmune disease characterised by dysregulation of innate and adaptive immunity, vasculopathy and fibrosis, which could affect several organ systems. Skin fibrosis (scleroderma) is the distinguishing hallmark of SSc, and microvascular injury and endothelial cell activation that results in vascular damage are considered to be the earliest, and possibly primary, events in SSc [Allanore et al 2015]. Changes in capillary morphology as investigated with nailfold videocapillaroscopy demonstrate a distinct and typical pattern [Ruaro et al 2017], but also small and medium size arteries are involved [Aïssou et al 2016]. There are four pathophysiological components of the vascular disease in SSc; vasospasm, vasculopathy, ischemia reperfusion injury and coagulation [Hughes & Herrick 2017].

Raynaud's phenomenon (RP), an episodic painful ischemic event affecting primarily fingers and toes in response to cold exposure or to emotional stress, is a very common manifestation of SSc. In the large EUSTAR database, including 9,182 patients with SSc, more than 95% reported RP [Elhai et al 2016]. The mean age at onset of RP, which usually is the first symptom of SSc, was 42 years and preceded symptoms from other organ manifestations with an average of 4 years [Meier et al 2012]. In an international survey of patients with RP, most subjects (78%) reported making at least one life adjustment due to RP, and quality of life was significantly reduced. Further, of those with current or previous use of medications for RP, only 16% reported at least one medication being effective [Hughes et al 2015], and hence a substantial unmet medical need for efficient treatment of RP exists.

3.2 Current Treatment for Raynaud's phenomenon in Systemic sclerosis

Non-pharmacological therapies involve reducing stress, avoiding cold temperatures and stopping smoking. EULAR recommends dihydropyridine calcium channel blockers as first-line pharmacological therapy for SSc-RP, but PDE-5 inhibitors should also be considered, and fluoxetine could be a useful alternative for patients who cannot tolerate or do not respond to vasodilators [Kowal-Bielecka et al 2017]. Other therapies used for RP include topical nitroglycerine.

3.3 Investigational Medicinal Product

The Investigational Medicinal Product (C21) is a selective angiotensin II type 2 receptor (AT_2R) agonist presented as a solution for oral administration.

3.4 Pre-Clinical Safety

The toxicity of C21 has been evaluated in single and repeated dose oral gavage studies of up to 13 weeks duration in rats, dogs and NHP, as well as in genotoxicity studies. Safety pharmacology studies on respiratory function, cardiovascular system and behavior/CNS activity have been performed in rats and dogs.

In a 13-week repeated dose study in rats with three different dose levels of C21 (6, 20 and 60 mg/kg/day) ophthalmology examinations showed that the 20 and 60 mg doses caused unilateral or bilateral lens opacity (clinical signs observed from week 7 and onwards) and with signs of progression following a 28-day recovery. There were also indications of a similar effect in the 4-

week rat study at 60 mg/kg/day. In the dog, no lens opacity was observed and in a subsequent ophthalmology specific 13 week NHP study doses up to 30 mg/kg/day was clinically well tolerated without any in-vivo or morphological ophthalmic findings. Thus, the no observed adverse effect level (NOAEL) was determined to be 30 mg/kg/day in the NHP. As in man, the eye is the primary sensory organ in the NHP and therefore the overall anatomy and function of the eye is close to humans. Also, based on the phylogenetic similarities between NHP and humans, it is reasonable to assume that NHP represent the most appropriate translational model for ocular changes. Thus, it is very unlikely that a single dose of C21 could cause lens opacity in humans.

No irreversible effects were detected in the dog. The main findings were increase in blood pressure at 1 mg/kg and evidence of ECG aberrations from 10 mg/kg in a telemetry study. In a 4-week general toxicity study increase in systolic and diastolic pressure was first noted at 25 mg/kg/day. In contrast, no blood pressure changes were seen in the 13-week repeated exposure study in doses up to 15 mg/kg/day. In the telemetry study ECG changes with PR- and QT/QTcR prolongations, AV-block I and II and isolated premature ventricular contractions were observed. Most of these findings could indicate a cardiac membrane stabilizing effect. The NOAEL in dogs based on data after exposure for 13 weeks was determined to 15 mg/kg/day. No NOAEL could be established for the effects on arterial blood pressure.

An IC50 value of 53.3 µM was determined for hERG inhibition by C21 in recombinant HEK-293 cells. This indicates low risk for QTc prolongation in humans at expected plasma concentrations of C21.

Other findings in rats with up to 60 mg/kg of C21 daily for 12 weeks, were associated with reversible organ weight and/or histopathological findings within the pituitary, adrenal glands, ovary, thyroid gland and liver and also reversible changes in some hematological and blood chemistry parameters. None of these findings could be associated with any observed effect on organ function. Other findings in dogs with doses of 15/25 mg/kg/day of C21 for up to 13 weeks were associated with reversible changes in faecal consistency food consumption and consequently a change in body weight gain, mild haemoconcentration (both sexes), slightly elevated monocyte count (males) and fibrinogen levels (both sexes), increased overnight urine volumes and an associated reduction in urine specific gravity (females).

There were no indications of any mutagenic or genotoxic potential of C21.

For further details on the non-clinical studies performed with C21, please refer to the current Investigator's Brochure (IB).

3.5 Clinical Safety

Phase I clinical safety, tolerability and PK properties of C21 has been evaluated in single and repeated dose oral studies of up to 8 days' duration in healthy male volunteers (Table 4).

Table 4. List of completed Clinical Phase I Studies with C21

Study ID	Objectives	Study Design	Population	Total N	Dose Regimens
C21-001-16 EudraCT: 2015-005718-32	Safety, tolerability, PK	Placebo-controlled single dose	Healthy male volunteers	48	0.3, 1, 3, 10, 30, 100 mg Oral solution
C21-002-16 EudraCT 2015-005719-33	Safety, tolerability, PK	Placebo-controlled multiple doses	Healthy male volunteers	24	25, 50, 100 mg/day Oral solution
			Overweight male volunteers	16	100 mg/day oral solution

In the single ascending dose (SAD) and multiple ascending dose (MAD) studies, C21 was rapidly absorbed, with a median t_{max} ranging from 20 to 40 min after dosing both after single dose and repeated dosing. Indications of multiphasic elimination was evident, with a very fast first distribution phase seen at lower doses of C21 (t½ of about 0.5 hours). A second slower phase, due to the elimination of C21, was observed at higher doses with a t½ of 5.37 hours. There was no accumulation of C21 at any of the investigated dose levels. Based on the SAD and MAD data, C21 seems to have a more than dose-proportional increase of C_{max} and AUC.

No serious adverse events (SAE) were observed in any of the clinical investigations, and generally the observed adverse event (AE) profile was comparable between the C21 and placebo groups. However, a single subject receiving a single low dose (3 mg) showed a prolonged PR interval one hour post dose. This was not seen or replicated in any other subject within the same dose group or at higher doses. The subject was excluded from the trial and examination weeks after the last dose revealed 1st and 2nd degree AV block, suggesting that predisposition for longer PR intervals/AV blocks may have been the reason for the observation during the study. Within the MAD study, one subject experienced a syncope on the first day of treatment (100 mg dose), shortly after the 20-minute blood sample collection. It was managed by the Investigator as a vasovagal reaction as the subject swiftly returned to consciousness with elevation of the legs. Vasovagal syncope is a common phenomenon in Phase 1 studies of young healthy volunteers, and this event could have been provoked by the blood sampling and apprehension on the first day of dosing. The AE was recorded as a syncope, was rated as moderate in severity and related to IMP intake. During the syncope a sinus arrest was observed, which is also described in the literature in connection with vasovagal syncope [Palmert and Kahn 1996]. The subject continued with the study and completed dosing on 7 consecutive days with no further untoward effects or ECG abnormalities.

A Phase 1, randomised, double blind, placebo-controlled SAD study is currently ongoing in healthy volunteers to test higher doses of C21 than previously investigated. So far, ten male and female subjects (8 active, 2 placebo) per dose group have been administered single doses of either 100 mg BID, 200 mg QD or 200 mg BID for assessments of safety, tolerability and PK of C21.

No SAEs were reported in either of the three dose groups tested. Furthermore, no clinically significant findings were observed in ECG, telemetry, vital signs or safety laboratory analyses. In

conclusion, the tested C21 doses were found to be well-tolerated and have an appropriate safety profile.

Furthermore, 10 male and female subjects (8 on active and 2 on placebo) received C21 doses of either 100 mg BID or 200 mg BID for 8 consecutive days. All doses in this multiple ascending dose (MAD) study were also found to have a good safety profile, no SAEs were reported and there were no clinical significant findings in ECG, telemetry, vital signs or safety laboratory. However, 5 of the 8 subjects exposed to 200 mg BID reported alopecia between 7 and 14 days after the 8 days treatment period was completed. Hair loss of different intensity was seen on all body parts This observation was assessed as probably related to IMP. The majority of subjects have reported regrowth of hair after one month and are presently being followed to assess the quality of the regrowing hair. For further details on the clinical experience with C21, please refer to the current Investigator's Brochure (IB) including addendum 1.0 dated 26-September-2019.

3.6 Rationale for Trial

C21 is intended to be used for the prevention and treatment of RP in patients with SSc. Current oral therapies for RP have limited efficacy, and there is a high medical need for new therapeutic alternatives. The aim of the present project is to achieve a vasodilatory effect by stimulation of the AT_2R.

Although the renin-angiotensin system (RAS) is best known as a major physiological regulator of blood pressure and fluid homeostasis, a number of other physiological functions including cell growth and differentiation, cell adhesion, inflammation and fibrosis are also regulated by the RAS. Angiotensin II (Ang II) is the major effector peptide of the RAS system.

Ang II has potent vasoconstrictor effects mediated by the angiotensin II type 1 receptor (AT_1R) [Forrester et al 2018]. The angiotensin II type 2 receptor (AT_2R) is described as a central component of the "protective arm" of the renin-angiotensin system [Unger et al., 2015]. In a study using micro-dialysis to assess vascular tone, Ang II infusion caused a dose dependent vasoconstriction; AT_2R inhibition with PD-123319 increased the vasoconstriction response, indicating a counterregulatory role of the receptor [Lang & Krajek 2019].

In adult human skin a complete RAS is present [Stecklings et al 2004], and it is upregulated with increased AT_2R expression under pathophysiological status such as SSc [Kawaguchi et al 2004]. The AT_2R is also upregulated in both vessels and septal areas in lungs from patients with SSc [Parra et al 2014].

Intra-arterial infusion of an AT_2R agonist in healthy volunteers mediates vasodilation in the forearm [Schinzari et al 2011]. Further, the AT_2R contributes to angiotensin II mediated vasodilation in resistance arteries of hypertensive diabetic patients treated with AT_1R blocker for one year [Savoia et al 2007].

In a pre-clinical study on human heart micro-coronaries, it was demonstrated that endothelial cells expressed the AT_2R, and that exposure to C21 caused relaxation of the vessels mediated through nitric oxide (NO) [Batenburg et al 2004]. AT_2R stimulation in human endothelial cells increases endothelial nitric oxide synthase (eNOS) activity through phosphorylation of activating eNOS residues and dephosphorylation of inactivating eNOS residues, thus increasing NO release [Peluso et al 2018].

3.7 Rationale for Trial Design

This is a randomised, double-blind, placebo controlled cold challenge study. A cross-over design is applied to control for inter-individual variability in response to cold challenge.

Randomisation is applied to minimise bias in the assignment of subjects. Double-blinded treatment is applied to reduce potential bias during data collection and evaluation of endpoints.

Time points for IMP administration, cold challenge and thermography is based on the pharmacokinetic properties of C21.

Overall, the study will provide important data to support the design of further studies.

3.8 Rationale for Dose and Dosing Regimen

The dose of C21 (200 mg) is selected to achieve sufficient coverage of the receptor during the warm-up phase after the cold challenge.

3.9 Risk-Benefit Assessment

The subjects' safety and wellbeing are of outmost importance. The risk to subjects will be minimised by compliance with the eligibility criteria and by close clinical monitoring. Cold challenge is a well-established test for the diagnosis of RP and will be conducted with a standard procedure, which is used routinely in clinical practise. The subjects may experience discomfort following withdrawal of concomitant vasodilatory medication. However, this is an important pre-requisite for an objective evaluation of the study results, and hence the Investigator must exclude any subject considered unlikely to comply with the specified restrictions (see exclusion criterion 17).

The subjects may experience transient discomforts during the cold challenge test and in relation with the use of medical devices for study specific evaluations (e.g. indwelling venous catheters) and blood-pressure measurements using a blood pressure cuff. These procedures and devices are however used routinely in clinical practise, and part of the regular and well-established assessments of this patient population. Hence, the risks associated with are deemed to be low and considered ethically justifiable.

All subjects are carefully monitored while receiving active compound and placebo. The C21 dose tested in the present trial has been evaluated in Part A of an ongoing Phase 1 study. Please refer to section 3.5 for further details. Overdosing of C21 is not likely to occur since the IMP will be administered by site personnel under medical surveillance.

Except for thorough health examinations, the subjects participating in the present study are not expected to experience any medical benefits, but their participation provides important data, which will be used for a thorough assessment of the efficacy, safety and tolerability of C21. This information may form the basis for improved future treatment of patients suffering from RP and SSc.

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

4 OBJECTIVES AND ENDPOINTS

4.1 Primary Objective

To evaluate the effect of a single dose C21 200 mg o.d. on cold-induced vasoconstriction in subjects with Raynaud's Phenomenon (RP) secondary to systemic sclerosis (SSc).

4.2 Secondary Objectives

To evaluate the safety of a single dose C21 200 mg o.d. in subjects with RP secondary to SSc.

To evaluate the effect of a single dose C21 200 mg o.d. on finger temperature in subjects with RP secondary to SSc.

4.3 Exploratory Objectives

To evaluate the effect of a single dose C21 200 mg o.d. on relevant biomarkers

4.4 Primary Endpoint

Area under the curve for rewarming of each finger after cold challenge (AUC) as measured by thermography.

4.5 Secondary Endpoints

- Maximum skin temperature after rewarming (MAX)
- The distal dorsal difference, defined as the difference in temperature between the dorsum and the finger (DDD)
- Gradient of rewarming in the first 2 minutes post–cold challenge (GRAD)
- Adverse events (AEs)

4.6 Exploratory Endpoints[1]

- Change in hand temperature from intake of IMP to start of cold challenge
- Nailfold capillaroscopy (including red blood cell velocity measurements)
- Potential analyses of biomarkers related to endothelium and platelets

5 TRIAL POPULATION

5.1 Inclusion Criteria

1) Written informed consent must be obtained before any trial related procedures are performed.
2) Subjects diagnosed with SSc according to European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) criteria [van den Hoogen et al 2013].

[1] The results on exploratory endpoints may not be included in the CSR

3) Age 19-75 years inclusive
4) RP secondary to SSc as determined by the investigator, and with a typical frequency of attacks during the winter months (November-March) of on average at least 5 per week.

5.2 Exclusion Criteria

1) Smoking (including E-cigarettes) or use of nicotine replacement therapy for three months prior to Visit 1 and during the trial.
2) BMI >35
3) Mixed connective tissue disease or "overlap" (i.e. those who satisfy more than one set of ACR criteria for a rheumatic disease).
4) Concurrent serious medical condition with special attention to cardiac or ophthalmic conditions which in the opinion of the investigator makes the patient inappropriate for this study
5) Malignancy within the past 5 years with the exception of in situ removal of basal cell carcinoma and cervical intraepithelial neoplasia grade I
6) Planned major surgery within the duration of the study
7) Subjects who forsake any alcohol intake or have known uncontrolled allergic conditions or allergy/hypersensitivity to any components of the trial drug or placebo excipients (see Section 7.1)
8) Blood donation (or corresponding blood loss) within three months prior to Visit 1
9) Treatment with any of the medications listed below within 4 weeks prior to Visit 1:
    - Any dose-change or initiation of vasoactive substances[2)], and not able or willing to withhold these medications for 3 days preceding Visit 2 and Visit 3, respectively
    - Iloprost
    - Any treatment with CYP3A4 inducers (e.g. rifampicin, phenytoin, St John's Wort)
    - Any treatment with CYP3A4 inhibitors (e.g. clarithromycin, ketoconazole, nefazodone, itraconazole, ritonavir)
    - Any treatment with medicines that are substrates of CYP1A2, CYP3A4 or CYP2C9 with a narrow therapeutic range[3]
    - Any experimental drug
    - Any systemic immunosuppressive therapy other than:
        - Inhaled corticosteroids which can be used throughout the trial period

[2)] Calcium channel blockers, Nitrates or nitric oxide donors, PDE5 inhibitors, Angiotensin receptor blockers (ARBs), ERA's, Alpha-blockers or Fluoxetine, Antithrombotic agents, Beta-blockers or Clonidine

[3] e.g. alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, phenytoin, pimozide, quinidine, sirolimus, tacrolimus, theophylline, pirfenidone, celecoxib and warfarin. Investigators will need to consult the product information of a concomitant drug as these lists may not be exhaustive.

- The continuation of stable doses of ≤10 mg prednisolone
- Mycophenolate mofetil (MMF) which must be withheld for 3 days preceding Visit 2 and Visit 3

10) Any of the following findings at the time of screening:
    - Finger temperature below 27°C after acclimatising at an ambient temperature of 23°C for a period of 20 minutes
    - Prolonged QTcF (>450 ms), cardiac arrhythmias or any clinically significant abnormalities in the resting ECG, as judged by the Investigator
    - Positive results for HBsAg, HCVAb or HIV 1+2 Ag/Ab
    - Positive serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG)
    - Clinically significant abnormal laboratory value at Visit 1 indicating a potential risk for the subject if enrolled in the trial as evaluated by the Investigator
11) Pregnant or breast-feeding female subjects.
12) Female subjects of childbearing potential not willing to use contraceptive methods described in Section 5.3.1.
13) Male subjects not willing to use contraceptive methods described in Section 5.3.1.
14) Participation in any other interventional trial during the trial period
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)

5.3 Restrictions during the study

5.3.1 Contraception Requirements

Women of child bearing potential (WOCBP) must practice abstinence (if that is their preferred lifestyle) from Visit 1 to Visit 4, or must agree to use a highly effective method of contraception with a failure rate of <1% to prevent pregnancy (combined [oestrogen and progestogen containing] hormonal contraception associated with inhibition of ovulation [oral, intravaginal, transdermal], progestogen-only hormonal contraception associated with inhibition of ovulation [oral, injectable, implantable], intrauterine device [IUD] or intrauterine hormone-releasing system [IUS]) from at least 4 weeks prior to dose to 4 weeks after last dose. Their male partner must agree to use a condom during the same time frame, unless he has had a demonstrated successful vasectomy more than 6 months ago

Males should use condom and their female partner of child-bearing potential must use a contraceptive method with a failure rate of <1% to prevent pregnancy (see above) and drug exposure of a partner and refrain from donating sperm from the date of dosing until 3 months after the last IMP administration.

5.3.2 Meals and Dietary Restrictions

IMP should be administrated after overnight fasting. Subjects will be allowed to drink water and take his/her usual medication (e.g. proton pump inhibitor) with water on the morning of the visits.

The following is not allowed prior to Visit 2 and Visit 3:

- Within 10 days: Consumption of grapefruit and/or grapefruit containing products
- Within 12 hours: Smoking or use of nicotine-containing products such as e-cigarettes, vaping, chewing tobacco, snuff or smoking cessation compounds
- Within 4 hours: Food, coffee, caffeine, xanthine and taurine (e.g. energy drinks such as Redbull) or alcohol

5.3.3 Exercise

Subjects should abstain from strenuous exercise for 4 hours before Visit 2 and Visit 3.

5.4 Withdrawal Criteria

5.4.1 Withhold requirements at Visits 2 and 3

The below requirements must be evaluated prior to performing the cold challenge test at Visit 2 and Visit 3. Subjects violating any of the requirements can be re-scheduled for a new Visit ≤ 10 days later. Re-scheduling can only occur once per visit.

Table 5. Overview of substances to be withheld before performing cold challenge test at Visit 2 & 3

Time to withhold	Substances
4 weeks before Visit 1	• Systemic immunosuppressive therapies[1)] with the exception of inhaled corticosteroids and MMF (see later in this table) • Iloprost • CYP3A4 inducers (e.g. rifampicin, phenytoin, St John's Wort) • CYP3A4 inhibitors (e.g. clarithromycin, ketoconazole, nefazodone, itraconazole, ritonavir) • CYP2C9, CYP3A4 and CYP1A2 substrates with a narrow therapeutic range[2)]
10 days	• Acetylsalicylic acid • Clopidogrel • Grapefruit and/or grapefruit containing products
3 days	• Vasoactive substances[3)] • Mycophenalate mofetil (MMF)
12 hours	• Smoking or use of nicotine-containing products such as e-cigarettes, vaping, chewing tobacco, snuff or smoking cessation compounds
4 hours	• Food • Coffee, Caffeine • Energy drinks • Alcohol • Rigorous exercise

[1)] e.g. cyclophosphamide, azathioprine, methotrexate, cyclosporine or systemic corticosteroids other than mycophenale mofetil (MFF) and continuation of stable doses of ≤ 10 mg predniosolone

[2)] e.g. alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, phenytoin, pimozide, quinidine, sirolimus, tacrolimus, theophylline, pirfenidone, celecoxib and warfarin. Investigators will need to consult the product information of a concomitant drug as these lists may not be exhaustive.

[3)] Calcium channel blockers, Nitrates or nitric oxide donors, PDE5 inhibitors, Angiotensin receptor blockers (ARBs), ERA's, Alpha-blockers or Fluoxetine, Antithrombotic agents, Beta-blockers or Clonidine

5.4.2 Withdrawal from Trial

- The subject receives disallowed treatment during the study period (see Section 7.8.2)
- Failure to comply with withhold requirements in the table in Section 5.4.1
- The Investigator judges it necessary due to medical reasons
- The subject experiences a serious adverse event evaluated as related to trial medication
- It is the wish if the subject for any reason
- Pregnancy
- Un-blinding of treatment

An End-of-Trial Visit (Visit 4) must be completed for all randomised subjects withdrawn from the trial

Subjects withdrawn due to pregnancy will be followed – as consented to – until termination or delivery and the infant must be followed at least until the age of one month.

6 TRIAL DESIGN

6.1 Overall Trial Design

This is a randomised, double-blind, placebo-controlled, cross-over cold challenge study

The subjects will come to the clinic for four visits:

- Visit 1: Screening
- Visit 2: IMP administration and cold challenge (3-21 days after Visit 1)
- Visit 3: IMP administration and cold challenge (3-7 days after Visit 2)
- Visit 4: End of trial (3-15 days after Visit 3 or after withdrawal from trial)

Each subject is expected to participate in the study for 11-51 days including a 3-21 days screening period.

6.2 Number of Subjects

The study will include 16 randomised subjects.

6.3 Trial Diagram

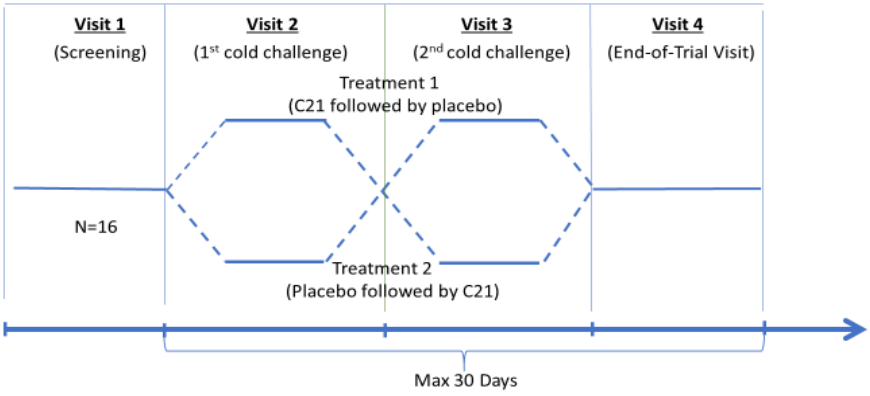

Figure 1. Trial Design

6.4 Trial Duration and Participating Centers

Planned first subject screened: Q4 2019

Planned last subject randomised: Q3 2020

Planned last subject last visit: Q4 2020

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

6.5 Schedule of Events

6.5.1 Screening (Visit 1)

Prior and no later than at start of screening (Visit 1) i.e. before any trial related activity takes place, the Investigator or a qualified designee will explain the nature of the trial, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. All explanations shall be in layman's language. The subject will be provided with a copy of the information sheet. The subject must be given sufficient time to consider the trial before deciding whether to participate or not.

After signed informed consent is obtained from the subject, the screening procedures can be initiated.

All subjects giving informed consent to participate in the trial will receive a screening number. During the screening visit, the subject is evaluated for eligibility (please refer to Section 5.1 and 5.2).

The following procedures are performed:

- Informed consent to be obtained
- Assignment of screening number
- Pregnancy testing (beta-HCG)

- Check of in- & exclusion criteria
- Application of thermal probe for check of finger temperature not being below 27°C (exclusion criterion 10)
- Assessment of eligibility which includes review of demographics, medical history, concomitant illnesses and medication, physical examination, height, weight, BMI and measurement of blood pressure and pulse
- Medical history and concomitant medication
- Raynaud's Condition Score
- Modified Rodnan skin score
- Application of thermal probe
- Nailfold capillaroscopy
- 12-lead ECG
- Blood sampling for safety and biomarker assessments (See Table 2 and Section 8)
- Information on restrictions prior to IMP administration at Visit 2 and Visit 3 (see Section 5.4.1)
- Reporting of AEs

6.5.2 Treatment (Visits 2 and 3)

Visit 2 can be scheduled as soon as the relevant screening assessments are available, and the subject has been found to be eligible. Visit 2 must occur 3- 21 days from Visit 1 (screening), to ensure that no eligibility assessments are older than 21 days when treatment is initiated.

Visit 3 can be scheduled 3-7 days days after Visit 2

The following procedures are performed:

Visit 2 only

a) Randomisation and assignment of randomisation number

Visit 2 and 3

1) Before IMP administration:
   a) Concomitant medication
   b) Withdrawal criteria to be checked (see Section 5.4)
   c) Pregnancy test (urine dip stick)
   d) Vital signs
   e) Physical examination (See Table 1 and Section 8.2.4)
   f) Raynaud's Condition Score
   g) Nailfold capillaroscopy
   h) Adverse events since last Visit
   i) Application of Holter ECG from 30 mins prior to IMP administration until 180 mins after time 0

Administration of IMP (time 0)

a) Capillaroscopy immediately before IMP administration
b) IMP administration (definition of the time 0 min)
c) Thermography image every 10 minutes

2) 40 min. after IMP (time 0) (Cold Challenge Test[4])
a) Last thermography image before cold challenge test
b) Capillaroscopy immediately before cold challenge
c) Immersion of both hands up to the metacarpophalangeal joints for 1 minute into cooled water (15°C)
d) Thermography images every 15 sec for 15 min
e) Capillaroscopy after thermography measurements have been completed

3) 55-60 min after IMP (time 0):
a) Blood sampling for potential analysis of C21 exposure (55 min after time 0)
b) Removal of temperature probe (60 min after time 0)

4) 120 min after IMP (time 0)
a) Meal

5) 180 min after IMP (time 0):
a) Removal of Holter ECG
b) Questions on Adverse Events during the day

For traceability purposes and to verify the subjects' existence, the Investigator must maintain an Identification List of all subjects who receive treatment. The list must contain full name, initials and date of birth.

6.5.3 Follow-up (Visit 4)

Visit 4 is performed 3 days after Visit 3. The visit must be performed no later than 30 days after Visit 2 (randomisation)

The following procedures are performed:

a) Recording of concomitant medication
b) Blood sampling for safety and biomarker assessments (See Table 2 and Section 8)
c) Urinanalysis
d) Pregnancy test (bloodsample)
e) Physical examination (See Table 1 and Section 8.2.4)
f) Vital signs
g) Reporting of AEs
h) 12-lead ECG

If a subject is withdrawn from treatment (see Section 5.3.2), a Visit 4 (End-of-Trial Visit) must be performed.

[4] According to standard protocol [Wilkinson et al 2018]

7 TRIAL TREATMENT

7.1 Investigational Medicinal Products

7.1.1 Active Treatment

Active substance: C21 is presented as a solution for oral administration. It is a solution of the sodium salt of C21 (3-[4-(1H-imidazol-1- ylmethyl)phenyl]- 5-(2- methylpropyl)t hiophene-2-[(N-butyloxylcarbamate)-sulphonamide] sodium salt). The concentration is 5.2 mg/mL of the sodium salt, equivalent to a 5 mg/mL of the parent acid.

Excipients:

Name of ingredient	**Reference to standard**
Sodium carbonate, anhydrous	Ph.Eur.
Sodium hydrogen carbonate	Ph.Eur.
Water, purified	Ph.Eur.

7.1.2 Reference Treatment (Placebo)

Active substance: None

Excipients:

Name of ingredient	**Reference to standard**
Citric acid monohydrate	Ph.Eur.
Denatonium benzoate	USP-NF
Ethanol (96 %)	Ph.Eur.
Hydrochloric acid	Ph.Eur.
Sodium hydroxide	Ph.Eur.
Water, purified	Ph.Eur.

7.2 Packaging, Labeling and Storage

IMP will be delivered in 50 mL vials containing 20 mL solutions of 100 mg C21 or placebo, and must be stored in a freezer (below -15°C). The IMP could however be stored in refrigerator (+2 to +8°C) for a maximum of 1 month prior to being administered to the patient. Details regarding

thawing conditions and storage of the thawed solution, will be specified in a separate trial specific document.

The study drug will be labelled according to applicable regulatory requirements including unique vial-numbers and a placeholder for the patient ID to clearly identify the vials given to the subjects.

At the trial site, IMP must be stored seperately from normal clinic stocks in a securely locked area only accessible to authorized trial personnel. Storage temperature must be monitored.

Labeling of the IMP will be done in compliance with GMP Annex 13 [GMP 2003] and local regulatory requirements.

7.3 Treatment Assignment

Eligible subjects will be randomised to receive either C21 or placebo in a random order at Visit 2 and the opposite medication at Visit 3. The doses administered to each subject is:

- Placebo
- C21 200 mg

Each subject will be assigned a randomisation code number.

Authorised trial staff will document the randomisation code number assigned in the subject's medical record and in the relevant electronic Case Report Forms (eCRFs).

7.4 Administration of Investigational Medicinal Products

At Visit 2, a single dose of either 200 mg C21 or placebo will be administered orally to subjects in fasted state together with 200 mL of water. At Visit 3 each subject will cross-over and receive the opposite medication. Subjects must stay fasted for minimum 4 hours before and minimum 1 hour after IMP intake.

IMP will be administered by the site staff and a trial staff member will oversee that the IMP is actually swallowed. The IMP must be administered 40 minutes before initiation of the Cold Challenge Test, at time 0 min.

7.5 Compliance Check and Drug Accountability

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

The Investigator will maintain a Storage and Accountability Log as well as a Drug Dispensing Log detailing the dates and quantities of study medication received, dispensed to and used by each subject . All details will be recorded in the eCRF.

After completed drug accountability, all unused and partly used IMP will be returned to Sponsor or Sponsor's designee for destruction. All returned IMP will be reconciled.

7.6 Blinding of the Trial

The study will be conducted in double-blind fashion and the allocation of treatments will not be disclosed until clean file has been declared and the database has been locked.

The packaging and labeling of IMP will reveal no evidence of IMP identity. C21 and the placebo are identical in appearance.. No difference can be sensed regarding smell. The placebo formulation contains an additive giving a bitter taste to obtain a medicinal taste. Hence, it is expected that subjects, Investigator and other trial personnel will remain unaware of treatment allocation.

7.7 Procedures for Unblinding

The Sponsor or Sponsor's designee will provide trial sites with one randomisation code envelope per each randomised subject (together with the IMP).

The treatment code may only be broken in case of a medical emergency. The Investigator shall only un-blind the treatment allocation of a subject in the course of a clinical trial, if un-blinding is relevant for the safety of the subject.

For expedited reporting purposes the Sponsor or Sponsor's designee will be able to perform un-blinding.

Whenever a randomisation code is broken at the site, the person breaking the code must record the time, date and reason as well as her/his initials in the subject's medical records.

The subject must be withdrawn immediately after code break.

7.8 Prior and Concomitant Medications

Concomitant medications are all medications being continued by the subject at trial entry and all medications 4 weeks prior to screening and received in addition to IMP during the trial period.

At each visit, the Investigator or qualified designee will ask the subject about concomitant medication. All concomitant medications will be documented in the subject's medical records and in the eCRF. Any changes in concomitant medications (e.g. new treatment, discontinuation of treatment or change in dosage) during the trial period must be documented in the subject's medical records and in the eCRF.

The following information will be recorded in the eCRF:

- Generic name (preferred) or trade name
- Reason for prescription
- Dose unit and frequency
- Route of administration
- Start date (if started > 3 months prior to Visit 1, then this can be stated instead of recording a date)
- Stop date (unless ongoing at trial termination)

7.8.1 Allowed Concomitant Medication

If considered unlikely to interfere with IMP or the outcome of the trial results, concomitant medication may be given according to local standard of care.

7.8.2 Disallowed Concomitant Medication

The following treatments are not allowed:

4 weeks before Visit 1	• Immunosuppressive therapies [1)] • Iloprost • CYP3A4 inducers (e.g. rifampicin, phenytoin, St John's Wort) • CYP3A4 inhibitors (e.g. clarithromycin, ketoconazole, nefazodone, itraconazole, ritonavir) • Treatment with medicines that are substrates of CYP1A2, CYP3A4 or CYP2C9 with a narrow therapeutic range
10 days before Visit 2 and Visit 3	• Acetylsalicylic acid • Clopidogrel
3 days before Visit 2 and Visit 3	• Vasoactive substances [2)] • Mycophenolate mofetil (MFF)

[1)] e.g. cyclophosphamide, azathioprine, methotrexate, cyclosporine or systemic corticosteroids other than Mycophenolate mofetil (MMF) and continuation of stable doses of ≤10 mg prednisolone

[2)] e.g. alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, phenytoin, pimozide, quinidine, sirolimus, tacrolimus, theophylline, pirfenidone, celecoxib and warfarin. Investigators will need to consult the product information of a concomitant drug as these lists may not be exhaustive.

[3)]

Calcium channel blockers, Nitrates or nitric oxide donors, PDE5 inhibitors, Angiotensin receptor blockers (ARBs), ERA's, Alpha-blockers or Fluoxetine, Antithrombotic agents, Beta-blockers or Clonidine

8 ASSESSMENTS

8.1 Efficacy Assessments

8.1.1 Cold challenge

Cold challenge will be performed following a standard protocol [Wilkinson et al 2018]. A baseline thermography will be performed, and a temperature probe will be attached to a finger before IMP is administrated.

Thermography will be initiated immediately prior to IMP intake (time 0). Images will be obtained every 10 minutes until immediately prior to cold challenge (40 minutes after time 0), where both hands will be immersed up to the metacarpophalangeal joints for 1 minute into cooled water (temperature of 15°C ±1°C). Reperfusion/rewarming will be imaged by thermography every 15 seconds at 4 frames per minute, for 15 minutes. Analysis of the images will be performed using Research IR Max (version 4.2; FLIR).

8.1.2 Biomarkers

Blood samples (plasma) for potential analysis of biomarkers related to platelet activation and endothelium will be obtained at the following timepoints:

- Visit 1
- Visit 2 and Visit 3:
  - Before IMP administration
  - Within 5 minutes before cold challenge
  - Within 1 minute after cold challenge
  - 15 minutes after cold challenge
- Visit 4

8.1.3 C21 Exposure

Blood sample for potential analysis of C21 plasma concentration will be obtained 15 min after cold challenge at Visit 2 and Visit 3 to check if subjects have been exposed to active treatment, if relevant.

8.2 Safety Assessments

8.2.1 Adverse Events

Adverse Events (AEs) will be reported from signing of informed consent until End of Trial participation (Visit 4)

AEs concerning cardiac or ophthalmic conditions are of special interest and must be reported to the Sponsor within 24 hours of obtaining knowledge of the event.

8.2.2 Medical History and Concomitant Illnesses

The medical history and concomitant illness will be obtained by interviewing the patient or by inspecting his/her medical records.

8.2.3 Pregnancy Test

Women of childbearing potential will undergo pregnancy tests at all visits [1)].

- Visit 1 and Visit 4: Blood sample
- Visit 2 and Visit 3: Urine dip-stick

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

8.2.4 Physical Examination

A complete physical examination including assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities will be performed at Visit 1 and Visit 4.

A short version of physical examination including assessments of selected body systems at the judgement of the Investigator will be performed at Visit 2 and Visit 3 and must include cardiac examination.

8.2.5 Vital Signs

Systolic and diastolic blood pressure, pulse and body temperature will be measured in supine position after 10 minutes of rest.

8.2.6 Electrocardiogram

12-lead ECG will be recorded at Visit 1 and Visit 4.

Holter ECG will be recorded at Visit 2 and Visit 3 from 30 mins prior to IMP administration until 180 mins after.

ECG evaluation will be performed by a centralised reader.

8.2.7 Safety Laboratory Parameters

Safety laboratory parameters will be taken at Visit 1 and Visit 4:

- Haematology: Haemoglobin (Hb), haematocrit (Erythrocyte volume fraction), platelet count (Trombocyte particle concentration [TPC]), leucocyte count, Mean Corpuscular Volume (MCV).
- Biochemistry: Albumin, alanine transferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase Gamma (ALP), bilirubin, Blood Urea Nitrogen (BUN), calcium, creatinine, C-Reactive Protein (CRP), Gamma Glutamyl Transferase (gGT), glucose, Lactate dehydrogenase (LD), potassium, sodium

Any laboratory abnormality, judged by the Investigator to be a clinically relevant worsening since Visit 1, should be reported as AEs if the laboratory abnormality required clinical intervention or further investigation, unless the laboratory abnormality is associated with an already reported event.

8.3 Other Assessments

8.3.1 Demographics and other Baseline Characteristics

Demographic and baseline characteristics include but are not limited to age at screening, sex, height, weight, date of first diagnosis of disease under study, and disease-specific scoring.

8.3.2 Raynaud's Condition Score

Subjects will complete the Raynaud's Condition Score (RCS), at Visit 1, Visit 2 and Visit 3 to assess the severity and impact of their RP for that day (Merkel et al 2002).

8.3.3 Nailfold Capillaroscopy

Capillaroscopy, including measurement of red blood cell velocity, will be performed at Visit 1 to assess the degree of vasculopathy as a baseline descriptor [Herrick & Murray 2018]. Exploratory

capillaroscopy will be performed at Visit 2 and 3 before IMP administration and before and after cold challenge (See Section 6.5.2)

8.3.4 Modified Rodnan Skin Score (mRSS)

The modified Rodnan skin score (mRSS) is a measure of skin involvement (Khanna et al 2017) and will be assessed at Visit 1 as a baseline descriptor.

8.3.5 Prior and concomitant medication

Prior medications taken will be obtained by subject interview in order to verify that the eligibility criteria are met.

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

9 ADVERSE EVENTS

9.1 Adverse Event Definitions

An Adverse Event (AE), an Adverse Drug Reaction (ADR) and a Serious Adverse Event (SAE) are defined according to ICH Guideline E2A [ICH 1994].

An AE is any untoward medical occurrence in a subject administered the IMP and which does not necessarily have to have a causal relationship with this IMP. An AE can therefore be any unfavorable and unintended sign (e.g. a significant abnormal laboratory finding, , symptom, or disease temporally associated with the use of the IMP, whether or not considered related to the IMP.

An ADR is any noxious and unintended response to an IMP related to any dose of the IMP.

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is judged medically important (this refers to an event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed)

A non-SAE is any AE that does not meet the definition of an SAE.

The following will not be considered an AE:

- Pre-planned procedure (documented at Visit 1) unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent form
- Concomitant illness identified as a result of screening procedures. However, if symptoms are worsened and/or become serious as defined in Section 9.1, this must be reported as a SAE.

9.2 Adverse Event Assessment Definitions

9.2.1 Severity

The investigator should assess the severity of all AEs according to the following definitions:

- Mild: awareness of sign or symptom, but easily tolerated (acceptable).
- Moderate: discomfort to interfere with usual activities (disturbing).
- Severe: incapacity to work or to perform usual activities (unacceptable).

Note the distinction between seriousness and severity: The term severe is used to describe the intensity of the event and a severe event is not necessarily serious. The seriousness criteria serve as a guide for defining regulatory reporting obligations.

9.2.2 Relationship to IMP

Assessment of causality is based on the following considerations: associative connections (time and/or place), pharmacological explanations, previous knowledge of the drug, presence of characteristic clinical or pathological phenomena, exclusion of other causes, and/or absence of alternative explanations.

The investigator will be asked to assess causal relationship to the trial treatment according to the following classifications:

Related:

- Time relationship exists; and previous knowledge of the trial product supports a causal relationship although another cause cannot be ruled out; and/or improvement on dechallenge or dose reduction has occurred (if performed); and/or recurrence of symptoms on rechallenge has occurred (if performed); and/or a specific laboratory test supports a causal relationship.

Not related:

- No time relationship between administration of the trial product and occurrence or worsening of the AE exists; and/or another cause is confirmed and no indication for involvement of the trial product in the occurrence/worsening of the AE exists. The alternative, most likely other cause(s) should be indicated.

9.2.3 Outcome

The investigator will be asked to record the most appropriate outcome of the following:

- Recovered

- Ongoing
- Not recovered
- Recovered with sequelae
- Death
- Unknown

9.3 Reporting of Adverse Events

All events meeting the definition of an AE must be reported in the period from the subject has signed the informed consent form until the end of trial participation (Visit 4).

At each visit the subject will be asked about AEs in an objective manner, *e.g.*: "Have you experienced any problems since the last visit?"

Only medically qualified personnel (investigators) must assess AEs.

AEs must be reported on the AE form. The diagnosis should be recorded, if available. If no diagnosis is available each sign and symptom should be recorded as individual AEs.

AEs concerning cardiac or ophthalmic conditions are of special interest and must be reported to the Sponsor within 24 hours of obtaining knowledge of the event.

SAEs, in addition, must be reported within 24 hours of obtaining knowledge of the event. The information to be reported will include assessment of severity, causal relationship to IMP or trial procedures, action taken, outcome, and a narrative description of the course of the event. Additional information may be subsequently provided.

All other relevant documents supporting the reported SAE (*e.g.* diagnostic procedures, hospital records, autopsy reports) must be faxed or scanned/emailed to Sponsor or Sponsor's designee.

The independent ethics committees (IEC) and regulatory authorities will be notified of SAEs according to current regulation and local requirements.

All Suspected, Unexpected Serious Adverse Reactions (SUSARs) are subject to expedited reporting to regulatory authorities. Pharmacovigilance will unblind such cases prior to reporting.

Investigators, the Sponsor and local IECs (if applicable) will remain blinded.

The expectedness of a SUSAR will be assessed against the reference safety information. Any SUSARs will be reported by the CRO to the relevant Competent Authority. SUSARS will also be reported to the Ethics Committee by the site/CRO. Fatal and life threatening SUSARs will be reported as soon as possible and no later than seven calendar days from the date of first knowledge of the event. Relevant follow-up information will subsequently be expedited within an additional eight days. All other SUSARs will be expedited no later than 15 calendar days of first knowledge of the event.

9.4 Follow-up on Adverse Events

All AEs should be followed until they are resolved or the subject's participation in the trial ends, whichever comes first.

SAEs and severe, non-serious AEs considered related to trial drug should be followed on a regular basis according to the investigator's clinical judgment until a final outcome has been established.

9.5 Pregnancies

Any pregnancy that occurs during trial participation must be reported and administration of trial drug must be terminated immediately. A pregnancy must be reported to Sponsor or designee within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and infant. Pregnancy complications and elective terminations for medical reasons must be reported as AEs or SAEs, as applicable. Spontaneous abortion must be reported as an SAE.

In addition, the investigator must attempt to collect pregnancy information on any female partners of male trial participants who become pregnant while the participant is enrolled in the trial. Pregnancy information must be reported to Sponsor as described above.

10 CHANGES TO TRIAL CONDUCT

10.1 Protocol Amendments

Before implementation of substantial changes (as defined in EU guidance documents [European Commission 2006, 2010]) unless considered an urgent safety measure, approval / favorable opinion must be obtained from the appropriate regulatory authority(ies) and IEC(s)

10.2 Premature Termination of the Trial

In case of premature termination of the trial, health authorities and IECs will be notified in writing, including the reason for premature termination.

Conditions that may warrant premature termination of the trial include, but are not limited to the following:

- The discovery of an unexpected and significant or unacceptable risk to the subjects enrolled in the trial
- A decision of the Sponsor to discontinue development of the drug

10.3 Premature Termination of a Trial Site

The Sponsor can decide to prematurely terminate a site. Conditions that may warrant termination include, but are not limited to:

- Insufficient adherence to protocol requirements
- Failure to enrol subjects at an acceptable rate

11 DATA HANDLING AND RECORD KEEPING

11.1 Data from Clinical Trial Sites

Data from clinical trial sites will be entered in an eCRF.

The Investigator will sign relevant eCRF sections by use of an electronic signature. Only the Investigator (i.e. medically qualified personnel) can sign data on medical assessments. Any corrections made by the Investigator or authorised staff to the eCRF after original entry will document in an audit trail. The person making the change and the date, time and reason for the

change will be identified in the audit trail. Changes to the data already approved/signed by an Investigator will require re-signature by the Investigator. The Investigator (principal Investigator or sub-Investigator) will sign all patient data in the eCRF by an electronic signature.

Subject data will be recorded anonymously and the subjects will be identified only by a screening number.

The monitor will check the eCRF for accuracy and completion and perform source data verification. Data entered in the eCRF will be verified against source data. The level of source data verification is described in Section 11.2.

11.2 Source Data

All data entered in the eCRF should be verifiable by source data in the subject's medical record or other records at the trial site, as applicable:

- Details of the trial (trial ID and subject screening and randomisation number)
- Date(s) of informed consent of the subject
- Data of each trial visit including signature and /or initials of person(s) conducting the visit
- Data and information of any relevant telephone contact with the subject and signature and/or initials of person(s) conducting or receiving the call
- Subject's date of birth
- Diagnosis of SSc including start date
- Medical history and concomitant illness including start and stop dates
- Concomitant medication including start and stop dates
- Overall conslusion of the subject's eligibility
- Conclusion for each in-/exclusion criterion with respect to fulfillment of trial eligibility or not
- Physical examination
- Height, body weight and BMI
- Blood pressure and pulse
- Laboratory data, including date and time of blood sampling
- Investigator's evaluation of haematology and biochemistry results being out of range
- Date and times of blood sampling
- Nailfold capilloscopy
- Modified Rodnan Skin Score
- Raynaud's Condition Score
- Thermography

- Cold challenge
- All AEs, SAEs and pregnancies described in details
- Fasting before IMP administration
- IMP dispensed including time of dispensing
- Premature withdrawal of subject from the trial including reason and withdrawal criteria fullfilled

11.3 Coding of Data

Medical history and AEs will be coded using the lastest version of Medical Dictionary for Regulatory Activities (MedDRA).

Concomitant medication will be coded using the latest version of World Health Organisation (WHO) Drug Reference List.

11.4 Subject Confidentiality

The confidentiality of the subject data and subject records shall be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.

12 RETENTION OF DOCUMENTS

The monitor will instruct the investigator to maintain source documents and the signed informed consent form for each subject.

Furthermore, the monitor will instruct the investigator to archive essential documents for the duration defined in the ICH Guideline E6 (Note for Guidance on Good Clinical Practice [ICH 1997] or for 15 years, whichever comes first.

The duration of archiving defined in the ICH Guideline E6 is as follows:

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor.

The Sponsor will notify the investigator when retention of the trial-related records is no longer required.

13 STATISTICAL METHODS

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

13.1 Sample Size and Power Considerations

A Total of 16 subjects will be included. With 14 subjects a difference of 0.104 in the primary endpoint (log(AUC)) could be detected with a power of 90% (and alpha=0.1) based on variability previously reported, intra-individual standard deviation of the differences of 0.126 (Wilkinson et al 2018). Two additional subjects will be included to compensate for potential drop-outs.

13.2 Analysis Data Sets

The Full Analysis Set (FAS) will consist of all subjects/subjects who have been randomised and received at least one dose of IMP and who has at least one post-baseline assessment of efficacy data allowing endpoint computation from each of the 2 treatment periods.

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

The Safety Analysis Set (SAS) will consist of all subjects who have been randomised and received at least one dose of IMP.

13.3 Subject Disposition

13.3.1 Baseline Characteristics

Demographics, medical history, baseline characteristics, and prior medications will be listed and summarized in terms of descriptive statistics: mean, SD, median and range for continuous outcomes and frequencies and percentages for categorical outcomes.

13.4 Efficacy Analysis

Rewarming after cold challenge will be assessed by thermography, and the following endpoints will be calculated:

- Area under the curve for reperfusion/rewarming in each finger (AUC) – Primary variable
- Maximum skin temperature after rewarming (MAX)
- The distal dorsal difference, defined as the difference in temperature between the dorsum and the finger (DDD)
- Gradient of rewarming in the first 2 minutes post–cold challenge (GRAD)

In addition, change in finger temperature during the first 60 minutes after administration of IMP will be assessed by temperature probe.

13.4.1 Efficacy Endpoint Analysis

Treatments will be compared using an analysis of (co)variance model (AN(C)OVA) adjusting for patient, period and treatment and including the baseline value of the period as a covariate if appropriate. Model for AUC will be multiplicative, with data being logged prior to analysis. Model estimates will be back-transformed giving the treatment contrast as a geometric mean ratio with 90% confidence intervals and associated, 2-sided p-value.

Secondary efficacy endpoints will be compared between treatment groups using similar AN(C)OVA models , multiplicative for MAX and GRAD and additive for other endpoints.

13.4.2 Statistical/Analytical Issues

13.4.2.1 Missing Data

Procedures for dealing with missing data will be described in the statistical analysis plan.

13.4.2.2 Examination of Subgroups

Important demographic and baseline value-defined subgroups will be examined and the results presented, *e.g.*, comparison of effects by smoking status, age, sex and baseline disease severity. A detailed description will be provided in the Statistical Analysis Plan.

13.5 Safety Analysis

13.5.1 Adverse Events

An overview of all treatment-emerging AEs including severity, relationship to IMP, serious AEs (SAEs) and AEs leading to withdrawals or death will be presented by treatment group.

AEs will be summarized by treatment group, system organ class (according to MedDRA) and preferred term (according to MedDRA) displaying number of subjects in treatment group, number and percentage of subjects having the AE as well as number of AEs. Furthermore, AEs will be summarized according to severity, relationship, outcome and seriousness.

SAEs and AEs leading to withdrawal will be listed and tabulated, if appropriate.

13.5.2 Electrocardiogram

Overall assesssment of 12-lead ECG at Visit 1 and Visit 4 will be summarized by visit.

Change from baseline (before IMP administration) of continuous HolterECG at Visit 2 and Visit 3 (treatment visits) will be systematically analysed and summarised by treatment group.

13.5.3 Vital Signs

Change from baseline (before IMP administration) of blood pressure and pulse will be summarized at Visit 2 and Visit 3 by treatment group.

13.5.4 Laboratory Safety Assessments

Changes in laboratory parameters over the study (Visit 1 to Visit 4) will be presented by descriptive statistics and by shift tables showing baseline values against values at end-of-study. Laboratory parameters will be categorised as ‘low’, ‘normal’ or ‘high’ (*i.e.* below, within, or above the reference ranges, respectively).

13.5.5 Physical examination

Results of full physical examination will be summarised for Visit 1 and Visit 4

14 GOOD CLINICAL PRACTICE

This trial will be carried out in compliance with the protocol, GCP, Standard Operating Procedures (SOPs) of the CROs and applicable regulatory requirements.

The investigator agrees, when signing this protocol, to adhere to the instructions and procedures described in it, to the principles of the Declaration of Helsinki, GCP and applicable regulatory requirements.

15 ETHICS

15.1 Independent Ethics Committees / Health Authorities

Before implementing this trial, the protocol, the proposed subject information and subject consent form, and other documents as required, will be reviewed by properly constituted Independent Ethics Committees (IECs) and by the national regulatory authorities.

A signed and dated statement that the protocol and subject information and subject consent form have been approved by the IECs and regulatory authorities will be obtained before trial initiation.

For each individual IEC the name and occupation of the chairman and the members of the IEC will be collected as well as a statement that the IEC works in accordance with ICH GCP.

IECs will receive updates on trial progress according to local regulations.

15.2 Informed Consent

The subject's signed and dated informed consent to participate in the trial will be obtained prior to any trial related procedure being carried out.

Before any trial related procedure the investigator will explain to the potential subject the aims, methods, reasonably expected benefits and potential hazards of the trial and any discomfort participation in the trial may entail. Subjects will be informed that participation in the trial is voluntary and that the subject may withdraw from the trial at any time and for any reason. Subjects will be informed that if they choose not to participate, this will not affect the care the subject will receive for the treatment of his or her disease. Finally, subjects will be informed that their records may be accessed by health authorities and authorized Sponsor staff without violating the confidentiality of the subject, to the extent permitted by the applicable laws or regulations.

All subjects will be given opportunity to ask questions and will be given sufficient time to consider before consenting. The subjects may choose to be accompanied, *e.g.* by a family member, during the information process. After having consented, a copy of the informed consent form will be given to the subject.

16 AUDITS AND INSPECTIONS

A representative of the Sponsor may visit the trial site(s) at any time during the trial or after completion of the trial to conduct an audit of the trial. These audits will require access to all trial records, including source documents, for inspection and comparison with the CRFs. Subject privacy will, however, be respected. The investigator and other trial personnel will be responsible

for being present and available for consultation during routinely scheduled site audit visits conducted by the Sponsor's representative.

Similar auditing procedures (inspections) may also be conducted by agents of regulatory health authorities, either as part of a national GCP compliance program or to review the results of this trial in support of a regulatory submission. The investigator should notify the Sponsor's representative or Sponsor immediately, if he/she has been contacted by a regulatory agency concerning an upcoming inspection.

17 MONITORING

Before trial initiation a monitor from Sponsor's representative will review the protocol and the CRF with the investigators and their trial personnel. During the trial the monitor will visit the trial site regularly to check the completeness of subject records, the accuracy of entries in CRFs, the adherence to the protocol and to GCP, the progress of enrolment and the handling and accounting of IMP. Key trial personnel must be available to assist the monitor during these visits.

The investigator must give the monitor direct access to source data/documents (*e.g.* relevant hospital or medical records) to confirm their consistency with the entries in CRFs. No information in these records about the identity of the subjects must leave the trial site.

18 REPORTING OF RESULTS

18.1 Integrated Clinical Trial Report

Data will be reported in an integrated clinical trial report in compliance with the requirements of the current version of ICH E3: Structure and Content of Clinical Study Report [ICH 1995]. The signatory investigator will review and sign the integrated clinical trial report.

18.2 Use of Information

All unpublished information relating to this trial and/or to the trial drug is considered confidential by the Sponsor and shall remain the sole property of the SSponsor.

The investigator must accept that the Sponsor may use the information from this clinical trial in connection with the development of the IMP, and therefore, may disclose it as required to other investigators, to government licensing authorities, to regulatory agencies of other governments, stock exchange market, and commercial partners.

18.3 Publication of Results

Basic information of this trial will be posted by the Sponsor on the website: www.clinicaltrials.gov before the first subject enters the trial.

The Sponsor is committed to publishing the trial results, whether positive or negative, in a peer-reviewed journal [Wager, 2003; Graf 2009].

The criteria for authorship as set out by the Committee of Medical Journal Editors (www.icmje.org) will be applied.

The contributorship model will be applied and contributors who do not meet the criteria for authorship will be listed in an acknowledgments section with descriptions of the role of each contributor in order to ensure indexation in the National Library of Medicine.

Publications are subject to the following conditions:

- Data are the property of the Sponsor and cannot be published without prior authorization from the Sponsor.
- Publications should be drafted with protection of individual privacy, intellectual property and contract rights in mind, and also conform to legislation and current national practices in patent and other laws.
- The primary publication (*i.e.* the results from all centers) should be published before, or in parallel with, any secondary publications.
- Publications shall not disclose any Sponsor confidential information or property.

19 INSURANCE AND LIABILITY

The Sponsor has subscribed to an insurance policy covering, in its terms and provision, its legal liability for injuries caused to participating subjects and arising out of trial procedures performed in accordance this protocol, in accordance with applicable law and with the ICH Guideline E6 (Note for Guidance on Good Clinical Practice) [ICH 1997].

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21 ABBREVIATIONS

ACR	American College of Rheumatology
ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
Ang II	Angiotensin II
ANOVA	Analysis of Variance
AP	Anterior-Posterior
ARB	Angiotensin receptor blocker
AST	Aspartate Aminotransferase
AT1R	Angiotensin II type 1 receptor
AT2R	Angiotensin II type 2 receptor
AUC	Area under the curve
AV	Atrioventricular
BMI	Body mass index
BUN	Blood Urea Nitrogen
cAMP	cyclic Adenosine Monophosphate
Cmax	Maximum plasma concentration
CNS	Central Nervous System
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive protein
CSR	Ckinical study report
DDD	Distal dorsal difference
eCRF	Electronic Case Report Form
ECG	Electrocardiography
EoT	End of Treatment
EMA	European Medicines Agency
eNOS	Endothelial nitric oxide synthase
ERA	Endothelin receptor antagonist
EU	European Union
EULAR	European League Against Rheumatism
FAS	Full Analysis Set
FSH	Follicle-stimulating Hormone
FU	Follow-up
GCP	Good Clinical Practice
GDF15	Growth Differentiation Factor 15
gGT	Gamma Glutamyl Transferase
GMP	Good manufacturing practise
GRAD	Gradient of rewarming
Hb	Haemoglobin
HBsAg	Hepatitis B virus s-antigen
HCG	Human chorionic gonadotropin
HCVAb	Hepatitis C virus antibodies
HEK	Human embryonic kidney
HIV	Human Immunodeficiency Virus
HDL	High-density Lipoprotein
hERG	Human Ether-a-go-go-related Gene
hs-CRP	High-sensitivity C-Reactive Protein
IB	Investigator's Brochure
ICH	International Conference on Harmonization

IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
ITT	Intention to Treat
IUD	Intrauterine device [IUD
IUS	Intrauterine hormone-releasing system
LD	Lactate dehydrogenase
LDL	Low-density Lipoprotein
LFT	Liver Function Test
MAD	Multiple ascending dose
MAX	Maximum skin temperature after rewarming
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MMF	Mycophenolate mofetil
mRSS	Modified Rodnan skin score
NHP	Non-Human Primate
NO	Nitric oxide
NOAEL	No Observed Adverse Effect Level
PDE-5	Phosphodiesterase 5
PK	Pharmacokinetic
PPAS	Per Protocol Analysis Set
QTcF	QT interval with Fridericia's correction
QTcR	QT interval with Rautaharju's correction
RAS	Renin-angiotensin system
RCS	Raynaud's Condition Score
RP	Raynaud's Phenomenon
SAD	Single ascending dose
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SAS	Safety Analysis Set
SSc	Systemic Sclerosis
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TPC	Trombocyte particle concentration
TSH	Thyroid Stimulating hormone
WHO	World Health Organization
WOCBP	Women of childbearing potential