Clinical trial results:
An Exploratory Trial Assessing Vascular Digital Perfusion, Pharmacokinetics, Safety and Tolerability Following a Single Dose of CAM2043 (Treprostinil Subcutaneous Depot) in Patients with Raynaud's Phenomenon Secondary to Systemic Sclerosis

Summary

EudraCT number	2019-002444-24
Trial protocol	GB
Global end of trial date	14 December 2021

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	HS-18-638

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	IRAS: 272415

Notes:

Sponsors

Sponsor organisation name	Camurus AB
Sponsor organisation address	Ideon Science Park, Lund, Sweden, 223 70
Public contact	Clinical Development, Camurus AB, +46 46 286 57 30,
Scientific contact	Clinical Development, Camurus AB, +46 46 286 57 30,

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	21 March 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 December 2021
Global end of trial reached?	Yes
Global end of trial date	14 December 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To explore the effect of a single subcutaneous (SC) dose of CAM2043 on skin temperature (an indirect measure of digital vascular perfusion), as evaluated by thermography following controlled cold challenge in patients with Raynaud's phenomenon secondary to systemic sclerosis

Protection of trial subjects:

Prophylactic treatment with ibuprofen or other non-steroid anti inflammatory drugs was provided on an attempt to avoid onset of pain.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 November 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 10
Worldwide total number of subjects	10
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)	9
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at one site in the UK.
Approximately 12 patients were planned to be included but recruitment was delayed due to issues caused by coronavirus disease 2019 (COVID-19) pandemic and only 10 patients received CAM2043 due to the delay in the enrollment.

Pre-assignment

Screening details:

Patients with a diagnosis of systemic sclerosis, as defined by 2013 American College of Rheumatology/European League against Rheumatism criteria.
Patients with Raynaud Phenomenon secondary to systemic sclerosis with a minimum of 5 Raynaud Phenomenon attacks per week.

Pre-assignment period milestones

Number of subjects started	13[1]
Number of subjects completed	10

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Pregnancy or breastfeeding: 3

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Eleven patients were screened, and 3 patients were screen failures, out of the 3 screen failures, 2 were rescreened and enrolled in the trial with new identification numbers.

Period 1

Period 1 title	Overall trial (Treatment and FU Periods) (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	CAM2043 arm

Arm description:

CAM2043, single, subcutaneous injection

Arm type	Experimental
Investigational medicinal product name	treprostinil subcutaneous depot
Investigational medicinal product code	CAM2043
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

CAM2043 (treprostinil subcutaneous depot), 10 mg/mL treprostinil, single dose, subcutaneous injection depot, injected in abdomen (upper or lower) or buttock.

Number of subjects in period 1	CAM2043 arm
Started	10
Completed	10

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial (Treatment and FU Periods)

Reporting group description:

Patients eligible for the 1-week open-label Treatment Period received a single dose of CAM2043. The second week of the trial was a Follow-up Period during which patients did not receive any IMP. At the end of the Follow-up Period (Day 15), patients visited the trial site for a Completion Visit where efficacy outcomes, PK sampling, and safety and tolerability were assessed.

Reporting group values	Overall trial (Treatment and FU Periods)	Total	
Number of subjects	10	10	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	9	9	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	54.9		
standard deviation	± 6.7	-	
Gender categorical Units: Subjects			
Female	10	10	
Male	0	0	
With antibodies present at screening Units: Subjects			
Anticentromere	10	10	
Anti-Scl-70	0	0	
Anti-RNA polymerase	0	0	
Known case of systemic sclerosis Units: Subjects			
yes	10	10	
no	0	0	
Known case of Raynaud’s phenomenon secondary to systemic sclerosis Units: Subjects			
yes	10	10	
no	0	0	
Child-Pugh score Units: Subjects			

Class A (5-6 points)	10	10	
Class B (7-9 points)	0	0	
Class C (10-15 points)	0	0	
Time since diagnosis of systemic sclerosis			
Units: years			
arithmetic mean	11.5		
standard deviation	± 9.4	-	
Time since diagnosis of Raynaud’s phenomenon secondary to systemic sclerosis			
Units: years			
arithmetic mean	16.5		
standard deviation	± 9.4	-	
Number of episodes noticed per week			
Units: episodes/week			
arithmetic mean	19.9		
standard deviation	± 9.9	-	
Time to screening since last episode			
Units: days			
arithmetic mean	1.2		
standard deviation	± 0.6	-	

Subject analysis sets

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

all patients who were administered CAM2043 and who had data from at least one time point after dosing.

Subject analysis set title	safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

all patients who were administered CAM2043 (identical to the intention-to-treat analysis set)

Subject analysis set title	Intention-to-treat (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intention-to-treat (ITT) analysis set comprises all patients treated with CAM2043

Reporting group values	Full analysis set (FAS)	safety analysis set	Intention-to-treat (ITT)
Number of subjects	10	10	10
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)	9	9	9
From 65-84 years	1	1	1

85 years and over	0	0	0

Age continuous			
Units: years			
arithmetic mean	54.9	54.9	54.9
standard deviation	± 6.7	± 6.7	± 6.7
Gender categorical			
Units: Subjects			
Female	10	10	10
Male	0	0	0
With antibodies present at screening			
Units: Subjects			
Anticentromere	10	10	10
Anti-Scl-70	0	0	0
Anti-RNA polymerase	0	0	0
Known case of systemic sclerosis			
Units: Subjects			
yes	10	10	10
no	0	0	0
Known case of Raynaud’s phenomenon secondary to systemic sclerosis			
Units: Subjects			
yes	10	10	10
no	0	0	0
Child-Pugh score			
Units: Subjects			
Class A (5-6 points)	10	10	10
Class B (7-9 points)	0	0	0
Class C (10-15 points)	0	0	0
Time since diagnosis of systemic sclerosis			
Units: years			
arithmetic mean	11.5	11.5	11.5
standard deviation	± 9.4	± 9.4	± 9.4
Time since diagnosis of Raynaud’s phenomenon secondary to systemic sclerosis			
Units: years			
arithmetic mean	16.5	16.5	16.5
standard deviation	± 9.4	± 9.4	± 9.4
Number of episodes noticed per week			
Units: episodes/week			
arithmetic mean	19.9	19.9	19.9
standard deviation	± 9.9	± 9.9	± 9.9
Time to screening since last episode			
Units: days			
arithmetic mean	1.2	1.2	1.2
standard deviation	± 0.6	± 0.6	± 0.6

End points

End points reporting groups

Reporting group title	CAM2043 arm
Reporting group description: CAM2043, single, subcutaneous injection	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: all patients who were administered CAM2043 and who had data from at least one time point after dosing.	
Subject analysis set title	safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description: all patients who were administered CAM2043 (identical to the intention-to-treat analysis set)	
Subject analysis set title	Intention-to-treat (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description: The intention-to-treat (ITT) analysis set comprises all patients treated with CAM2043	

Primary: Change from baseline to 6 hours post-dose in the AUCtherm as derived from thermography measurements

End point title	Change from baseline to 6 hours post-dose in the AUCtherm as derived from thermography measurements[1]
End point description: The AUCtherm was derived from thermography measurements across 8 fingers (thumbs not included) over 15 minutes after the cold challenge. The temperature measurement prior to pre-dose cold challenge on Day 1 was used as a common baseline temperature for AUCtherm values derived at each post-dose time point. Summaries included 95% CIs and provided for observed cases and by using last observation carried forward (LOCF) on the FAS.	
End point type	Primary
End point timeframe: From pre-dose on Day 1 to 6 hours post-dose on Day 1	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Not applicable. Single-arm treatment trial. Only descriptive statistics were used.

End point values	CAM2043 arm			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: C x sec				
arithmetic mean (confidence interval 95%)	192.7 (-727.1 to 1112.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentrations of treprostinil

End point title	Plasma concentrations of treprostinil

End point description:

The FAS was used for the the summary of data

End point type	Secondary

End point timeframe:

Pre-dose (within 45 minutes of administration), 3 hours±15 minutes, 6 hours±30 minutes, 24±1 hours, 72 ±2 hours, 168 hours±1 day and 336 hours±1 day after administration.

End point values	CAM2043 arm			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: ng/mL				
arithmetic mean (standard deviation)				
Pre-dose (n=10)	0.0000 (± 0.0000)			
3 hours post-dose (n=10)	1.5615 (± 0.6937)			
6 hours post-dose (n=9)	2.1478 (± 1.0366)			
24 hours post-dose (n=8)	0.5700 (± 0.2616)			
72 hours post-dose (n=10)	0.3252 (± 0.1897)			
168 hours post-dose (n=10)	0.1182 (± 0.0645)			
336 hours post-dose (n=10)	0.0474 (± 0.0432)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Day 8 and Day 15 in Raynaud's Condition Score

End point title	Change from baseline to Day 8 and Day 15 in Raynaud's Condition Score

End point description:

The Raynaud's Condition Score (RCS) is a self-assessment, graded on a scale of 0 to 10 (corresponding to 'no difficulty'- 'extreme difficulty'), based on the patient's perceived impact of the frequency, duration, and severity of the Raynaud's Phenomenon.
Summaries included 95% CIs for quantitative changes in scores. The FAS was used for the the summary of data.

End point type	Secondary

End point timeframe:

From pre-dose on Day 1 to Day 8 and Day 15

End point values	CAM2043 arm			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: score units				
arithmetic mean (confidence interval 95%)				
Day 8	-1.6 (-2.68 to -0.52)			
Day 15	-1.6 (-3.33 to 0.19)			

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Assessment on Day 8

End point title	Patient Global Assessment on Day 8

End point description:

Patients rated their perception of change from baseline in their Raynaud's Phenomenon during the trial using a PGA scale. The FAS was used for the the summary of data.

End point type	Secondary

End point timeframe:

On Day 8

End point values	CAM2043 arm			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: number of patients				
Much better	0			
A little better	4			
The same	6			
A little worse	0			
Much worse	0			
Missing	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Assessment on Day 15

End point title	Patient Global Assessment on Day 15

End point description:

Patients rated their perception of change from baseline in their Raynaud's Phenomenon during the trial using a PGA scale. The FAS was used for the the summary of data.

End point type	Secondary

End point timeframe:
On Day 15

End point values	CAM2043 arm			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: number of patients				
Much better	1			
A little better	3			
The same	1			
A little worse	2			
Much worse	0			
Missing	3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent AEs (TEAEs): following start of treatment until end of trial participation. Serious AEs: from enrolment (informed consent signed) until end of trial participation.

Adverse event reporting additional description:

Post-trial events: SAEs assessed as "possibly" or "probably" related to IMP were to be reported to the Sponsor by the Investigator regardless of the time that has elapsed.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	CAM2043

Reporting group description: -

Serious adverse events	CAM2043		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	CAM2043		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)		
Investigations			
Blood urea increased	Additional description: TEAEs		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Serum ferritin decreased	Additional description: TEAEs		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Vascular disorders			
Flushing	Additional description: TEAEs		
subjects affected / exposed	4 / 10 (40.00%)		
occurrences (all)	4		

Hypotension	Additional description: TEAEs		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Nervous system disorders			
Headache	Additional description: TEAEs		
subjects affected / exposed	9 / 10 (90.00%)		
occurrences (all)	12		
Presyncope	Additional description: TEAEs		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Sinus headache	Additional description: TEAEs		
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
General disorders and administration site conditions			
Injection site erythema	Additional description: TEAEs only		
subjects affected / exposed	10 / 10 (100.00%)		
occurrences (all)	26		
Injection site pain	Additional description: TEAEs		
subjects affected / exposed	10 / 10 (100.00%)		
occurrences (all)	28		
Injection site swelling	Additional description: TEAEs		
subjects affected / exposed	9 / 10 (90.00%)		
occurrences (all)	23		
Ear and labyrinth disorders			
Tinnitus	Additional description: TEAEs		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Eye disorders			
Photophobia	Additional description: TEAEs		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea	Additional description: TEAEs		
subjects affected / exposed	5 / 10 (50.00%)		
occurrences (all)	6		
Nausea	Additional description: TEAEs		

subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Vomiting	Additional description: TEAEs		
subjects affected / exposed	5 / 10 (50.00%)		
occurrences (all)	5		
Skin and subcutaneous tissue disorders			
Dry skin	Additional description: TEAEs		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Pain of skin	Additional description: TEAEs		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Pruritus	Additional description: TEAEs		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Skin ulcer haemorrhage	Additional description: TEAEs		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Renal and urinary disorders			
Renal impairment	Additional description: TEAEs		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Pain in jaw	Additional description: TEAEs		
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Musculoskeletal pain	Additional description: TEAEs		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Pain in extremity	Additional description: TEAEs		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis	Additional description: TEAEs		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		

Metabolism and nutrition disorders			
Hypercholesterolaemia	Additional description: TEAEs		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Hyperlipidaemia	Additional description: TEAEs		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Hyperuricaemia	Additional description: TEAEs		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2020	• The dose of CAM2043 was lowered from 5 to 2.5 mg • The section 'Treatments for Injection Site Pain' was amended to include consideration for patients with systemic sclerosis who could not tolerate ibuprofen or other non-steroid anti-inflammatory drugs (NSAIDs).
11 May 2021	• The exclusion of patients with 2 thermography assessments with more than 20% difference on the day of screening, was removed. • Administration of CAM2043 as an SC injection in the buttock by a trained healthcare professional was added to increase the number of sites for SC injection.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
14 December 2021	The recruitment was delayed due to issues caused by coronavirus disease 2019 (COVID-19) pandemic. This led to that only 10 patients received CAM2043 as the investigational medicinal product (IMP) batch reached its expiry date.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The COVID-19 pandemic and lockdown restrictions had a major impact on the conduct of the trial, difficulting screening and enrollment of patients.

Notes: