Clinical trial results:
An interventional, multicenter, single arm, phase I/IIa clinical trial to investigate the efficacy and safety of allo-APZ2-EB on epidermolysis bullosa (EB)

Summary

EudraCT number	2018-001009-98
Trial protocol	DE AT GB FR IT
Global end of trial date	26 November 2021

Results information

Result version number	v1 (current)
This version publication date	07 July 2022
First version publication date	07 July 2022

Trial information

Trial identification

Sponsor protocol code	allo-APZ2-EB-II-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03529877
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	RHEACELL GmbH & Co. KG
Sponsor organisation address	Im Neuenheimer Feld 517, Heidelberg, Germany, 69120
Public contact	Information Office, RHEACELL GmbH & Co. KG, 49 6221718330, office@rheacell.com
Scientific contact	Information Office, RHEACELL GmbH & Co. KG, 49 6221718330, office@rheacell.com

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	22 February 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this clinical trial was to investigate the efficacy (by monitoring overall improvement of EB symptoms measured by epidermolysis bullosa disease activity and scarring index [EBDASI] score and instrument for scoring clinical outcome of research for epidermolysis bullosa [iscorEB], wound healing assessed by photo documentation, change in pain and itch perception and subjects quality of life in EB [QOLEB] assessment) and safety (by monitoring adverse events [AEs]) of the investigational medicinal product (IMP) allo-APZ2-EB administered intravenously to subjects with EB in three applications (Day 0, Day 17 ±3, Day 35 ±3).

Protection of trial subjects:

For safety reasons to rule out an autoimmune response, subjects tested positive for antibodies against basement membrane proteins on salt-split skin were excluded from clinical trial participation.
To ensure the subjects' safety and to investigate possible transient effects, subjects were monitored during the treatment and efficacy period up to Week 12. The long-term safety was assessed at Month 12 in all countries involved and was additionally assessed at Month 24 in France and the UK.
Emergency medications for management of anaphylaxis were available and clinical monitoring was to be done for the full duration of the infusion visit with a post-dosing in-clinic observation period of at least 2 hours. The subject was to be clinically stable before being discharged.
A Data Monitoring Committee (DMC) was established to assess the safety and tolerability of the IMP before opening the clinical trial for the next cohort and younger subjects.
Subjects were enrolled in a staggered design in age cohorts (Cohort 1: adult subjects [≥18 to ≤55 years]; Cohort 2: subjects aged ≥12 to <18 years; Cohort 3: subjects aged ≥5 to <12 years; Cohort 4: subjects aged ≥12 months to <5 years; Cohort 5: subjects aged 0 to <12 months, only in the UK) of at least 3 subjects, starting with the successive enrollment of 3 subjects ≥18 years. The second and third adult subject were only to be enrolled if the safety and tolerability of the first allo-APZ2-EB administration in the previous subject was acceptable. After the last of the 3 initially treated adult subjects was followed up for 2 weeks after his/her third IMP application, the safety of the IMP was to be assessed by a DMC before opening the clinical trial for younger subjects to minimize the burden and risk in minors. Subjects were to be enrolled only in Cohorts 2, 3, 4 and 5 if the precedent cohort was approved by the DMC (2 weeks after first treatment [in France after third treatment] of third subject).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 February 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	Austria: 2
Country: Number of subjects enrolled	United States: 2
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	France: 2

Country: Number of subjects enrolled	Germany: 4
Worldwide total number of subjects	16
EEA total number of subjects	8

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)	5
Adolescents (12-17 years)	4
Adults (18-64 years)	7
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects aged 0 to 55 years with RDEB (diagnosed by genotype assessment [mutation analysis] and phenotype assessment [wound assessment]) and without antibodies against basement membrane proteins on salt-split skin were screened in Europe, UK and USA. First subject signed informed consent form on 07-Feb-2019 and last subject on 09-Feb-2020.

Pre-assignment

Screening details:

18 subjects signed the informed consent form. 2 subjects were screening failures and not treated with IMP. 7 subjects were enrolled in Cohort 1 (adults), each 4 subjects in Cohorts 2 (≥12 to <18 years) and 3 (≥5 to <12 years), and 1 subject in Cohort 4 (≥12 months to <5 years).

Period 1

Period 1 title	Treatment and 12-month follow-up
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1

Arm description:

Subjects aged ≥18 to ≤55 years.

Arm type	Experimental
Investigational medicinal product name	allo-APZ2-EB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

allo-APZ2-EB at a dose of 2 x 10E6 allogeneic ABCB5-positive mesenchymal stem cells/kg was to be administered at Day 0, Day 17 ±3, and Day 35 ±3 by intravenous infusion using a syringe pump at a flow rate of 1-2 mL/min at the investigator's discretion and tube flushing was to be done with Ringer's lactate solution (volume/drop rate at discretion of the investigator).
All subjects were to follow the same schedule.

Arm title	Cohort 2

Arm description:

Subjects aged ≥12 to <18 years.

Arm type	Experimental
Investigational medicinal product name	allo-APZ2-EB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

allo-APZ2-EB at a dose of 2 x 10E6 allogeneic ABCB5-positive mesenchymal stem cells/kg was to be administered at Day 0, Day 17 ±3, and Day 35 ±3 by intravenous infusion using a syringe pump at a flow rate of 1-2 mL/min at the investigator's discretion and tube flushing was to be done with Ringer's lactate solution (volume/drop rate at discretion of the investigator).
All subjects were to follow the same schedule.

Arm title	Cohort 3

Arm description:

Subjects aged ≥5 to <12 years.

Arm type	Experimental
Investigational medicinal product name	allo-APZ2-EB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

allo-APZ2-EB at a dose of 2 x 10E6 allogeneic ABCB5-positive mesenchymal stem cells/kg was to be administered at Day 0, Day 17 ±3, and Day 35 ±3 by intravenous infusion using a syringe pump at a flow rate of 1-2 mL/min at the investigator's discretion and tube flushing was to be done with Ringer's lactate solution (volume/drop rate at discretion of the investigator).
All subjects were to follow the same schedule.

Arm title	Cohort 4

Arm description:

Subjects aged ≥12 months to <5 years.

Arm type	Experimental
Investigational medicinal product name	allo-APZ2-EB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

allo-APZ2-EB at a dose of 2 x 10E6 allogeneic ABCB5-positive mesenchymal stem cells/kg was to be administered at Day 0, Day 17 ±3, and Day 35 ±3 by intravenous infusion using a syringe pump at a flow rate of 1-2 mL/min at the investigator's discretion and tube flushing was to be done with Ringer's lactate solution (volume/drop rate at discretion of the investigator).
All subjects were to follow the same schedule.

Number of subjects in period 1	Cohort 1	Cohort 2	Cohort 3
Started	7	4	4
First IMP application received	7	4	4
Second IMP application received	7	4	4
Third IMP application received	7	3	4
12-week efficacy follow-up	7	3	4
Completed	7	3	4
Not completed	0	1	0
Physician decision	-	1	-

Number of subjects in period 1	Cohort 4
Started	1
First IMP application received	1
Second IMP application received	1
Third IMP application received	0 [1]
12-week efficacy follow-up	1

Completed	1
Not completed	0
Physician decision	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The patient in Cohort 4 received no third IMP application, but stayed in the trial and completed the 12-month follow-up.

Period 2

Period 2 title	24-month safety follow-up
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1

Arm description:

Subjects aged ≥18 to ≤55 years.

Arm type	Experimental
Investigational medicinal product name	allo-APZ2-EB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

allo-APZ2-EB at a dose of 2 x 10E6 allogeneic ABCB5-positive mesenchymal stem cells/kg was to be administered at Day 0, Day 17 ±3, and Day 35 ±3 by intravenous infusion using a syringe pump at a flow rate of 1-2 mL/min at the investigator's discretion and tube flushing was to be done with Ringer's lactate solution (volume/drop rate at discretion of the investigator).
All subjects were to follow the same schedule.

Arm title	Cohort 2

Arm description:

Subjects aged ≥12 to <18 years.

Arm type	Experimental
Investigational medicinal product name	allo-APZ2-EB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

allo-APZ2-EB at a dose of 2 x 10E6 allogeneic ABCB5-positive mesenchymal stem cells/kg was to be administered at Day 0, Day 17 ±3, and Day 35 ±3 by intravenous infusion using a syringe pump at a flow rate of 1-2 mL/min at the investigator's discretion and tube flushing was to be done with Ringer's lactate solution (volume/drop rate at discretion of the investigator).
All subjects were to follow the same schedule.

Arm title	Cohort 3

Arm description:

Subjects aged ≥5 to <12 years.

Arm type	Experimental

Investigational medicinal product name	allo-APZ2-EB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

allo-APZ2-EB at a dose of 2 x 10E6 allogeneic ABCB5-positive mesenchymal stem cells/kg was to be administered at Day 0, Day 17 ±3, and Day 35 ±3 by intravenous infusion using a syringe pump at a flow rate of 1-2 mL/min at the investigator's discretion and tube flushing was to be done with Ringer's lactate solution (volume/drop rate at discretion of the investigator).
All subjects were to follow the same schedule.

Number of subjects in period 2[2]	Cohort 1	Cohort 2	Cohort 3
Started	4	2	1
12-month safety follow-up	4	2	1
Completed	3	2	1
Not completed	1	0	0
Subject's decision	1	-	-

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: One patient in Cohort 1 discontinued the trial prematurely after the 12-month follow-up by own decision and did not perform the 24-month follow-up visit.

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1
Reporting group description: Subjects aged ≥18 to ≤55 years.	
Reporting group title	Cohort 2
Reporting group description: Subjects aged ≥12 to <18 years.	
Reporting group title	Cohort 3
Reporting group description: Subjects aged ≥5 to <12 years.	
Reporting group title	Cohort 4
Reporting group description: Subjects aged ≥12 months to <5 years.	

Reporting group values	Cohort 1	Cohort 2	Cohort 3
Number of subjects	7	4	4
Age categorical Units: Subjects			
Age continuous Units: years			
median	25	13	8
full range (min-max)	20 to 36	12 to 17	6 to 10
Gender categorical Units: Subjects			
Female	5	3	1
Male	2	1	3
Race Units: Subjects			
Asian	0	1	0
Caucasian	7	2	3
Other	0	1	1
Body weight Units: kilogram(s)			
median	41.0	29.2	20.3
full range (min-max)	23.3 to 59.8	26.6 to 51.5	18.9 to 45.9
Body mass index Units: kilogram(s)/square metre			
median	17.6	15.2	12.7
full range (min-max)	13.0 to 18.9	12.7 to 18.1	11.5 to 21.5

Reporting group values	Cohort 4	Total	
Number of subjects	1	16	
Age categorical Units: Subjects			

Age continuous Units: years			
median	4		
full range (min-max)	4 to 4	-	
Gender categorical Units: Subjects			
Female	0	9	
Male	1	7	
Race Units: Subjects			
Asian	0	1	
Caucasian	1	13	
Other	0	2	
Body weight Units: kilogram(s)			
median	15.0		
full range (min-max)	15.0 to 15.0	-	
Body mass index Units: kilogram(s)/square metre			
median	14.7		
full range (min-max)	14.7 to 14.7	-	

End points

End points reporting groups

Reporting group title	Cohort 1
Reporting group description:	
Subjects aged ≥18 to ≤55 years.	
Reporting group title	Cohort 2
Reporting group description:	
Subjects aged ≥12 to <18 years.	
Reporting group title	Cohort 3
Reporting group description:	
Subjects aged ≥5 to <12 years.	
Reporting group title	Cohort 4
Reporting group description:	
Subjects aged ≥12 months to <5 years.	
Reporting group title	Cohort 1
Reporting group description:	
Subjects aged ≥18 to ≤55 years.	
Reporting group title	Cohort 2
Reporting group description:	
Subjects aged ≥12 to <18 years.	
Reporting group title	Cohort 3
Reporting group description:	
Subjects aged ≥5 to <12 years.	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
All enrolled subjects who received allo-APZ2-EB at least once.	
Subject analysis set title	Per-protocol set
Subject analysis set type	Per protocol
Subject analysis set description:	
All enrolled subjects who received allo-APZ2-EB at least once and had no major protocol deviation as defined at the data review meeting.	

Primary: Percentage change of EBDASI score at Week 12 (with LOCF)

End point title	Percentage change of EBDASI score at Week 12 (with LOCF)[1]
End point description:	
The primary efficacy endpoint was the overall improvement of EB symptoms 12 weeks after first IMP application or at last available post-baseline measurement if the Week 12 measurement was missing (last observation carried forward [LOCF]), and was measured by percentage change of a subject's EBDASI score (overall score, activity score, and damage score) from Baseline (Day 0, pre-dose).	
End point type	Primary
End point timeframe:	
From Baseline (Day 0, pre-dose) until the end of the 12-week efficacy follow-up (Week 12).	

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: In a post-hoc analysis, statistical hypothesis testing was performed in the FAS for the primary endpoint and the null hypothesis H0: median change = 0 using a Wilcoxon signed rank test. The following p-values, median values and 95% confidence intervals (lower; upper) were reported:
- EBDASI overall score: p=0.0580; -3.4 (-9.4; 0.0)%
- EBDASI activity score: p=0.0494; -13.0 (-30.0; -2.9)%
- EBDASI damage score: p=0.2661; -0.7 (-6.9; 3.2)%

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	3[2]	4	1[3]
Units: Percentage				
median (full range (min-max))				
Overall score	-3.4 (-27.1 to 9.0)	-9.4 (-12.2 to -6.2)	-1.3 (-7.2 to 13.1)	-3.1 (-3.1 to -3.1)
Activity score	-10.0 (-67.9 to 24.0)	-31.4 (-34.8 to -9.1)	-6.5 (-25.9 to 53.3)	-21.4 (-21.4 to -21.4)
Damage score	-0.9 (-12.7 to 5.5)	-5.5 (-7.3 to -0.7)	1.6 (-3.2 to 3.8)	2.0 (2.0 to 2.0)

Notes:

[2] - 1 subject terminated the trial prematurely due to physician's decision, no post-baseline measurement

[3] - Week 12 measurement was missing, LOCF method was applied and Day 17 data were used

End point values	Full analysis set	Per-protocol set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15[4]	14		
Units: Percentage				
median (full range (min-max))				
Overall score	-3.4 (-27.1 to 13.1)	-4.8 (-27.1 to 13.1)		
Activity score	-13.0 (-67.9 to 53.3)	-11.5 (-67.9 to 53.3)		
Damage score	-0.7 (-12.7 to 5.5)	-0.8 (-12.7 to 5.5)		

Notes:

[4] - 1 subject terminated the trial prematurely due to physician's decision, no post-baseline measurement

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From administration of the IMP until the end of 12-month follow-up (Month 12) in Austria, Germany and USA and until the end of 24-month follow-up (Month 24) in France and the UK.	
Adverse event reporting additional description:	
Adverse event reporting ended in 1 subject before Week 12 because of premature trial termination due to physician's decision and in 1 subject in France at Month 12 because of premature trial termination due to subject's decision.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	Cohort 1
Reporting group description:	
Subjects aged ≥18 to ≤55 years.	
Reporting group title	Cohort 2
Reporting group description:	
Subjects aged ≥12 to <18 years.	
Reporting group title	Cohort 3
Reporting group description:	
Subjects aged ≥5 to <12 years.	
Reporting group title	Cohort 4
Reporting group description:	
Subjects aged ≥12 months to <5 years.	

Serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 7 (28.57%)	2 / 4 (50.00%)	0 / 4 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Precancerous skin lesion			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Osteitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin bacterial infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 4		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Precancerous skin lesion			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin bacterial infection			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	4 / 4 (100.00%)	3 / 4 (75.00%)
Investigations			
Blood cholinesterase decreased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Joint dislocation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Lip injury			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Procedural pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Nervous system disorders			
Neuralgia			

subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Iron deficiency anaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Lymphadenopathy			
subjects affected / exposed	2 / 7 (28.57%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	4	0	0
Eye disorders			
Conjunctival bleb			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Corneal erosion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Dental caries			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Dysphagia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Lip blister			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Oesophageal stenosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	2 / 4 (50.00%)
occurrences (all)	0	1	12
Oral mucosa erosion			

subjects affected / exposed	0 / 7 (0.00%)	2 / 4 (50.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Oral mucosal blistering			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Vomiting			
subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 7 (0.00%)	2 / 4 (50.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Dermal cyst			
subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Henoch-Schonlein purpura			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Skin erosion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	2 / 7 (28.57%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Pseudosyndactyly			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Beta haemolytic streptococcal infection			

subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Blister infected			
subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Conjunctivitis viral			
subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Cystitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Ear infection fungal			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Skin bacterial infection			
subjects affected / exposed	2 / 7 (28.57%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	5	1	0
Skin candida			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Skin infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Staphylococcal skin infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	3
Tooth abscess			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Viral upper respiratory tract infection			

subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Wound infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Wound infection bacterial			
subjects affected / exposed	1 / 7 (14.29%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	2	2	0

Non-serious adverse events	Cohort 4		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)		
Investigations			
Blood cholinesterase decreased			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Joint dislocation			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Lip injury			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Procedural pain			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Neuralgia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Iron deficiency anaemia subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Lymphadenopathy subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Eye disorders			
Conjunctival bleb subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Corneal erosion subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Gastrointestinal disorders			
Constipation subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Dental caries subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Dysphagia subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Lip blister subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Oesophageal stenosis subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Oral mucosa erosion subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Oral mucosal blistering			

subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0		
Skin and subcutaneous tissue disorders Blister subjects affected / exposed occurrences (all) Dermal cyst subjects affected / exposed occurrences (all) Henoch-Schonlein purpura subjects affected / exposed occurrences (all) Skin erosion subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all) Pseudosyndactyly subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		
Infections and infestations Beta haemolytic streptococcal infection subjects affected / exposed occurrences (all) Blister infected	 0 / 1 (0.00%) 0 		

subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Conjunctivitis viral				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Cystitis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Ear infection fungal				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Gastroenteritis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Skin bacterial infection				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Skin candida				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Skin infection				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Staphylococcal skin infection				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Tooth abscess				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Upper respiratory tract infection				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Viral upper respiratory tract infection				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Wound infection				

subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Wound infection bacterial			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
16 March 2020	Subject recruitment was stopped due to the COVID-19 pandemic and related restritions. In addition, IMP production was halted due to impairments and failures in the logistics chain as a result of the COVID 19 pandemic.	-

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34665781