Clinical trial results:
A First-in-Human, Double-Blind, Randomised, Vehicle Controlled Phase I/II Proof of Concept Study to Investigate the Safety, Tolerability, Pharmacokinetics and Efficacy of BEN2293 in Patients with Mild to Moderate Atopic Dermatitis (AD).

Summary

EudraCT number	2020-003143-28
Trial protocol	GB PL NL HU
Global end of trial date	26 January 2023

Results information

Result version number	v1 (current)
This version publication date	01 November 2023
First version publication date	01 November 2023
Summary attachment (see zip file)	synopsis-2020-003143-28 (synopsis-2020-003143-28.pdf)

Trial information

Trial identification

Sponsor protocol code	BB-2293-101b

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04737304
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	BenevolentAI Bio Limited
Sponsor organisation address	4-8 Maple Street, London, United Kingdom, W1T 5HD
Public contact	Chief Scientific Officer, BenevolentAI Bio Limited, anne.phelan@benevolent.ai
Scientific contact	Chief Scientific Officer, BenevolentAI Bio Limited, anne.phelan@benevolent.ai

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	17 August 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 January 2023
Global end of trial reached?	Yes
Global end of trial date	26 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to assess the safety and tolerability of BEN2293, administered as multiple topical doses to increasing body surface areas, in patients with mild to moderate AD.

Protection of trial subjects:

In this study, safety will be monitored closely both by subjective reporting and by objective means i.e., serial assessments of vital signs, clinical laboratory evaluations data, physical examinations, local tolerability and 12-lead electrocardiogram (ECG). Part A of this study will be run in a Clinical Research Unit (CRU) with immediate access to hospital facilities for the treatment of medical emergencies. Sentinel dosing will be used for all cohorts in Part A of this study, and for the first two cohorts in Part A, sentinel patients will be given a choice as to whether they reside in the CRU for the full duration of Day -1 to Day 9, or reside from Day -1 to Day 3, as per the remainder of the cohort. Other participants in Part A will reside in the CRU for the first 2 days of dosing, will be closely monitored and will only be discharged from the CRU if the Investigator deems it safe to do so. Part B of this study will be run across multiple sites and safety will be monitored on visit days.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 October 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Georgia: 8
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	United Kingdom: 82
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Netherlands: 20
Worldwide total number of subjects	123
EEA total number of subjects	33

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)	123
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Part A: Thirty-two patients were enrolled, randomised evenly across treatment groups and dosed during Part A of the study. Thirty-one patients completed Part A of the study; one patient withdrew consent. Part B: Ninety-one patients were enrolled during Part B of the study. Eighty patients completed Part B of the study and 11 patients discontinued.

Pre-assignment

Screening details:

All subjects satisfied the inclusion/exclusion criteria prior to entry in the study.

Period 1

Period 1 title	Overall Trial (full study) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

This study is a double-blinded (Investigator- and patient-blinded) during the double-blind treatment period. The study will be single-blind (patient-blinded) during the run-in phase (Part B only). In Part A, the randomisation list will be kept in a secure location until the end of the study. Only the Pharmacy staff involved in handling the study drug will have access to the randomisation list. In Part B, an externally provided IRT system will be used to randomly allocate patients to treatment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A - Cohort 1

Arm description:

0.25% BEN2293 ointment daily for 7 days on 10% of body surface area

Arm type	Experimental
Investigational medicinal product name	BEN2293 0.25% w/w
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical

Dosage and administration details:

BEN2293 0.25% w/w ointment QD for 7 days to 10% BSA

Arm title	Part A - Cohort 2

Arm description:

1.0% BEN2293 ointment daily for 7 days on 10% of body surface area

Arm type	Experimental
Investigational medicinal product name	BEN2293 1.0% w/w
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical

Dosage and administration details:

BEN2293 1.0% w/w QD for 7 days to 10% BSA

Arm title	Part A - Cohort 3

Arm description:

1.0% BEN2293 ointment daily for 14 days on up to 30% of body surface area

Arm type	Experimental
Investigational medicinal product name	BEN2293 1.0% w/w
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical

Dosage and administration details:

BEN2293 1.0% w/w QD for 14 days to up to 30% BSA

Arm title	Part A - Cohort 4

Arm description:

1.0% BEN2293 ointment twice-daily for 14 days on up to 30% of body surface

Arm type	Experimental
Investigational medicinal product name	BEN2293 1.0% w/w
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical

Dosage and administration details:

BEN2293 1.0% w/w BID for 14 days to up to 30% BSA

Arm title	Part B - Active

Arm description:

1.0% BEN2293 ointment twice-daily for 28 days on up to 33% of body surface area

Arm type	Experimental
Investigational medicinal product name	BEN2293 1.0% w/w
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical

Dosage and administration details:

BEN2293 1.0% w/w BID for 28 days to a maximum of 33% BSA

Arm title	Part A - Placebo

Arm description:

Placebo ointment on regimen matched to active cohort

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical

Dosage and administration details:

Placebo ointment on regimen matched to active cohort

Arm title	Part B - Placebo

Arm description:

Placebo ointment twice-daily for 28 days on up to 33% of body surface area

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical

Dosage and administration details:

Placebo ointment twice-daily for 28 days on up to 33% of body surface area

Number of subjects in period 1	Part A - Cohort 1	Part A - Cohort 2	Part A - Cohort 3
Started	6	6	6
Completed	5	6	6
Not completed	1	0	0
Consent withdrawn by subject	1	-	-
Physician decision	-	-	-
Adverse event, non-fatal	-	-	-
Circumstances of contraception changed	-	-	-

Number of subjects in period 1	Part A - Cohort 4	Part B - Active	Part A - Placebo
Started	6	49	8
Completed	6	42	8
Not completed	0	7	0
Consent withdrawn by subject	-	3	-
Physician decision	-	1	-
Adverse event, non-fatal	-	2	-
Circumstances of contraception changed	-	1	-

Number of subjects in period 1	Part B - Placebo
Started	42
Completed	38
Not completed	4
Consent withdrawn by subject	3
Physician decision	1
Adverse event, non-fatal	-
Circumstances of contraception changed	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial (full study)

Reporting group description: -

Reporting group values	Overall Trial (full study)	Total	
Number of subjects	123	123	
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)	123	123	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	66	66	
Male	57	57	

Subject analysis sets	
Subject analysis set title	Part A Cohort 1: 0.25% BEN2293 daily for 7 days on 10% of BSA
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS will include all randomised patients who received at least one application of randomised therapy. Patients will be analysed according to their randomised treatment.

Subject analysis set title	Part A - Cohort 2 1.0% BEN2293 daily for 7 days on 10% of BSA
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS will include all randomised patients who received at least one application of randomised therapy. Patients will be analysed according to their randomised treatment.

Subject analysis set title	Part A - Cohort 3 1.0% BEN2293 daily for 14 days up to 30% BSA
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS will include all randomised patients who received at least one application of randomised therapy. Patients will be analysed according to their randomised treatment.

Subject analysis set title	Part A - Cohort 4 1.0% BEN2293 twice daily 14 days to 30% BSA
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS will include all randomised patients who received at least one application of randomised therapy. Patients will be analysed according to their randomised treatment.

Subject analysis set title	Part A - Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS will include all randomised patients who received at least one application of randomised therapy. Patients will be analysed according to their randomised treatment.

Subject analysis set title	Part B Active: 1.0% BEN2293 twice daily for 28 days to 33% BSA
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS will include all randomised patients who received at least one application of randomised therapy. Patients will be analysed according to their randomised treatment.

Subject analysis set title	Part B - Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS will include all randomised patients who received at least one application of randomised therapy. Patients will be analysed according to their randomised treatment.

Reporting group values	Part A Cohort 1: 0.25% BEN2293 daily for 7 days on 10% of BSA	Part A - Cohort 2 1.0% BEN2293 daily for 7 days on 10% of BSA	Part A - Cohort 3 1.0% BEN2293 daily for 14 days up to 30% BSA
Number of subjects	6	6	6
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)	6	6	6
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	4	1	3
Male	2	5	3

Reporting group values	Part A - Cohort 4 1.0% BEN2293 twice daily 14 days to 30% BSA	Part A - Placebo	Part B Active: 1.0% BEN2293 twice daily for 28 days to 33% BSA
Number of subjects	6	8	49
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)	6	8	49

From 65-84 years	0	0	0
85 years and over	0	0	0

Gender categorical Units: Subjects			
Female	5	1	28
Male	1	7	21

Reporting group values	Part B - Placebo		
Number of subjects	42		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	42		
From 65-84 years	0		
85 years and over	0		
Gender categorical Units: Subjects			
Female	24		
Male	18		

End points

End points reporting groups

Reporting group title	Part A - Cohort 1
Reporting group description:	
0.25% BEN2293 ointment daily for 7 days on 10% of body surface area	

Reporting group title	Part A - Cohort 2
Reporting group description:	
1.0% BEN2293 ointment daily for 7 days on 10% of body surface area	

Reporting group title	Part A - Cohort 3
Reporting group description:	
1.0% BEN2293 ointment daily for 14 days on up to 30% of body surface area	

Reporting group title	Part A - Cohort 4
Reporting group description:	
1.0% BEN2293 ointment twice-daily for 14 days on up to 30% of body surface	

Reporting group title	Part B - Active
Reporting group description:	
1.0% BEN2293 ointment twice-daily for 28 days on up to 33% of body surface area	

Reporting group title	Part A - Placebo
Reporting group description:	
Placebo ointment on regimen matched to active cohort	
Reporting group title	Part B - Placebo
Reporting group description:	
Placebo ointment twice-daily for 28 days on up to 33% of body surface area	
Subject analysis set title	Part A Cohort 1: 0.25% BEN2293 daily for 7 days on 10% of BSA
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS will include all randomised patients who received at least one application of randomised therapy. Patients will be analysed according to their randomised treatment.	
Subject analysis set title	Part A - Cohort 2 1.0% BEN2293 daily for 7 days on 10% of BSA
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS will include all randomised patients who received at least one application of randomised therapy. Patients will be analysed according to their randomised treatment.	
Subject analysis set title	Part A - Cohort 3 1.0% BEN2293 daily for 14 days up to 30% BSA
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS will include all randomised patients who received at least one application of randomised therapy. Patients will be analysed according to their randomised treatment.	
Subject analysis set title	Part A - Cohort 4 1.0% BEN2293 twice daily 14 days to 30% BSA
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS will include all randomised patients who received at least one application of randomised therapy. Patients will be analysed according to their randomised treatment.

Subject analysis set title	Part A - Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS will include all randomised patients who received at least one application of randomised therapy. Patients will be analysed according to their randomised treatment.

Subject analysis set title	Part B Active: 1.0% BEN2293 twice daily for 28 days to 33% BSA
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS will include all randomised patients who received at least one application of randomised therapy. Patients will be analysed according to their randomised treatment.

Subject analysis set title	Part B - Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS will include all randomised patients who received at least one application of randomised therapy. Patients will be analysed according to their randomised treatment.

Primary: Part A: Local tolerance

End point title	Part A: Local tolerance[1]

End point description:

Adverse events related to local tolerability

End point type	Primary

End point timeframe:

Recorded from informed consent through 14 days after the last dose

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: Safety parameters are listed and summarised using descriptive statistics.

End point values	Part A Cohort 1: 0.25% BEN2293 daily for 7 days on 10% of BSA	Part A - Cohort 2 1.0% BEN2293 daily for 7 days on 10% of BSA	Part A - Cohort 3 1.0% BEN2293 daily for 14 days up to 30% BSA	Part A - Cohort 4 1.0% BEN2293 twice daily 14 days to 30% BSA
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	6	6
Units: Participants				
Application site pain	1	0	0	0
Application site paraesthesia	0	0	2	0
Application site pruritus	0	0	0	0
Application site rash	0	0	0	0
COVID-19	0	0	0	1
Post-procedural infection	0	0	0	1
Paraesthesia	0	0	1	0
Dry skin	0	0	0	0
Eczema	0	1	0	1
Pruritus	0	0	0	0
Skin exfoliation	0	0	1	0

End point values	Part A - Placebo			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: Participants				
Application site pain	1			
Application site paraesthesia	0			
Application site pruritus	1			
Application site rash	1			
COVID-19	0			
Post-procedural infection	0			
Paraesthesia	0			
Dry skin	1			
Eczema	1			
Pruritus	1			
Skin exfoliation	0			

Statistical analyses

No statistical analyses for this end point

Primary: Part B: Local tolerance

End point title	Part B: Local tolerance[2]

End point description:

Adverse events related to local tolerability

End point type	Primary

End point timeframe:

Recorded from informed consent through 14 days after the last dose

Notes:

[2] - 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: Safety parameters are listed and summarised using descriptive statistics.

End point values	Part B Active: 1.0% BEN2293 twice daily for 28 days to 33% BSA	Part B - Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	42		
Units: Participants				
Application site bruise	1	0		
Application site discomfort	1	0		
Application site pain	1	0		
Pain	1	0		
Arthropod bite	0	1		
Dizziness	1	0		
Insomnia	1	0		
Eczema	2	0		
Pain of skin	0	1		
Pruritus	2	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were recorded from screening through until follow up.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups	
Reporting group title	Part A: Cohort 1: Treatment Emergent AE
Reporting group description: -	
Reporting group title	Part A: Cohort 2: Treatment Emergent AE
Reporting group description: -	
Reporting group title	Part A: Cohort 3: Treatment Emergent AE
Reporting group description: -	
Reporting group title	Part A: Cohort 4: Treatment Emergent AE
Reporting group description: -	
Reporting group title	Part A: Placebo: Treatment Emergent AE
Reporting group description: -	
Reporting group title	Part B: Active: Treatment Emergent AE
Reporting group description: -	
Reporting group title	Part B: Placebo: Treatment Emergent AE
Reporting group description: -	

Serious adverse events	Part A: Cohort 1: Treatment Emergent AE	Part A: Cohort 2: Treatment Emergent AE	Part A: Cohort 3: Treatment Emergent AE
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Part A: Cohort 4: Treatment Emergent AE	Part A: Placebo: Treatment Emergent AE	Part B: Active: Treatment Emergent AE
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Part B: Placebo: Treatment Emergent AE		

Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 42 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Part A: Cohort 1: Treatment Emergent AE	Part A: Cohort 2: Treatment Emergent AE	Part A: Cohort 3: Treatment Emergent AE
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 6 (83.33%)	5 / 6 (83.33%)	5 / 6 (83.33%)
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Application site pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Application site paraesthesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Application site pruritus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Application site rash			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Medical device site rash			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Vaccination site pain			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Vessel puncture site bruise			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Vessel puncture site phlebitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vessel puncture site reaction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Application site bruise			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Application site discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tenderness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			

Oropharyngeal pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory symptom			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Haemoglobin decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Transaminases increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Alanine aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin abnormal			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Red blood cell sedimentation rate increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urine analysis abnormal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Post procedural pruritus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Scar			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Arthropod bite			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Procedural pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Paraesthesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Presyncope			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tension headache			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Sciatica			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oral pruritus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Eczema			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	2 / 6 (33.33%)
occurrences (all)	1	1	3
Pruritus			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	3
Skin exfoliation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Dermatitis allergic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dermatitis atopic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Miliaria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pain of skin			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Back pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			

COVID-19			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Post procedural infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Onychomycosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Viral infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part A: Cohort 4: Treatment Emergent AE	Part A: Placebo: Treatment Emergent AE	Part B: Active: Treatment Emergent AE
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 6 (66.67%)	7 / 8 (87.50%)	21 / 49 (42.86%)
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	3 / 49 (6.12%)
occurrences (all)	0	0	4
General disorders and administration site conditions			
Application site pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	1 / 49 (2.04%)
occurrences (all)	0	1	1
Application site paraesthesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Application site pruritus			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 49 (0.00%)
occurrences (all)	0	2	0
Application site rash			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Medical device site rash			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	2
Vaccination site pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Vessel puncture site bruise			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Vessel puncture site phlebitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Vessel puncture site reaction			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Application site bruise			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Application site discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Influenza like illness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Tenderness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 49 (0.00%)
occurrences (all)	0	2	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Epistaxis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Respiratory symptom			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	1 / 49 (2.04%)
occurrences (all)	0	1	1
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Haemoglobin decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Transaminases increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 49 (4.08%)
occurrences (all)	0	0	3
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Blood bilirubin abnormal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Red blood cell sedimentation rate increased			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Urine analysis abnormal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	1 / 49 (2.04%)
occurrences (all)	1	0	1
Post procedural pruritus			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Scar			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Arthropod bite			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Procedural pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	0 / 6 (0.00%)	2 / 8 (25.00%)	2 / 49 (4.08%)
occurrences (all)	0	4	2
Paraesthesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Presyncope			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Tension headache			

subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Sciatica			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	1 / 49 (2.04%)
occurrences (all)	1	0	1
Oral pruritus			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 6 (0.00%)	3 / 8 (37.50%)	0 / 49 (0.00%)
occurrences (all)	0	4	0
Eczema			
subjects affected / exposed	2 / 6 (33.33%)	2 / 8 (25.00%)	2 / 49 (4.08%)
occurrences (all)	2	2	2
Pruritus			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	2 / 49 (4.08%)
occurrences (all)	1	1	3
Skin exfoliation			

subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Dermatitis allergic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Dermatitis atopic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 49 (4.08%)
occurrences (all)	0	0	2
Hyperhidrosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Miliaria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Pain of skin			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Neck pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	2 / 49 (4.08%)
occurrences (all)	1	1	2
Post procedural infection			

subjects affected / exposed	2 / 6 (33.33%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	2	0	0
Gastroenteritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Herpes zoster			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	3 / 49 (6.12%)
occurrences (all)	0	0	4
Onychomycosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Viral infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part B: Placebo: Treatment Emergent AE		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 42 (52.38%)		
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Application site pain			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Application site paraesthesia			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Application site pruritus			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Application site rash			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Medical device site rash			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Vaccination site pain			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Vessel puncture site bruise			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Vessel puncture site phlebitis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		

Vessel puncture site reaction subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0		
Application site bruise subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0		
Application site discomfort subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0		
Influenza like illness subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Pyrexia subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Tenderness subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2		
Epistaxis subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0		
Nasal congestion subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0		

Respiratory symptom subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	 0 / 42 (0.00%) 0 1 / 42 (2.38%) 1		
Investigations Blood pressure increased subjects affected / exposed occurrences (all) Haemoglobin decreased subjects affected / exposed occurrences (all) Transaminases increased subjects affected / exposed occurrences (all) Alanine aminotransferase increased subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all) Blood bilirubin abnormal subjects affected / exposed occurrences (all) Red blood cell sedimentation rate increased subjects affected / exposed occurrences (all) Urine analysis abnormal subjects affected / exposed occurrences (all)	 0 / 42 (0.00%) 0 0 / 42 (0.00%) 0 0 / 42 (0.00%) 0 1 / 42 (2.38%) 1 0 / 42 (0.00%) 0 0 / 42 (0.00%) 0 1 / 42 (2.38%) 1 1 / 42 (2.38%) 1		
Injury, poisoning and procedural			

complications			
Contusion			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Post procedural pruritus			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Scar			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Arthropod bite			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	5 / 42 (11.90%)		
occurrences (all)	5		
Paraesthesia			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Presyncope			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Tension headache			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Sciatica			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Syncope			

subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	 1 / 42 (2.38%) 1		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Oral pruritus subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	 0 / 42 (0.00%) 0 0 / 42 (0.00%) 0 0 / 42 (0.00%) 0 0 / 42 (0.00%) 0		
Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all) Eczema subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Skin exfoliation subjects affected / exposed occurrences (all) Dermatitis allergic subjects affected / exposed occurrences (all) Dermatitis atopic	 0 / 42 (0.00%) 0 0 / 42 (0.00%) 0 0 / 42 (0.00%) 0 0 / 42 (0.00%) 0 0 / 42 (0.00%) 0		

subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Hyperhidrosis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Miliaria			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Night sweats			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Pain of skin			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Post procedural infection			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Gastrointestinal infection			

subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Herpes zoster			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Onychomycosis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Viral infection			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 December 2020	• Amend the Principal Investigator. • Inclusion /exclusion criteria amendments based on the Sponsor's experience in Screening during the trial • Amend the requirement for sentinel patients in Cohorts 1 and 2 to reside in the CRU from Day -1 to Day 9. • Allow an alternative emollient and shower cream to be used for the washout period and throughout the study at the Investigator's discretion. • Add a body weight measurement on Day 1 for all cohorts in Part A and Part B to allow individual calculation of dose. • Remove 12-lead electrocardiogram (ECG) and vital signs assessment at 24 hours postdose on Day 1, Day 2 (and Day 7 [Cohorts 1 and 2] or Day 14 [Cohorts 3 and 4] for 12-lead ECGs) for all cohorts in Part A, due to predose assessments being performed the following day at the same time. • Remove the 5% time window for all procedures performed at 1 and 2 hours postdose except pharmacokinetic sampling, and replace this with a ±10 minute window, for all cohorts in Part A and Part B for logistical reasons. It was also clarified that there will be no time window for predose assessments. • Clarify that four blood samples will be taken for pharmacogenomic analysis.
12 January 2021	Incorporate updates from Version 2.0 (dated 14 September 2020) to Version 3.0 (dated 02 December 2020) as part of the overall Protocol amendment. The rationale for this substantial amendment was to address the comments from the MHRA on Version 3.0 with respect to Exclusion Criteria #14 and #20. In addition to the amendments in V3.0, the following points were amended in V3. 1 of the Protocol: • Clarify the eligibility criteria in exclusion criteria points (14) and (20) to allow the Investigator to determine patient eligibility without prior consultation with the Medical Monitor.
17 February 2021	The purpose of this substantial amendment was to amend the range of BSA of treatable skin (not including face, scalp, genital area, palms of hands or soles of feet) affected by mild to moderate AD from ≥5% to ≤15% to ≥5% to ≤30% for Cohorts 1 and 2 in Part A (inclusion criterion [9]). The rationale for this change was to ensure that the patients entering Cohorts 1 and 2 had the same severity and extent of AD as all other patients in the study. This homogeneity of the study populations was important because the primary objective of Part A of this study was to assess the safety and tolerability of increasing dose levels of BEN2293. Restricting the BSA in Cohorts 1 and 2 may therefore have led to the inclusion only of patients with more mild disease, with the potential to skew the emergent safety data from these initial cohorts. Previously, the rationale for limiting the BSA in Cohorts 1 and 2 was to facilitate the collection of efficacy data. However, the Sponsor concluded that collection of robust efficacy data from Cohorts 1 and 2 is unlikely due to the short duration of dosing (once daily for 7 days) and the limited BSA affected by AD that was to be dosed (5%). The IMP application in Cohorts 1 and 2 in Part A remained as 5% BSA healthy skin and 5% BSA AD skin. Study emollient continued to be applied to any untreated areas for the duration of the study. The Investigator maintained close monitoring of the patients for any exacerbations in their AD and managed these as described in the Protocol.

21 April 2021	The purpose of this substantial amendment was to amend the eligibility criteria to allow patients who received a COVID-19 or other routine vaccination within 28 days of Day 1, and throughout the study, to take part in the study (exclusion criterion point [20]). Additionally, requirements for study emollient use during the washout, treatment and Follow-up periods were clarified. A time window of 2 hours postdose (± 60 minutes) was also added for skin biopsies to be taken on the last day of dosing.
18 August 2021	The purpose of this substantial amendment was to amend the exclusion criteria, the criteria for stopping dose escalation, individual stopping criteria, baseline and on study clinical laboratory evaluations, and the sentinel observation period, in response to increased liver transaminases observed in one patient in Cohort 3. Overall, the following changes to the Protocol were made: • For Cohort 4, the sentinel patients were dosed for 14 days, and their safety data reviewed before the remainder of the cohort could be dosed. • An extra inpatient visit was added for Cohort 4 on Day 9 for additional safety assessments; this was previously just a telephone contact. • Dose escalation stopping criteria were updated to state that if one or more patients experienced an increase in ALT and/or AST to ≥2 x ULN (confirmed upon repeat) or ≥3 x ULN (no repeat required), then dosing of all enrolled patients would stop and no further patients would be enrolled. Dosing could then only recommence following approval of a substantial Protocol amendment. • The exclusion criteria were amended to exclude any patient who had AST, ALT, GGT or total bilirubin levels above the ULN at Screening or Day -1, with no repeat testing permitted. • Added additional clinical chemistry assessments for IgG and IgE at baseline for Cohort 4 onwards, and added an extra clinical laboratory evaluation sample on Day 9 for Cohort 4.
21 December 2021	The purpose of this amendment was to amend the inclusion criteria related to % BSA affected by AD, to amend the number of sites to be used in Part B and to amend or clarify skin, urine and plasma sampling in Part B. Overall, the following changes to the Protocol were made: • The exploratory objectives and endpoints were amended to include the evaluation of BEN2293 and metabolite BEN6403 in urine in Part A only, and the evaluation of biomarkers in skin biopsies in Part B only. • Part B would be conducted across multiple sites in the United Kingdom, Europe and Israel. • The inclusion criteria were amended to include patients with AD affecting between ≥1% to ≤30% BSA of treatable skin; this was previously ≥5% to ≤30% BSA of treatable skin. • Patients in Part B were to be supplied with a double ended medicine spoon (5 mL/2.5 mL) to remove their ointment from the jar prior to application. • An externally provided IRT system would be used to randomise patients in Part B. • Urine PK sampling was removed from the Part B Schedule of Assessments. • The skin biopsy to be conducted at the Follow-up visit was removed from the Part B Schedule of Assessments. • The Part B Sampling Summary was amended to include two additional blood samples (2 x 40 mL) for MetaHeps testing, to be conducted if the hepatic transaminase threshold criteria were reached, or if there were any liver enzyme changes or trends of concern.

22 March 2022	The purpose of this amendment was to amend the design of Part B following completion of Part A. The main changes are listed below: • The adaptive study design was updated to clarify that up to 90 patients would be enrolled to be treated in two treatment arms of approximately 45 patients each. Patients would be randomised to receive either BEN2293 ointment or matching placebo ointment with a 1:1 parallel design. This was decided based on updated sample size determination calculations following completion of Part A of the study. • A single-blind placebo run-in period was added in which patients applied placebo ointment twice daily from Day -3 to Day -1. • Patients showing an improvement of ≥3 points in mean pruritus NRS scores (worst itch over the last 24 hours) between the end of the washout phase (mean of scores on Day 5, Day -4 and Day -3 [predose]), and the run-in phase (mean of scores on Day -2, Day 1 and Day 1 [predose]) were to be excluded from starting the double blind treatment period on Day 1. • The inclusion criteria on BP was amended • Ointment would be applied to all treatable lesioned skin (up to a maximum of 30% BSA at Day 1). Study ointment would also be applied to new treatable AD lesions that arose during the study (up to a total maximum of 33% BSA), following discussion with, or assessment by, the Investigator. • The Day 35 Follow-up visit was removed as it was not required based on Part A exposure data. • There would be only one application of BEN2293 or placebo on the final day of dosing (Day 28). • Pruritus NRS (current itch) assessments were added at predose and at 2, 4 and 8 hours postdose on Day 28. • Any participant with an affected BSA requiring treatment above 33% BSA was added to the withdrawal criteria.
16 September 2022	The main changes to the protocol are listed below: • Include the option to extend the run-in phase in Part B of the study by a maximum of 1 day, at the Investigator's discretion. Inclusion Criteria 10 and Exclusion Criteria 32 were updated to reflect this. • Clarify that it was imperative that patients should not use the placebo ointment administered during the run-in phase before attending the clinic on the morning of Day 1 for first dosing. • Clarify that in Part B, patients would be monitored for 30 minutes in the unit after their first doses in the run-in phase and on Day 1. • Update Exclusion Criteria 21 to allow patients to take paracetamol (intermittent use of less than or equal to 2 g/day) for up to 24 hours before dosing on Day 1 of the treatment period. • Remove grapefruit juice as a potent CYP3A4 inhibitor. However, a dietary restriction for grapefruit juice remained. • Amend the Protocol to state that in countries where there was no validated translated PROMIS scale available in the local language, the assessment would not be performed. • Clarify that after Day 1, the %BSA to be treated (sum of Day 1 %BSA treated and new AD lesions in treatable areas) should be any treated, new and resolved lesions which must not have exceeded 33% BSA after Day 1 postdose, and that this would be documented. • Clarify that patients in Part B must have refrained from consuming poppy seeds 48 hours prior to Screening and Day -3 to avoid a positive result on the drugs of abuse screen.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The secondary endpoints were not reported however, the synopsis (which includes description of the study endpoints) has been included.

Notes: