Clinical trial results:
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)

Summary

EudraCT number	2019-003203-35
Trial protocol	GB
Global end of trial date	14 December 2020

Results information

Result version number	v1 (current)
This version publication date	11 January 2022
First version publication date	11 January 2022

Trial information

Trial identification

Sponsor protocol code	VP-C21-004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04388176
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vicore Pharma AB
Sponsor organisation address	Kronhusgatan 11, Göteborg, Sweden, SE-411 05
Public contact	Anne Katrine Cohrt, Vicore Pharma AB, +45 20111391, anne-katrine.cohrt@vicorepharma.com
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Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 December 2020
Global end of trial reached?	Yes
Global end of trial date	14 December 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

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).

Protection of trial subjects:

None

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 November 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 20
Worldwide total number of subjects	20
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	15
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial planned to include 16 subjects, however as recruitment was challenging during the COVID-19 pandemic, enrolment was stopped prematurely when 12 subjects were randomised. This ensured that trial results could be available in a timely manner.

Pre-assignment

Screening details:

A total of 20 unique subjects provided informed consent and were enrolled in the trial. Seven of these were screening failures. In addition, 2 subjects were not randomised; 1 subject due to the COVID-19 pandemic and 1 subject due technical issues with the Holter ECG. The latter subject was re-screened. A total of 12 subjects were randomised.

Pre-assignment period milestones

Number of subjects started	20
Number of subjects completed	12

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	Physician decision: 1
Reason: Number of subjects	Sponsor decision: 1
Reason: Number of subjects	Did not fulfill eligibility criteria: 4
Reason: Number of subjects	Not randomised due to COVID-19 pandemic: 1

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	PLA-C21

Arm description:

Placebo followed by C21

Arm type	Experimental
Investigational medicinal product name	C21
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

A single oral dose of 200 mg

Investigational medicinal product name	Reference treatment (placebo)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

A single oral dose

Arm title	C21-PLA

Arm description:

C21 followed by placebo

Arm type	Experimental
Investigational medicinal product name	C21
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

A single oral dose of 200 mg

Investigational medicinal product name	Reference treatment (placebo)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

A single oral dose

Number of subjects in period 1[1]	PLA-C21	C21-PLA
Started	6	6
Completed	6	6

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 20 subjects provided informed consent and were enrolled in the trial. 12 of these subjects completed the pre-assignment period, were included in the baseline period and were randomised to treatment.

Period 2

Period 2 title	Treatment period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	No

Arm title	C21 200 mg
Arm description: 200 mg C21	
Arm type	Experimental
Investigational medicinal product name	C21
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: A single oral dose of 200 mg	
Arm title	Placebo
Arm description: Placebo	
Arm type	Placebo
Investigational medicinal product name	Reference treatment (placebo)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: A single oral dose	

Number of subjects in period 2	C21 200 mg	Placebo
Started	12	12
Completed	12	12

Baseline characteristics

Reporting groups	
Reporting group title	PLA-C21
Reporting group description: Placebo followed by C21	
Reporting group title	C21-PLA
Reporting group description: C21 followed by placebo	

Reporting group values	PLA-C21	C21-PLA	Total
Number of subjects	6	6	12
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	5	4	9
From 65-84 years	1	2	3
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	51.5	59.5	
full range (min-max)	35 to 67	46 to 69	-
Gender categorical Units: Subjects			
Female	6	6	12
Male	0	0	0
Race Units: Subjects			
White	6	6	12
Ethnicity Units: Subjects			
Not hispanic or latino	6	6	12
Height Units: cm			
arithmetic mean	164.25	163.07	
full range (min-max)	155.0 to 171.5	154.0 to 180.0	-
Weight Units: kg			
arithmetic mean	64.92	68.32	
full range (min-max)	54.0 to 79.8	50.8 to 90.0	-
BMI Units: kg/m2			

arithmetic mean	24.2	25.6	
full range (min-max)	19.2 to 29.3	20.2 to 29.0	-

End points

End points reporting groups

Reporting group title	PLA-C21
Reporting group description: Placebo followed by C21	
Reporting group title	C21-PLA
Reporting group description: C21 followed by placebo	
Reporting group title	C21 200 mg
Reporting group description: 200 mg C21	
Reporting group title	Placebo
Reporting group description: Placebo	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis set (FAS) consisted of all subjects/subjects who were randomised and received at least 1 dose of IMP and who had at least one post-baseline assessment of efficacy data allowing endpoint computation from each of the 2 treatment periods.	
Subject analysis set title	PPAS
Subject analysis set type	Per protocol
Subject analysis set description: The per protocol analysis set (PPAS) was a subset of FAS and consisted of all subjects who were randomised and completed the trial without any major protocol deviations that were judged to compromise the analysis of the data. In this trial, PPAS was equal to FAS.	
Subject analysis set title	SAS
Subject analysis set type	Safety analysis
Subject analysis set description: The safety analysis set (SAS) consisted of all subjects who were randomised and received at least 1 dose of IMP.	

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

End point title	Area under the curve for rewarming of each finger after cold challenge (AUC) as measured by thermography
End point description:	
End point type	Primary
End point timeframe: For 15 minutes after cold challenge (40-55 minutes after a single dose of C21 or placebo)	

End point values	C21 200 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: C*sec				
geometric mean (geometric coefficient of variation)	20045.96 (± 7.68)	19558.43 (± 4.36)		

Statistical analyses

Statistical analysis title	Analysis of Thermography AUC
Comparison groups	C21 200 mg v Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.3801
Method	ANCOVA
Parameter estimate	Ratio in least-square means
Point estimate	1.0146
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.9859
upper limit	1.0442

Secondary: Maximum skin temperature after rewarming (MAX)	
End point title	Maximum skin temperature after rewarming (MAX)
End point description:	
End point type	Secondary
End point timeframe:	
For 15 min after cold challenge (40-55 min after IMP administration)	

End point values	C21 200 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: °C				
geometric mean (geometric coefficient of variation)	23.5336 (± 8.49)	22.5043 (± 3.73)		

Statistical analyses

Statistical analysis title	Analysis of thermography MAX
Comparison groups	C21 200 mg v Placebo

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0356
Method	ANCOVA
Parameter estimate	Ratio for least square means
Point estimate	1.0346
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.0086
upper limit	1.0613

Secondary: The distal dorsal difference, defined as the difference in temperature between the dorsum and the finger (DDD)

End point title	The distal dorsal difference, defined as the difference in temperature between the dorsum and the finger (DDD)

End point description:

End point type	Secondary

End point timeframe:

From administration of IMP until before cold challenge (0 to 40 min)

End point values	C21 200 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: °C				
arithmetic mean (standard error)				
Baseline	-2.4215 (± 0.4950)	-2.810 (± 0.3375)		
10 min	-3.395 (± 0.4580)	-3.2378 (± 0.3045)		
20 min	-3.1419 (± 0.4792)	-3.0596 (± 0.2323)		
30 min	-3.0347 (± 0.4037)	-3.1005 (± 0.1903)		
40 min	-2.9448 (± 0.333)	-2.7921 (± 0.1918)		

Statistical analyses

Statistical analysis title	Analysis of thermography DDD at 10 min
Comparison groups	Placebo v C21 200 mg

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0154
Method	ANCOVA
Parameter estimate	Difference in LS-means
Point estimate	-0.4991
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.8234
upper limit	-0.1749

Secondary: Gradient of rewarming in the first 2 minutes post-cold challenge (GRAD)

End point title	Gradient of rewarming in the first 2 minutes post-cold challenge (GRAD)

End point description:

End point type	Secondary

End point timeframe:

2 min after cold challenge (40-42 min after IMP administration)

End point values	C21 200 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: °C/min				
geometric mean (geometric coefficient of variation)	0.4482 (± 39.35)	0.5412 (± 42.26)		

Statistical analyses

Statistical analysis title	Analysis of thermography GRAD
Comparison groups	C21 200 mg v Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.282
Method	ANCOVA
Parameter estimate	Least square mean ratio
Point estimate	0.8301

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.6206
upper limit	1.1102

Other pre-specified: Change in finger temperature from intake of IMP to start of cold challenge

End point title	Change in finger temperature from intake of IMP to start of cold challenge

End point description:

End point type	Other pre-specified

End point timeframe:

From intake of IMP to start of cold challenge (0-40 min)

End point values	C21 200 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: °C				
arithmetic mean (standard error)	-1.347 (± 0.343)	-0.697 (± 0.471)		

Statistical analyses

Statistical analysis title	Analysis of change in finger temperature
Comparison groups	C21 200 mg v Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.3722
Method	ANCOVA
Parameter estimate	Difference in least square means
Point estimate	-0.3989
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.1718
upper limit	0.3739

Other pre-specified: Nailfold capillaroscopy

End point title	Nailfold capillaroscopy

End point description:

End point type	Other pre-specified

End point timeframe:

Before cold challenge (at 40 min) and post-recovery (at 55 min)

End point values	C21 200 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: mm/sec				
arithmetic mean (standard error)				
Baseline	0.369 (± 0.193)	0.122 (± 0.042)		
Before cold	0.207 (± 0.054)	0.302 (± 0.175)		
Post recovery	0.323 (± 0.149)	0.318 (± 0.140)		

Statistical analyses

Statistical analysis title	Analysis of capillaroscopy, before cold
Comparison groups	C21 200 mg v Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.4982
Method	ANCOVA
Parameter estimate	Difference in least square means
Point estimate	-0.109
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.4074
upper limit	0.1895

Statistical analysis title	Analysis of capillaroscopy, post recovery
Comparison groups	C21 200 mg v Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.6219
Method	ANCOVA
Parameter estimate	Difference in least square means
Point estimate	-0.0637

Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.3037
upper limit	0.1763

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From signing of informed consent until end of trial participation	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	C21 200 mg
Reporting group description: -	

Serious adverse events	Placebo	C21 200 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Placebo	C21 200 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 12 (25.00%)	5 / 12 (41.67%)	
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Hypoaesthesia			

subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Tremor			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Skin tightness			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 12 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 October 2020	There was 1 protocol amendment during the conduct of the trial (protocol version 4.0, dated 22-Oct-2020). The key changes introduced in the protocol version 4.0 were as follows: Exclusion criteria number 2 with respect to body mass index (BMI) > 30 was changed to BMI > 35 to facilitate completion of recruitment. No subjects were recruited after the approval of this amendment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
18 March 2020	The trial was on hold once (from 18-Mar-2020 to 17-Aug-2020) due to lock down in the UK during the COVID-19 pandemic.	17 August 2020

Notes:

Limitations and caveats

None reported