Clinical trial results:
A Randomized, Double-Blind, Parallel Group, Vehicle-Controlled Phase 2 Study to Evaluate the Safety and Efficacy of Topical ATx201 OINTMENT in Adolescents and Adults with Mild to Moderate Atopic Dermatitis

Summary

EudraCT number	2019-002771-33
Trial protocol	DK PL BG
Global end of trial date	22 October 2020

Results information

Result version number	v1 (current)
This version publication date	26 November 2021
First version publication date	26 November 2021
Summary attachment (see zip file)	ATx201-207 CTR Synopsis for EudraCT (ATx201-207 CTR synopsis for EudraCT.pdf)

Trial information

Trial identification

Sponsor protocol code	ATX201-207

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04339985
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Union Therapeutics A/S
Sponsor organisation address	Tuborg Havnevej 18, 2900 Hellerup, Denmark,
Public contact	Union Therapeutics A/S, Union Therapeutics A/S, +45 61777435, clinicaltrials@uniontherapeutics.com
Scientific contact	Union Therapeutics A/S, Union Therapeutics A/S, +45 61777435, rclinicaltrials@uniontherapeutics.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 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 October 2020
Global end of trial reached?	Yes
Global end of trial date	22 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate clinical efficacy of ATx201 in subjects with mild to moderate atopic dermatitis.

Protection of trial subjects:

This study was performed according to the principles of the current edition of the Declaration of Helsinki, all applicable legislation and regulation, and to Good Clinical Practice (GCP) as denoted in the International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use E6 requirements for GCP. The Investigator conducted all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities. Personal data of investigators and subjects were collected, stored, and processed in accordance with the General Data Protection Regulation (GDPR); appropriate organizational measures were taken to protect these data by preventing their disclosure to unauthorized third parties.

Background therapy:

-

Evidence for comparator:

-

Actual start date of recruitment	16 September 2019
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	Poland: 26
Country: Number of subjects enrolled	Bulgaria: 184
Country: Number of subjects enrolled	Denmark: 2
Worldwide total number of subjects	212
EEA total number of subjects	212

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)	20
Adults (18-64 years)	192
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first subject was enrolled on 05 November 2019.

Pre-assignment

Screening details:

Subjects (age ≥12 and <60 years) with a diagnosis of atopic dermatitis (AD) per the protocol were included. Subjects with actively infected AD or acute exacerbation or flare as defined in the protocol were excluded.

Period 1

Period 1 title	Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

In the main study, the study medications were double-blinded. The blinding codes were available to the investigator in a secured manner.

Arms

Are arms mutually exclusive?	Yes
Arm title	ATx201 OINTMENT 4%

Arm description:

ATx201; 4% OINTMENT; topical application 2 mg/cm^2, twice daily to treatable area

Arm type	Experimental
Investigational medicinal product name	ATx201 OINTMENT
Investigational medicinal product code	ATx201
Other name	niclosamide
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

ATx201 4% OINTMENT, dermal topical application, apply 2 mg/cm^2 twice daily to treatable area.

Arm title	ATx201 OINTMENT 7%

Arm description:

ATx201 7% OINTMENT, topical application, 2 mg/cm^2 twice daily to treatable area

Arm type	Experimental
Investigational medicinal product name	ATx201 OINTMENT
Investigational medicinal product code	ATx201
Other name	niclosamide
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

ATx201 7% OINTMENT, dermal topical application, apply 2 mg/cm^2 twice daily to treatable area.

Arm title	OINTMENT vehicle

Arm description:

Placebo, OINTMENT 0% (vehicle), topical application, 2 mg/cm^2 twice daily to treatable area

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	OINTMENT vehicle
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical

Dosage and administration details:

OINTMENT vehicle, 0% vehicle, 2 mg/cm^2 twice daily to treatable area

Number of subjects in period 1	ATx201 OINTMENT 4%	ATx201 OINTMENT 7%	OINTMENT vehicle
Started	70	70	72
Completed	65	63	68
Not completed	5	7	4
Consent withdrawn by subject	3	5	-
Adverse event, non-fatal	2	1	2
Patient decision to resign from study	-	-	1
Lack of efficacy	-	1	1

Baseline characteristics

Reporting groups	
Reporting group title	ATx201 OINTMENT 4%
Reporting group description:	
ATx201; 4% OINTMENT; topical application 2 mg/cm^2, twice daily to treatable area	
Reporting group title	ATx201 OINTMENT 7%
Reporting group description:	
ATx201 7% OINTMENT, topical application, 2 mg/cm^2 twice daily to treatable area	
Reporting group title	OINTMENT vehicle
Reporting group description:	
Placebo, OINTMENT 0% (vehicle), topical application, 2 mg/cm^2 twice daily to treatable area	

Reporting group values	ATx201 OINTMENT 4%	ATx201 OINTMENT 7%	OINTMENT vehicle
Number of subjects	70	70	72
Age categorical			
<18 years			
Units: Subjects			
Adolescents (12-17 years)	5	7	8
Adults (18-59 years)	65	63	64
Age continuous			
Units: years			
arithmetic mean	38	38	35
standard deviation	± 13	± 14	± 13
Gender categorical			
Units: Subjects			
Female	45	42	46
Male	25	28	26
Race			
Units: Subjects			
Caucasian	70	70	72
Treatable Body Surface Area			
Units: percent			
arithmetic mean	12	13	14
standard deviation	± 7	± 6	± 8
Baseline IGA			
Units: Score			
arithmetic mean	2.30	2.31	2.38
standard deviation	± 0.46	± 0.47	± 0.49
Baseline EASI Score			
Units: Score			
arithmetic mean	5.41	5.79	5.63
standard deviation	± 3.68	± 4.48	± 3.32

Reporting group values	Total		
Number of subjects	212		

Age categorical			
<18 years			
Units: Subjects			
Adolescents (12-17 years)	20		
Adults (18-59 years)	192		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	133		
Male	79		
Race			
Units: Subjects			
Caucasian	212		
Treatable Body Surface Area			
Units: percent			
arithmetic mean			
standard deviation	-		
Baseline IGA			
Units: Score			
arithmetic mean			
standard deviation	-		
Baseline EASI Score			
Units: Score			
arithmetic mean			
standard deviation	-		

Subject analysis sets

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety population included all enrolled subjects who received any amount of the IMP.

Subject analysis set title	Intent-to-Treat Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intent to Treat Analysis Set included data from all randomized subjects regardless of whether IMP was administered (not including open-label PK sub-study).

Reporting group values	Safety Population	Intent-to-Treat Population	
Number of subjects	212	212	
Age categorical			
<18 years			
Units: Subjects			
Adolescents (12-17 years)	20	20	
Adults (18-59 years)	192	192	
Age continuous			
Units: years			
arithmetic mean	37	37	

standard deviation	± 13	± 13	

Gender categorical Units: Subjects			
Female	133	133	
Male	79	79	
Race Units: Subjects			
Caucasian	212	212	
Treatable Body Surface Area Units: percent			
arithmetic mean	13	13	
standard deviation	± 7	± 7	
Baseline IGA Units: Score			
arithmetic mean			
standard deviation	±	±	
Baseline EASI Score Units: Score			
arithmetic mean			
standard deviation	±	±	

End points

End points reporting groups

Reporting group title	ATx201 OINTMENT 4%
Reporting group description:	
ATx201; 4% OINTMENT; topical application 2 mg/cm^2, twice daily to treatable area	
Reporting group title	ATx201 OINTMENT 7%
Reporting group description:	
ATx201 7% OINTMENT, topical application, 2 mg/cm^2 twice daily to treatable area	
Reporting group title	OINTMENT vehicle
Reporting group description:	
Placebo, OINTMENT 0% (vehicle), topical application, 2 mg/cm^2 twice daily to treatable area	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety population included all enrolled subjects who received any amount of the IMP.	
Subject analysis set title	Intent-to-Treat Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The Intent to Treat Analysis Set included data from all randomized subjects regardless of whether IMP was administered (not including open-label PK sub-study).	

Primary: EASI mean change from baseline at Week 6

End point title	EASI mean change from baseline at Week 6
End point description:	
End point type	Primary
End point timeframe:	
Baseline to Week 6	

End point values	ATx201 OINTMENT 4%	ATx201 OINTMENT 7%	OINTMENT vehicle	Intent-to-Treat Population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	70	70	72	0[1]
Units: score				
arithmetic mean (standard deviation)	-3.38 (± 3.55)	-2.86 (± 3.22)	-2.95 (± 4.67)	()

Notes:

[1] - Overall not analysed

Attachments (see zip file)	EASI Mean Change from Baseline ANCOVA Analysis/EASI mean

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	ATx201 OINTMENT 4% v ATx201 OINTMENT 7% v OINTMENT vehicle

Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Least squares mean
Confidence interval	
level	95 %

Secondary: EASI-50 at Week 6

End point title	EASI-50 at Week 6
End point description:	

End point type	Secondary
End point timeframe:	
Up to Week 6	

End point values	ATx201 OINTMENT 4%	ATx201 OINTMENT 7%	OINTMENT vehicle	Intent-to-Treat Population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	70	70	72	212
Units: percent				
number (not applicable)	45	40	45	130

Attachments (see zip file)	CMH Statistics for EASI-50/CMH Statistics for EASI-50 -ITT

Statistical analyses

Statistical analysis title	Cohran-Mantel-Haenszel Test
Comparison groups	ATx201 OINTMENT 4% v ATx201 OINTMENT 7% v OINTMENT vehicle
Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Cochran-Mantel-Haenszel

Secondary: EASI-75 at Week 6

End point title	EASI-75 at Week 6
End point description:	

End point type	Secondary
End point timeframe:	
Up to Week 6	

End point values	ATx201 OINTMENT 4%	ATx201 OINTMENT 7%	OINTMENT vehicle	Intent-to-Treat Population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	70	70	72	212
Units: percent				
number (not applicable)	31	21	33	85

Attachments (see zip file)	CMH Statistics for EASI-75/CMH Statistics for EASI-75.pdf

Statistical analyses

Statistical analysis title	Cohran-Mantel-Haenszel Test
Comparison groups	ATx201 OINTMENT 4% v ATx201 OINTMENT 7% v OINTMENT vehicle
Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Cochran-Mantel-Haenszel

Secondary: IGA success at Week 6

End point title	IGA success at Week 6
End point description:	

End point type	Secondary
End point timeframe:	
Up to Week 6	

End point values	ATx201 OINTMENT 4%	ATx201 OINTMENT 7%	OINTMENT vehicle	Intent-to-Treat Population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	70	70	72	212
Units: subjects	20	16	23	59

Attachments (see zip file)	CMH Statistics for IGA Success/CMH Statistics for IGA Success.

Statistical analyses

Statistical analysis title	Cohran-Mantel-Haenszel Test
Comparison groups	ATx201 OINTMENT 4% v ATx201 OINTMENT 7% v OINTMENT vehicle
Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Cochran-Mantel-Haenszel

Secondary: Distribution of IGA scores at change from baseline at Week 6

End point title	Distribution of IGA scores at change from baseline at Week 6
End point description:	
End point type	Secondary
End point timeframe:	
Up to Week 6	

End point values	ATx201 OINTMENT 4%	ATx201 OINTMENT 7%	OINTMENT vehicle	Intent-to-Treat Population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	70	70	72	212
Units: Frequency distribution				
IGA score 0	10	8	13	31
IGA Score 1	29	26	22	77
IGA Score 2	27	30	27	84
IGA Score 3	4	6	10	20
IGA Score 4	0	0	0	0

Attachments (see zip file)	CMH Statistics for IGA scores based on ridit score/CMH

Statistical analyses

Statistical analysis title	Cohran-Mantel-Haenszel Test
Comparison groups	ATx201 OINTMENT 4% v ATx201 OINTMENT 7% v OINTMENT vehicle

Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Cochran-Mantel-Haenszel

Secondary: Proportion of subjects with a treatable BSA <5% at Week 6

End point title	Proportion of subjects with a treatable BSA <5% at Week 6
End point description:	

End point type	Secondary
End point timeframe:	
Up to Week 6	

End point values	ATx201 OINTMENT 4%	ATx201 OINTMENT 7%	OINTMENT vehicle	Intent-to-Treat Population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	70	70	72	212
Units: Subjects	27	21	25	73

Attachments (see zip file)	CMH Statistics for BSA less than 5%/CMH Statistics for BSA

Statistical analyses

Statistical analysis title	Cohran-Mantel-Haenszel Test
Comparison groups	ATx201 OINTMENT 4% v ATx201 OINTMENT 7% v OINTMENT vehicle
Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Cochran-Mantel-Haenszel

Secondary: Target lesion Total Sign Score mean change from baseline at Week 6

End point title	Target lesion Total Sign Score mean change from baseline at Week 6
End point description:	

End point type	Secondary
End point timeframe:	
Up to Week 6	

End point values	ATx201 OINTMENT 4%	ATx201 OINTMENT 7%	OINTMENT vehicle	Intent-to-Treat Population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	70	70	72	0[2]
Units: Score				
arithmetic mean (standard deviation)	-3.16 (± 1.95)	-2.97 (± 2.2)	-3.17 (± 2.37)	()

Notes:

[2] - Overall not analysed

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to Week 6	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	22
Reporting groups	
Reporting group title	ATx201 OINTMENT 4%
Reporting group description: ATx201; 4% ointment; topical application 2 mg/cm^2, twice daily to treatable area	
Reporting group title	ATx201 OINTMENT 7%
Reporting group description: ATx201 7% OINTMENT, topical application, 2 mg/cm^2 twice daily to treatable area	
Reporting group title	OINTMENT vehicle
Reporting group description: Placebo, OINTMENT 0% (vehicle), topical application, 2 mg/cm^2 twice daily to treatable area	
Reporting group title	Overall Study
Reporting group description: Total for all study groups combined	

Serious adverse events	ATx201 OINTMENT 4%	ATx201 OINTMENT 7%	OINTMENT vehicle
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 71 (0.00%)	0 / 69 (0.00%)	0 / 72 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Overall Study		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 212 (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	ATx201 OINTMENT 4%	ATx201 OINTMENT 7%	OINTMENT vehicle
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 71 (30.99%)	18 / 69 (26.09%)	14 / 72 (19.44%)
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 71 (1.41%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Vein collapse			
subjects affected / exposed	1 / 71 (1.41%)	1 / 69 (1.45%)	0 / 72 (0.00%)
occurrences (all)	1	1	0
General disorders and administration site conditions			
Drug intolerance			
subjects affected / exposed	1 / 71 (1.41%)	2 / 69 (2.90%)	2 / 72 (2.78%)
occurrences (all)	1	2	2
Influenza like illness			
subjects affected / exposed	1 / 71 (1.41%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 71 (0.00%)	1 / 69 (1.45%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	1 / 71 (1.41%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 71 (1.41%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Blood iron decreased			
subjects affected / exposed	0 / 71 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 71 (0.00%)	1 / 69 (1.45%)	0 / 72 (0.00%)
occurrences (all)	0	1	0

Arthropod sting			
subjects affected / exposed	1 / 71 (1.41%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 71 (1.41%)	1 / 69 (1.45%)	0 / 72 (0.00%)
occurrences (all)	2	1	0
Headache			
subjects affected / exposed	2 / 71 (2.82%)	2 / 69 (2.90%)	2 / 72 (2.78%)
occurrences (all)	2	2	2
Eye disorders			
Eyelid irritation			
subjects affected / exposed	1 / 71 (1.41%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 71 (0.00%)	1 / 69 (1.45%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	1 / 71 (1.41%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Constipation			
subjects affected / exposed	0 / 71 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	0 / 71 (0.00%)	1 / 69 (1.45%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dermal cyst			
subjects affected / exposed	0 / 71 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Dermatitis atopic			
subjects affected / exposed	2 / 71 (2.82%)	1 / 69 (1.45%)	2 / 72 (2.78%)
occurrences (all)	2	1	2
Dermatitis contact			
subjects affected / exposed	0 / 71 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1

Dry skin			
subjects affected / exposed	3 / 71 (4.23%)	3 / 69 (4.35%)	1 / 72 (1.39%)
occurrences (all)	3	3	2
Perioral dermatitis			
subjects affected / exposed	0 / 71 (0.00%)	1 / 69 (1.45%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	0 / 71 (0.00%)	1 / 69 (1.45%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 71 (0.00%)	1 / 69 (1.45%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Skin irritation			
subjects affected / exposed	3 / 71 (4.23%)	6 / 69 (8.70%)	3 / 72 (4.17%)
occurrences (all)	3	6	3
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 71 (0.00%)	1 / 69 (1.45%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Corona virus infection			
subjects affected / exposed	1 / 71 (1.41%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Folliculitis			
subjects affected / exposed	1 / 71 (1.41%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	1 / 71 (1.41%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	2 / 71 (2.82%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences (all)	2	0	1
Oral herpes			
subjects affected / exposed	1 / 71 (1.41%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Rhinitis			

subjects affected / exposed	0 / 71 (0.00%)	1 / 69 (1.45%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 71 (0.00%)	1 / 69 (1.45%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Fluid retention			
subjects affected / exposed	0 / 71 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Vitamin D deficiency			
subjects affected / exposed	0 / 71 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1

Non-serious adverse events	Overall Study		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 212 (25.47%)		
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 212 (0.47%)		
occurrences (all)	1		
Vein collapse			
subjects affected / exposed	2 / 212 (0.94%)		
occurrences (all)	2		
General disorders and administration site conditions			
Drug intolerance			
subjects affected / exposed	5 / 212 (2.36%)		
occurrences (all)	5		
Influenza like illness			
subjects affected / exposed	2 / 212 (0.94%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 212 (0.47%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			

Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 212 (0.47%) 1		
Investigations Blood creatinine increased subjects affected / exposed occurrences (all) Blood iron decreased subjects affected / exposed occurrences (all)	 1 / 212 (0.47%) 1 1 / 212 (0.47%) 1		
Injury, poisoning and procedural complications Arthropod bite subjects affected / exposed occurrences (all) Arthropod sting subjects affected / exposed occurrences (all)	 1 / 212 (0.47%) 1 1 / 212 (0.47%) 1		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	 2 / 212 (0.94%) 3 6 / 212 (2.83%) 6		
Eye disorders Eyelid irritation subjects affected / exposed occurrences (all)	 1 / 212 (0.47%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Constipation	 1 / 212 (0.47%) 1 2 / 212 (0.94%) 2		

subjects affected / exposed	1 / 212 (0.47%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	1 / 212 (0.47%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dermal cyst			
subjects affected / exposed	1 / 212 (0.47%)		
occurrences (all)	1		
Dermatitis atopic			
subjects affected / exposed	5 / 212 (2.36%)		
occurrences (all)	5		
Dermatitis contact			
subjects affected / exposed	1 / 212 (0.47%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	7 / 212 (3.30%)		
occurrences (all)	8		
Perioral dermatitis			
subjects affected / exposed	1 / 212 (0.47%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 212 (0.47%)		
occurrences (all)	1		
Seborrhoeic dermatitis			
subjects affected / exposed	1 / 212 (0.47%)		
occurrences (all)	1		
Skin irritation			
subjects affected / exposed	12 / 212 (5.66%)		
occurrences (all)	12		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 212 (0.47%)		
occurrences (all)	1		
Infections and infestations			

Corona virus infection subjects affected / exposed occurrences (all)	1 / 212 (0.47%) 1		
Folliculitis subjects affected / exposed occurrences (all)	1 / 212 (0.47%) 1		
Influenza subjects affected / exposed occurrences (all)	1 / 212 (0.47%) 1		
Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 212 (1.42%) 3		
Oral herpes subjects affected / exposed occurrences (all)	1 / 212 (0.47%) 1		
Rhinitis subjects affected / exposed occurrences (all)	1 / 212 (0.47%) 1		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 212 (0.47%) 1		
Metabolism and nutrition disorders Fluid retention subjects affected / exposed occurrences (all)	1 / 212 (0.47%) 1		
Vitamin D deficiency subjects affected / exposed occurrences (all)	1 / 212 (0.47%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 July 2019	Clinical Study Protocol Version 2.0 made the following changes: -Corrected discrepancies regarding what procedures could be performed either at day -1 or day 1 (this was correctly assigned in the appendix E Schedule of Study Procedures, but erroneously described in the protocol text sections 7.2 and 7.7). This was for clarification. -Corrected an error in sections 7.1 and 7.2 that erroneously put the hematology and serum chemistry at the baseline visit, rather than at the screening visit. The same error was also in sections 7.7.1 and 7.7.2 for the PK Sub-study. -Simplified Appendix B re. microbiological sampling to not include a description of the processing of the samples. Discussion with the local laboratories, who will perform the sampling revealed that procedures and preferred materials varied slightly from country to country. It was deemed to be preferable to capture these procedures in the laboratory protocols instead of the study protocol, to allow for local variations and thus allow laboratories to use their current standard operating procedures and supplies that they are already trained in using and that have been validated on site.
30 October 2019	Clinical Study Protocol Version 3.0 made the following changes: -Changed the process for weighing of returned kits (Sections 6.5 and 7.3-7.7), so weighing to happens at each visit as opposed to all returned kits from one subject being weighed of at the end of study (for that subject). Monitoring the actual dosing of subjects continuously during the study allows the investigators to intervene in cases where subjects are dosing much higher or lower than expected and by doing so hopefully adjust the dosing in order for the study results to reflect 'normal' dosing of an ointment. -Added a triplicate set of ECGs to be taken 1 hour after application of IMP at the Day 1 (Section 7.7.2) and Week 2 (Section 7.7.4) visits in addition to the ECGs already planned at those Visits 2, 4, and 12 hours after application. (This change only impacted the PK substudy.) Adding an additional set of ECGs will strengthen the data collected on cardiac safety. Adding a set of ECGs 1 hour after application ensures that in the case that maximum systemic exposure (Cmax) occurs before 2 hours after application, the study will still produce the desired data on cardiac safety at Cmax. -Added a list of Adverse Events of Special Interest (AESIs) in Section 8.1 to require additional and prompt reporting if such AEs arose.
19 February 2020	Clinical Study Protocol Version 4.0 made the following changes: -Allowed the use of emollient in lesional areas, if subjects develop dry skin in the areas treated by IMP and if so authorized on a case-by-case basis based on the medical judgment of the investigator (Previously the use of emollient was only allowed in areas around, but not overlapping, the treatable areas.) Feedback has been received from investigators in the study that some patients, while showing improvement of redness, developed skin dryness. Following discussion with the investigators, it was concluded that the use of an emollient on such areas would be beneficial for subject comfort and compliance with study procedures. -Removed collection of full body photo documentation at the Week 2 and 4 visits (was still collected at Day -1/1 [baseline] and Week 6 [end-of-treatment] visits). The image procedure is challenging and takes a lot of time for both subjects and study staff. Therefore it was decided to limit the photo requirements to the 2 timepoints most important for efficacy assessment, baseline and end-of-treatment. -Clarification added that IP application is not performed during Week 6 visit.

02 June 2020	Clinical Study Protocol Version 5.0 made the following changes: -Changed the estimated date for the completion of the last subject from June 2020 to November 2020. Recruitment of new subjects was not possible during the months where societies have been closed down due to COVID-19. -Added interim analysis based on the 89/210 subjects that have been randomized and completed or dropped-out of the study by end-of-May. Due to COVID-19 restrictions making recruitment and visit attendance difficult, it was decided to assess an early stop of the study, either for futility or efficacy. -Removed an erroneous statement specifying that the trough level PK sample at the Week 6 visit should be collected "prior to morning or evening application." -Clarification added to Appendix C Assessment Measurements (Local Tolerability Score) that Severe Irritation should also be reported as adverse event. By mistake severe irritation was not marked as requiring reporting as adverse event.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported