Clinical trial results:
A Phase 1/2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Arm Study of the Safety and Efficacy of LX3305, a Sphingosine-1-Phosphate Lyase Inhibitor, for Treatment of Darier's Disease or Hailey-Hailey Disease

Summary

EudraCT number	2018-000373-80
Trial protocol	FR
Global end of trial date	03 December 2018

Results information

Result version number	v1 (current)
This version publication date	03 April 2020
First version publication date	03 April 2020

Trial information

Trial identification

Sponsor protocol code	DERM-101

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Dermecular Therapeutics, Inc.
Sponsor organisation address	421 Kipling Street, Palo Alto, CA, United States, 94301
Public contact	Baird Ruch, Dermecular, +1 978-440-0694, br@dermecular.com
Scientific contact	Curtis Scribner MD, Dermecular, +1 510 914 8368, curt@clscribs.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	31 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 December 2018
Global end of trial reached?	Yes
Global end of trial date	03 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of LX3305 compared to placebo in participants with Darier's Disease (DD) or Hailey-Hailey Disease (HHD).

Protection of trial subjects:

The study was performed in accordance with ethical principles that had their origin in the Declaration of Helsinki and were consistent with International Conference for Harmonisation/Good Clinical Practice, applicable regulatory requirements and the Sponsor's policy on Bioethics.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 July 2018
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	France: 33
Worldwide total number of subjects	33
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)	32
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 33 participants were enrolled and randomized in this study. Participants were stratified according to disease (DD or HHD) and randomized 2:1 to receive either LX3305 or placebo.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Darier’s Disease: LX3305

Arm description:

Participants with Darier’s Disease received one 250-milligrams (mg) capsule of LX3305 orally once daily for the first 7 days of treatment period. If the participant did not experience any adverse events, then starting on Day 8, participants received two 250-mg capsules (total dose of 500 mg) of LX3305 orally once daily for the remaining 11 weeks of the treatment period.

Arm type	Experimental
Investigational medicinal product name	LX3305
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

LX3305 was administered per the dose and schedule specified in the arm.

Arm title	Darier’s Disease: Placebo

Arm description:

Participants with Darier’s Disease received 1 capsule of placebo matched to LX3305 orally once daily for the first 7 days of treatment period. If the participant did not experience any adverse events, then starting on Day 8, participants received 2 capsules of placebo matched to LX3305 orally once daily for the remaining 11 weeks of the treatment period.

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

Dosage and administration details:

Placebo matched to LX3305 was administered per schedule specified in the arm.

Arm title	Hailey-Hailey Disease: LX3305

Arm description:

Participants with Hailey-Hailey Disease received one 250-mg capsule of LX3305 orally once daily for the first 7 days of treatment period. If the participant did not experience any adverse events, then starting on Day 8, participants received two 250-mg capsules (total dose of 500 mg) of LX3305 orally once daily for the remaining 11 weeks of the treatment period.

Arm type	Experimental

Investigational medicinal product name	LX3305
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

LX3305 was administered per the dose and schedule specified in the arm.

Arm title	Hailey-Hailey Disease: Placebo

Arm description:

Participants with Hailey-Hailey Disease received 1 capsule of placebo matched to LX3305 orally once daily for the first 7 days of treatment period. If the participant did not experience any adverse events, then starting on Day 8, participants received 2 capsules of placebo matched to LX3305 orally once daily for the remaining 11 weeks of the treatment period.

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

Dosage and administration details:

Placebo matched to LX3305 was administered per schedule specified in the arm.

Number of subjects in period 1	Darier's Disease: LX3305	Darier's Disease: Placebo	Hailey-Hailey Disease: LX3305
Started	12	5	10
Received at least 1 dose of study drug	12	5	10
mITT population	12	5	10
Completed	11	4	9
Not completed	1	1	1
Adverse event, non-fatal	1	1	-
Other than specified	-	-	1

Number of subjects in period 1	Hailey-Hailey Disease: Placebo
Started	6
Received at least 1 dose of study drug	6
mITT population	6
Completed	6
Not completed	0
Adverse event, non-fatal	-
Other than specified	-

Baseline characteristics

Reporting groups	
Reporting group title	Darier's Disease: LX3305
Reporting group description:	
Participants with Darier's Disease received one 250-milligrams (mg) capsule of LX3305 orally once daily for the first 7 days of treatment period. If the participant did not experience any adverse events, then starting on Day 8, participants received two 250-mg capsules (total dose of 500 mg) of LX3305 orally once daily for the remaining 11 weeks of the treatment period.	
Reporting group title	Darier's Disease: Placebo
Reporting group description:	
Participants with Darier's Disease received 1 capsule of placebo matched to LX3305 orally once daily for the first 7 days of treatment period. If the participant did not experience any adverse events, then starting on Day 8, participants received 2 capsules of placebo matched to LX3305 orally once daily for the remaining 11 weeks of the treatment period.	
Reporting group title	Hailey-Hailey Disease: LX3305
Reporting group description:	
Participants with Hailey-Hailey Disease received one 250-mg capsule of LX3305 orally once daily for the first 7 days of treatment period. If the participant did not experience any adverse events, then starting on Day 8, participants received two 250-mg capsules (total dose of 500 mg) of LX3305 orally once daily for the remaining 11 weeks of the treatment period.	
Reporting group title	Hailey-Hailey Disease: Placebo
Reporting group description:	
Participants with Hailey-Hailey Disease received 1 capsule of placebo matched to LX3305 orally once daily for the first 7 days of treatment period. If the participant did not experience any adverse events, then starting on Day 8, participants received 2 capsules of placebo matched to LX3305 orally once daily for the remaining 11 weeks of the treatment period.	

Reporting group values	Darier's Disease: LX3305	Darier's Disease: Placebo	Hailey-Hailey Disease: LX3305
Number of subjects	12	5	10
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	36.3	36.8	50.3
standard deviation	± 12.99	± 11.80	± 9.92
Gender categorical Units: Subjects			
Female	8	3	7
Male	4	2	3

Reporting group values	Hailey-Hailey Disease: Placebo	Total	
Number of subjects	6	33	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	54.2		
standard deviation	± 6.79	-	

Gender categorical Units: Subjects			
Female	3	21	
Male	3	12	

End points

End points reporting groups

Reporting group title	Darier's Disease: LX3305

Reporting group description:

Participants with Darier's Disease received one 250-milligrams (mg) capsule of LX3305 orally once daily for the first 7 days of treatment period. If the participant did not experience any adverse events, then starting on Day 8, participants received two 250-mg capsules (total dose of 500 mg) of LX3305 orally once daily for the remaining 11 weeks of the treatment period.

Reporting group title	Darier's Disease: Placebo

Reporting group description:

Participants with Darier's Disease received 1 capsule of placebo matched to LX3305 orally once daily for the first 7 days of treatment period. If the participant did not experience any adverse events, then starting on Day 8, participants received 2 capsules of placebo matched to LX3305 orally once daily for the remaining 11 weeks of the treatment period.

Reporting group title	Hailey-Hailey Disease: LX3305

Reporting group description:

Participants with Hailey-Hailey Disease received one 250-mg capsule of LX3305 orally once daily for the first 7 days of treatment period. If the participant did not experience any adverse events, then starting on Day 8, participants received two 250-mg capsules (total dose of 500 mg) of LX3305 orally once daily for the remaining 11 weeks of the treatment period.

Reporting group title	Hailey-Hailey Disease: Placebo

Reporting group description:

Participants with Hailey-Hailey Disease received 1 capsule of placebo matched to LX3305 orally once daily for the first 7 days of treatment period. If the participant did not experience any adverse events, then starting on Day 8, participants received 2 capsules of placebo matched to LX3305 orally once daily for the remaining 11 weeks of the treatment period.

Primary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs), Deaths, and Discontinuations Due to Adverse Events (AEs)

End point title	Number of Participants With Treatment-Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs), Deaths, and Discontinuations Due to Adverse Events (AEs)[1]

End point description:

An AE was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship to the study drug. TEAE was defined as any AE occurring after the first dose of study drug. SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. AEs included both SAEs and non-serious AEs. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system (Version 21.0). A summary of other non-serious AEs and all SAEs, regardless of causality is located in the 'Reported AE section'. Safety population included all participants who were randomized and received any amount of study drug.

End point type	Primary

End point timeframe:

Baseline (Day 1) up to Week 16

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: The endpoint is descriptive in nature and statistical analysis is not applicable.

End point values	Darier's Disease: LX3305	Darier's Disease: Placebo	Hailey-Hailey Disease: LX3305	Hailey-Hailey Disease: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	5	10	6
Units: participants				
TEAEs	10	5	8	6
SAEs	1	1	0	0
Death	0	0	0	0
Discontinuations Due to AEs	1	1	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With at Least a 1-Grade Improvement From Baseline in Investigator's Global Signs Assessment (IGSA) Score at Any Time During the Trial; and at Weeks 4, 8, and 12

End point title	Percentage of Participants With at Least a 1-Grade Improvement From Baseline in Investigator's Global Signs Assessment (IGSA) Score at Any Time During the Trial; and at Weeks 4, 8, and 12

End point description:

IGSA uses a 5 point scale to score severity in Darier's Disease and Hailey-Hailey Disease. IGSA score ranges from 0 to 4, where 0=clear, 1=almost clear, 2=mild,3=moderate, and 4=severe. Higher score indicated worsening. Percentage is based on an IGSA score improvement of at least 1-grade from baseline in the primary lesion. Percentage of participants with at least a 1-grade improvement at each visit are mutually exclusive. Therefore, a participant responding over time may be counted in multiple visits. Clopper Exact 95% confidence interval was used. Modified intent-to-treat (mITT) population included all participants who were randomized, received at least 1 dose of study drug, and had a baseline and at least 1 post-baseline IGSA assessment, unless they discontinued early due to toxicity. Participants who discontinued early due to toxicity (that is, a dose limiting toxicity [DLT]) were to be included in the mITT population, even if they did not have a post-baseline IGSA assessment.

End point type	Secondary

End point timeframe:

Baseline; at any time during the trial (up to Week 12); at Weeks 4, 8, and 12

End point values	Darier's Disease: LX3305	Darier's Disease: Placebo	Hailey-Hailey Disease: LX3305	Hailey-Hailey Disease: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	5	10	6
Units: percentage of participants				
number (confidence interval 95%)				
At anytime	33.3 (9.9 to 65.1)	40.0 (5.3 to 85.3)	50.0 (18.7 to 81.3)	83.3 (35.9 to 99.6)
Week 4	8.3 (0.2 to 38.5)	0 (0 to 0)	20.0 (2.5 to 55.6)	33.3 (4.3 to 77.7)
Week 8	16.7 (2.1 to 48.4)	20.0 (0.5 to 71.6)	10.0 (0.3 to 44.5)	50.0 (11.8 to 88.2)
Week 12	25.0 (5.5 to 57.2)	40.0 (5.3 to 85.3)	50.0 (18.7 to 81.3)	83.3 (35.9 to 99.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Achieved at Least a 2-Grade Improvement From Baseline in IGSA Score at Any Time During the Trial, and at Weeks 4, 8, and 12

End point title	Percentage of Participants who Achieved at Least a 2-Grade Improvement From Baseline in IGSA Score at Any Time During the Trial, and at Weeks 4, 8, and 12

End point description:

IGSA uses a 5 point scale to score severity in Darier's Disease and Hailey-Hailey Disease. IGSA score ranges from 0 to 4, where 0=clear, 1=almost clear, 2=mild,3=moderate, and 4=severe. Higher score indicated worsening. Percentage is based on an IGSA score improvement of at least 1-Grade from baseline in primary lesion. Percentage is based on an IGSA score improvement of at least 2-grades from baseline in primary lesion. Percentage of participants with at least a 2-grade improvement at each visit are mutually exclusive. Therefore, a participant responding over time may be counted in multiple visits. Clopper Exact 95% CI was used. mITT population: all participants who were randomized, received at least 1 dose of study drug, and had a baseline and at least 1 post-baseline IGSA assessment, unless they discontinued early due to toxicity. Participants who discontinued early due to toxicity were to be included in mITT population, even if they did not have a post-baseline IGSA assessment.

End point type	Secondary

End point timeframe:

Baseline; at any time during the trial (up to Week 12); Weeks 4, 8, and 12

End point values	Darier's Disease: LX3305	Darier's Disease: Placebo	Hailey-Hailey Disease: LX3305	Hailey-Hailey Disease: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	5	10	6
Units: percentage of participants				
number (confidence interval 95%)				
At anytime	25.0 (5.5 to 57.2)	40.0 (5.3 to 85.3)	40.0 (12.2 to 73.8)	66.7 (22.3 to 95.7)
Week 4	8.3 (0.2 to 38.5)	0 (0 to 0)	20.0 (2.5 to 55.6)	16.7 (0.4 to 64.1)
Week 8	8.3 (0.2 to 38.5)	20.0 (0.5 to 71.6)	10.0 (0.3 to 44.5)	50.0 (11.8 to 88.2)
Week 12	16.7 (2.1 to 48.4)	40.0 (5.3 to 85.3)	40.0 (12.2 to 73.8)	66.7 (22.3 to 95.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Time-to-Response for 1-Grade Improvement From Baseline in IGSA Score

End point title	Time-to-Response for 1-Grade Improvement From Baseline in IGSA Score

End point description:

Time to response for 1-grade improvement in IGSA score in primary lesion: time from date of randomization to first date of IGSA assessment that showed at least a 1-grade improvement from baseline. It was estimated by Kaplan-Meier method. IGSA uses a 5 point scale to score severity in Darier's Disease and Hailey-Hailey Disease. IGSA score ranges from 0 to 4, where 0=clear,1=almost clear,2=mild,3=moderate,4=severe. Higher score indicated worsening. Participants who did not have at least a 1-grade improvement in primary lesion were censored on date of last IGSA assessment. mITT population:all randomized participants who received at least 1 dose of study drug, had a baseline and at least 1 postbaseline IGSA assessment, unless they discontinued early due to toxicity. Participants who discontinued early due to toxicity were to be included in mITT population, even if they did not have a postbaseline IGSA assessment. '99999'=data not calculated due to low number of participants with an event.

End point type	Secondary

End point timeframe:

Randomization until first improvement in IGSA score from baseline of at least 1-grade (up to Week 12)

End point values	Darier's Disease: LX3305	Darier's Disease: Placebo	Hailey-Hailey Disease: LX3305	Hailey-Hailey Disease: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	5	10	6
Units: days				
median (confidence interval 95%)	99999 (57.00 to 99999)	99999 (57.00 to 99999)	85.00 (31.00 to 99999)	69.50 (29.00 to 99999)

Statistical analyses

No statistical analyses for this end point

Secondary: Time-to-Response for 2-Grade Improvement From Baseline in IGSA Score

End point title	Time-to-Response for 2-Grade Improvement From Baseline in IGSA Score

End point description:

Time to response for 2-grade improvement in IGSA score in primary lesion: time from date of randomization to first date of IGSA assessment that showed at least a 2-grade improvement from baseline. It was estimated by Kaplan-Meier method. IGSA uses a 5 point scale to score severity in Darier's Disease and Hailey-Hailey Disease. IGSA score ranges from 0 to 4, where 0=clear,1=almost clear,2=mild,3=moderate,4=severe. Higher score indicated worsening. Participants who did not have at least a 2-grade improvement in primary lesion were censored on date of last IGSA assessment. mITT population:all randomized participants who received at least 1 dose of study drug, had a baseline and at least 1 postbaseline IGSA assessment, unless they discontinued early due to toxicity. Participants who discontinued early due to toxicity were to be included in mITT population, even if they did not have a postbaseline IGSA assessment. '99999'=data not calculated due to low number of participants with an event.

End point type	Secondary

End point timeframe:

Randomization until first improvement in IGSA score from baseline of at least 2-grade (up to Week 12)

End point values	Darier's Disease: LX3305	Darier's Disease: Placebo	Hailey-Hailey Disease: LX3305	Hailey-Hailey Disease: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	5	10	6
Units: days				
median (confidence interval 95%)	99999 (85.00 to 99999)	99999 (57.00 to 99999)	99999 (31.00 to 99999)	75.50 (29.00 to 99999)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response for 1-Grade Improvement From Baseline in IGSA Score

End point title	Duration of Response for 1-Grade Improvement From Baseline in IGSA Score

End point description:

Duration of response for 1-grade improvement in IGSA score: time from first occurrence of at least a 1-grade IGSA score improvement in primary lesion to date the score returned to baseline grade or higher. It was estimated by Kaplan-Meier methodology. Responders whose IGSA score return to baseline grade or higher or who dropped out or died prior to their IGSA score returning to baseline or higher were censored on date of last IGSA assessment. mITT population: all randomized participants who received at least 1 dose of study drug, had a baseline and at least 1 post-baseline IGSA assessment, unless they discontinued early due to toxicity. Participants who discontinued early due to toxicity were to be included in mITT population, even without a post-baseline IGSA assessment. Here, 'number of participants analyzed'= participants who experienced at least a 1-grade improvement in IGSA score. '-99999 and 99999'=data not calculated due to low number of participants with an event.

End point type	Secondary

End point timeframe:

From first improvement in IGSA score from baseline of at least 1-grade until return to baseline grade or higher (up to Week 12)

End point values	Darier's Disease: LX3305	Darier's Disease: Placebo	Hailey-Hailey Disease: LX3305	Hailey-Hailey Disease: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	2	5	5
Units: days				
median (confidence interval 95%)	50.00 (-99999 to 99999)	99999 (99999 to 99999)	99999 (34.00 to 99999)	99999 (99999 to 99999)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response for 2-Grade Improvement From Baseline in IGSA Score

End point title	Duration of Response for 2-Grade Improvement From Baseline in IGSA Score

End point description:

Duration of response for 2-grade improvement in IGSA score: time from first occurrence of at least a 2-grade IGSA score improvement in primary lesion to date the score returned to baseline grade or higher. It was estimated by Kaplan-Meier methodology. Responders whose IGSA score return to baseline grade or higher or who dropped out or died prior to their IGSA score returning to baseline or higher were censored on date of last IGSA assessment. mITT population: all randomized participants who received at least 1 dose of study drug, had a baseline and at least 1 post-baseline IGSA assessment, unless they discontinued early due to toxicity. Participants who discontinued early due to toxicity were to be included in mITT population, without a post-baseline IGSA assessment. Here, 'number of participants analyzed'= participants who experienced at least a 2-grade improvement in IGSA score. '-99999 and 99999'=data not calculated due to low number of participants with an event.

End point type	Secondary

End point timeframe:

From first improvement in IGSA score from baseline of at least 2-grade until return to baseline grade or higher (up to Week 12)

End point values	Darier's Disease: LX3305	Darier's Disease: Placebo	Hailey-Hailey Disease: LX3305	Hailey-Hailey Disease: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	2	4	4
Units: days				
median (confidence interval 95%)	50.00 (-99999 to 99999)	99999 (99999 to 99999)	99999 (34.00 to 99999)	99999 (99999 to 99999)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Affected Body Surface Area (BSA) at Weeks 4, 8, and 12

End point title	Change from Baseline in Affected Body Surface Area (BSA) at Weeks 4, 8, and 12

End point description:

mITT population included all participants who were randomized, received at least 1 dose of study drug, and had a baseline and at least 1 post-baseline IGSA assessment, unless they discontinued early due to toxicity. Participants who discontinued early due to toxicity (that is, a DLT) were to be included in the mITT population, even if they did not have a post-baseline IGSA assessment.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, and 12

End point values	Darier's Disease: LX3305	Darier's Disease: Placebo	Hailey-Hailey Disease: LX3305	Hailey-Hailey Disease: Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	5	10	6
Units: percentage of BSA				
arithmetic mean (standard deviation)				
Baseline	25.7 (± 19.95)	32.8 (± 17.71)	5.4 (± 3.69)	7.0 (± 8.07)
Change at Week 4 (n=12, 5, 9, 6)	7.1 (± 8.31)	-1.8 (± 13.33)	0.2 (± 5.14)	2.3 (± 2.66)
Change at Week 8 (n=12, 4, 10, 6)	1.0 (± 15.34)	-4.3 (± 12.01)	2.2 (± 12.40)	-0.7 (± 2.42)
Change at Week 12 (n=12, 5, 10, 6)	1.1 (± 17.17)	-6.8 (± 17.20)	0.9 (± 7.84)	-0.3 (± 1.75)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline (Day 1) up to Week 16

Adverse event reporting additional description:

Safety population included all participants who were randomized and received any amount of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Darier's Disease: LX3305

Reporting group description:

Participants with Darier's Disease received one 250-milligrams (mg) capsule of LX3305 orally once daily for the first 7 days of treatment period. If the participant did not experience any adverse events, then starting on Day 8, participants received two 250-mg capsules (total dose of 500 mg) of LX3305 orally once daily for the remaining 11 weeks of the treatment period.

Reporting group title	Darier's Disease: Placebo

Reporting group description:

Participants with Darier's Disease received 1 capsule of placebo matched to LX3305 orally once daily for the first 7 days of treatment period. If the participant did not experience any adverse events, then starting on Day 8, participants received 2 capsules of placebo matched to LX3305 orally once daily for the remaining 11 weeks of the treatment period.

Reporting group title	Hailey-Hailey Disease: LX3305

Reporting group description:

Participants with Hailey-Hailey Disease received one 250-mg capsule of LX3305 orally once daily for the first 7 days of treatment period. If the participant did not experience any adverse events, then starting on Day 8, participants received two 250-mg capsules (total dose of 500 mg) of LX3305 orally once daily for the remaining 11 weeks of the treatment period.

Reporting group title	Hailey-Hailey Disease: Placebo

Reporting group description:

Participants with Hailey-Hailey Disease received 1 capsule of placebo matched to LX3305 orally once daily for the first 7 days of treatment period. If the participant did not experience any adverse events, then starting on Day 8, participants received 2 capsules of placebo matched to LX3305 orally once daily for the remaining 11 weeks of the treatment period.

Serious adverse events	Darier's Disease: LX3305	Darier's Disease: Placebo	Hailey-Hailey Disease: LX3305
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 12 (8.33%)	1 / 5 (20.00%)	0 / 10 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Infections and infestations			
Superinfection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 5 (20.00%)	0 / 10 (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

Viral infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 10 (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

Serious adverse events	Hailey-Hailey Disease: Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Infections and infestations			
Superinfection			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	0 / 6 (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	Darier's Disease: LX3305	Darier's Disease: Placebo	Hailey-Hailey Disease: LX3305
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 12 (83.33%)	4 / 5 (80.00%)	8 / 10 (80.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Superficial spreading melanoma stage unspecified			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			

subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Chills			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Condition aggravated			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Feeling hot			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Congenital, familial and genetic disorders			
Benign familial pemphigus			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Keratosis follicular			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0

Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	0 / 12 (0.00%)	3 / 5 (60.00%)	2 / 10 (20.00%)
occurrences (all)	0	4	9
Migraine			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Deafness transitory			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Blepharitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Dry eye			
subjects affected / exposed	0 / 12 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Vitreous floaters			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Abdominal pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Aphthous ulcer			

subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	4 / 12 (33.33%)	2 / 5 (40.00%)	3 / 10 (30.00%)
occurrences (all)	6	2	4
Faeces soft			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Haemorrhoids			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Tendonitis			

subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Bronchitis haemophilus			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Cystitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Herpes virus infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Localised infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Superinfection			
subjects affected / exposed	1 / 12 (8.33%)	1 / 5 (20.00%)	3 / 10 (30.00%)
occurrences (all)	1	1	3
Urinary tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hypoglycaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Hailey-Hailey Disease: Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Melanocytic naevus			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Superficial spreading melanoma stage unspecified			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Chills			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Condition aggravated			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Feeling hot			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Rhinitis			

subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Congenital, familial and genetic disorders			
Benign familial pemphigus			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Keratosis follicular			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Migraine			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Deafness transitory			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Eye disorders			
Blepharitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Dry eye			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Vitreous floaters			

subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Aphthous ulcer			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Faeces soft			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Haemorrhoids			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Tendonitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bronchitis haemophilus			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Cystitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Herpes virus infection			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Localised infection			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Superinfection			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			

Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Hypoglycaemia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 May 2018	Protocol amendment included the following substantive changes to the protocol: • For female participants of childbearing potential and male participants of reproductive potential who were having intercourse with female partners of childbearing potential, the required use of 2 highly effective methods of birth control during the study was lengthened from 1 month to 90 days after the last dose of study drug. • Stopping rules were clarified to explain that laboratory DLT and DLT referred to a lymphocyte laboratory value of Grade greater than or equal to (≥) 3, and that TEAE referred to any non-lymphocyte TEAE of Grade ≥2. • Reporting requirements for TEAEs were clarified. Rather than reporting within 1 business day of the first awareness of an event, SAEs were to be reported to the Sponsor immediately upon the first awareness of the event. Additional follow-up information, if required or available, was to be sent electronically to the Sponsor immediately upon receipt and should have been completed on a follow-up SAE form, placed with the original SAE information, and kept with the appropriate section of the case report form (CRF) and/or study file.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported