Clinical trial results:
Efficacy and safety of twice-daily application of delgocitinib cream 20 mg/g for 6 weeks in subjects with active discoid lupus erythematosus. A phase 2a exploratory, randomised, double-blind, vehicle-controlled, within-subject, multi-centre trial.

Summary

EudraCT number	2018-003615-22
Trial protocol	DE DK FR
Global end of trial date	30 April 2020

Results information

Result version number	v1 (current)
This version publication date	30 April 2021
First version publication date	30 April 2021

Trial information

Trial identification

Sponsor protocol code	EXP-1373

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03958955
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	LEO Pharma A/S
Sponsor organisation address	Industriparken 55, Ballerup, Denmark, 2750
Public contact	Clinical Disclosure Specialist, LEO Pharma A/S, +45 4494 5888, disclosure@leo-pharma.com
Scientific contact	Clinical Disclosure Specialist, LEO Pharma A/S, +45 4494 5888, disclosure@leo-pharma.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	06 July 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 April 2020
Global end of trial reached?	Yes
Global end of trial date	30 April 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy of delgocitinib cream 20 mg/g twice daily on active discoid lupus erythematosus (DLE) target lesions.

Protection of trial subjects:

This clinical trial was conducted in accordance with the revision, current at the start of the trial, of the World Medical Association's Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. All subjects received written and verbal information concerning the clinical trial. This information emphasised that participation in the clinical trial was voluntary and that the subject could withdraw from the clinical trial at any time and for any reason. All subjects were given an opportunity to ask questions and were given sufficient time to consider before consenting. Subjects' signed and dated informed consent to participate in the clinical trial were obtained prior to any trial related activities being carried out in accordance with ICH Good Clinical Practice (GCP) Section 4.8 and all applicable laws and regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 July 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	Denmark: 1
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	27
EEA total number of subjects	23

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	25
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

37 subjects screened.
27 subjects randomised.
26 subjects completed.

Pre-assignment

Screening details:

A screening visit took place 7 to 28 days before the first application of investigational medicinal product (IMP). To be eligible for participation in the trial each subject had to have at least 2 discoid lupus erythematosus (DLE) target lesions with active disease (referred to as lesions 1 and 2) fulfilling the inclusion criteria.

Period 1

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

Blinding implementation details:

The packaging and labelling of the IMPs were indistinguishable with no evidence of their identity. There was a slight difference in colour between the 2 IMPs, which was only discernible on close inspection with both IMPs compared side by side. To avoid accidental investigator unblinding, the first application of IMPs and instructions to the subjects was only done by designated trial site staff who were not involved in clinical evaluations.

Arms

Are arms mutually exclusive?	No
Arm title	Delgocitinib cream 20 mg/g

Arm description:

This arm represents the DLE lesion that was treated with active IMP - delgocitinib cream 20 mg/g. All 27 subjects received delgocitinib cream 20 mg/g on one DLE target lesion and delgocitinib cream vehicle on another DLE target lesion twice daily for 6 weeks.

Arm type	Experimental
Investigational medicinal product name	Delgocitinib cream 20 mg/g
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

The IMPs (delgocitinib cream and vehicle) were administered as topical applications twice daily, approximately 12 hours apart in the morning and in the evening, in an even layer to cover the entire treatment area, for 6 weeks. The treatment area of each of the 2 target lesions (lesions 1 and 2) of a subject was defined as the lesion area at baseline plus a margin of approximately 1 cm. The amount of IMP to be applied to each treatment area was dependent on the size of the target lesions. If a target lesion was:

- Unchanged or decreased in size, the treatment area was kept constant during the treatment period, even if the symptoms improved.
- Increased in size, the treatment area was increased correspondingly.

Arm title	Delgocitinib cream vehicle

Arm description:

This arm represents the DLE lesion that was treated with vehicle - delgocitinib cream vehicle. All 27 subjects received delgocitinib cream 20 mg/g on one DLE target lesion and delgocitinib cream vehicle on another DLE target lesion twice daily for 6 weeks.

Arm type	Placebo

Investigational medicinal product name	Delgocitinib vehicle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

The IMPs (delgocitinib cream and vehicle) were administered as topical applications twice daily, approximately 12 hours apart in the morning and in the evening, in an even layer to cover the entire treatment area, for 6 weeks. The treatment area of each of the 2 target lesions (lesions 1 and 2) of a subject was defined as the lesion area at baseline plus a margin of approximately 1 cm. The amount of IMP to be applied to each treatment area was dependent on the size of the target lesions. If a target lesion was:

- Unchanged or decreased in size, the treatment area was kept constant during the treatment period, even if the symptoms improved.
- Increased in size, the treatment area was increased correspondingly.

Number of subjects in period 1	Delgocitinib cream 20 mg/g	Delgocitinib cream vehicle
Started	27	27
Completed	26	26
Not completed	1	1
Adverse event, non-fatal	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial
Reporting group description:	
Baseline	

Reporting group values	Overall trial	Total	
Number of subjects	27	27	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	25	25	
From 65-84 years	2	2	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	45.7		
standard deviation	± 13.4	-	
Gender categorical Units: Subjects			
Female	15	15	
Male	12	12	

Subject analysis sets	
Subject analysis set title	Randomised subjects
Subject analysis set type	Full analysis
Subject analysis set description:	
All 27 randomised subjects were included in the full analysis set (FAS).	
Subject analysis set title	Exposed subjects
Subject analysis set type	Safety analysis
Subject analysis set description:	
27 subjects received at least 1 dose of IMP.	
Subject analysis set title	Primary analysis set
Subject analysis set type	Per protocol
Subject analysis set description:	
5 subjects were excluded from the per protocol (PP) analysis set as the primary endpoint data were compromised. The PP analysis set hence comprised 22 (81.5%) subjects. Data at Week 8 was excluded from the PP analysis set for 2 subjects, as they used prohibited concomitant medication in the safety follow-up period.	

Reporting group values	Randomised subjects	Exposed subjects	Primary analysis set
Number of subjects	27	27	22
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	25	25	
From 65-84 years	2	2	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean			
standard deviation	±	±	±
Gender categorical Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Delgocitinib cream 20 mg/g

Reporting group description:

This arm represents the DLE lesion that was treated with active IMP - delgocitinib cream 20 mg/g. All 27 subjects received delgocitinib cream 20 mg/g on one DLE target lesion and delgocitinib cream vehicle on another DLE target lesion twice daily for 6 weeks.

Reporting group title	Delgocitinib cream vehicle

Reporting group description:

This arm represents the DLE lesion that was treated with vehicle - delgocitinib cream vehicle. All 27 subjects received delgocitinib cream 20 mg/g on one DLE target lesion and delgocitinib cream vehicle on another DLE target lesion twice daily for 6 weeks.

Subject analysis set title	Randomised subjects
Subject analysis set type	Full analysis

Subject analysis set description:

All 27 randomised subjects were included in the full analysis set (FAS).

Subject analysis set title	Exposed subjects
Subject analysis set type	Safety analysis

Subject analysis set description:

27 subjects received at least 1 dose of IMP.

Subject analysis set title	Primary analysis set
Subject analysis set type	Per protocol

Subject analysis set description:

5 subjects were excluded from the per protocol (PP) analysis set as the primary endpoint data were compromised. The PP analysis set hence comprised 22 (81.5%) subjects. Data at Week 8 was excluded from the PP analysis set for 2 subjects, as they used prohibited concomitant medication in the safety follow-up period.

Primary: Target lesions with Investigator’s Global Assessment (IGA)a score of 0 or 1 at Week 6.

End point title	Target lesions with Investigator’s Global Assessment (IGA)a score of 0 or 1 at Week 6.

End point description:

End point type	Primary

End point timeframe:

At week 6

End point values	Delgocitinib cream 20 mg/g	Delgocitinib cream vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: lesions	3	6		

Statistical analyses

Statistical analysis title	Primary endpoint: IGA score of 0 or 1

Statistical analysis description:

22 subjects with 2 DLE lesions each (44 DLE lesions in total). Each subject had one DLE lesion treated with delgocitinib cream 20 mg/g and another DLE lesion treated with delgocitinib cream vehicle.

Attributable risk is defined as the difference in estimated probability of treatment success of delgocitinib compared to vehicle. Success is defined as having an IGA score of 0 (clear) or 1 (almost clear) at Week 6.

Comparison groups	Delgocitinib cream 20 mg/g v Delgocitinib cream vehicle
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4531 [1]
Method	Mcnemar
Parameter estimate	Attributable risk
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	0.09

Notes:

[1] - Exact p-value of McNemar's test

Secondary: Number of Adverse Events (AEs) up to Week 6

End point title	Number of Adverse Events (AEs) up to Week 6

End point description:

End point type	Secondary

End point timeframe:

Week 0 to week 6

End point values	Exposed subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	27[2]			
Units: Adverse events	8			

Notes:

[2] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With AEs up to Week 6

End point title	Number of Subjects With AEs up to Week 6

End point description:

End point type	Secondary

End point timeframe: Week 0 to week 6

End point values	Exposed subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	27[3]			
Units: subjects	8			

Notes:

[3] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Lesion-specific, Treatment-related AEs up to Week 6.

End point title	Number of Lesion-specific, Treatment-related AEs up to Week 6.

End point description:

End point type	Secondary

End point timeframe:

Week 0 to week 6

End point values	Delgocitinib cream 20 mg/g	Delgocitinib cream vehicle	Exposed subjects	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	27	27	27[4]	
Units: adverse events	2	0	2	

Notes:

[4] - Per protocol (PP) analysis set

Statistical analyses

Statistical analysis title	Lesions with IMP related lesion-specific AEs

Statistical analysis description:

27 subjects with 2 DLE lesions each (54 DLE lesions in total). Each subject had one DLE lesion treated with delgocitinib cream 20 mg/g and another DLE lesion treated with delgocitinib cream vehicle.

Attributable risk is defined as the difference in estimated probability of treatment success of delgocitinib compared to vehicle.

Comparison groups	Delgocitinib cream 20 mg/g v Delgocitinib cream vehicle

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5 [5]
Method	Mcnemar
Parameter estimate	Attributable risk
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.17

Notes:

[5] - Exact p-value of McNemar's test.

Secondary: A ≥2-point Reduction in IGA Score at Week 6 Compared to Baseline.

End point title	A ≥2-point Reduction in IGA Score at Week 6 Compared to Baseline.

End point description:

End point type	Secondary

End point timeframe:

baseline to Week 6

End point values	Delgocitinib cream 20 mg/g	Delgocitinib cream vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: lesions ≥2-point reduction in IGA at W6				
number (not applicable)	3	6		

Statistical analyses

Statistical analysis title	At least 2-point reduction in IGA score at Week 6

Statistical analysis description:

22 subjects with 2 DLE lesions each (44 DLE lesions in total). Each subject had one DLE lesion treated with delgocitinib cream 20 mg/g and another DLE lesion treated with delgocitinib cream vehicle.

Attributable risk is defined as the difference in estimated probability of treatment success of delgocitinib compared to vehicle.

Success is defined as having at least a 2-point reduction in IGA score from baseline to Week 6.

Comparison groups	Delgocitinib cream 20 mg/g v Delgocitinib cream vehicle

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4531 [6]
Method	Mcnemar
Parameter estimate	Attributable risk
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	0.09

Notes:

[6] - Exact p-value of McNemar's test.

Secondary: A ≥2-point Reduction in Erythema Score at Week 6 Compared to Baseline.

End point title	A ≥2-point Reduction in Erythema Score at Week 6 Compared to Baseline.

End point description:

End point type	Secondary

End point timeframe:

baseline to Week 6

End point values	Delgocitinib cream 20 mg/g	Delgocitinib cream vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: lesions with ≥2-point reduction at W6				
number (not applicable)	5	5		

Statistical analyses

Statistical analysis title	At least 2-point reduction in erythema score at W6

Statistical analysis description:

22 subjects with 2 DLE lesions each (44 DLE lesions in total). Each subject had one DLE lesion treated with delgocitinib cream 20 mg/g and another DLE lesion treated with delgocitinib cream vehicle.

Attributable risk is defined as the difference in estimated probability of treatment success of delgocitinib compared to vehicle.

Success is defined as having at least a 2-point reduction in IGA score from baseline to Week 6.

Comparison groups	Delgocitinib cream 20 mg/g v Delgocitinib cream vehicle

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [7]
Method	McNemar's test
Parameter estimate	Attributable risk
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	0.22

Notes:

[7] - Exact p-value of McNemar's test.

Secondary: Erythema Score at Week 6

End point title	Erythema Score at Week 6

End point description:

End point type	Secondary

End point timeframe:

Week 6

End point values	Delgocitinib cream 20 mg/g	Delgocitinib cream vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22[8]	22[9]		
Units: Erythema score				
median (inter-quartile range (Q1-Q3))	1.5 (1 to 2)	1.5 (1 to 2)		

Notes:

[8] - Per protocol (PP) analysis set

[9] - Per protocol (PP) analysis set

Statistical analyses

Statistical analysis title	Erythema score at Week 6

Statistical analysis description:

22 subjects with 2 DLE lesions each (44 DLE lesions in total). Each subject had one DLE lesion treated with delgocitinib cream 20 mg/g and another DLE lesion treated with delgocitinib cream vehicle.

Erythema is scored as 0=absent, 1=pink, faint, 2=red, 3=dark red, purple/violaceous/crusted/haemorrhagic.

Comparison groups	Delgocitinib cream 20 mg/g v Delgocitinib cream vehicle
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5797 [10]
Method	Wilcoxon signed rank test

Notes:

[10] - p-value of the Wilcoxon signed rank test.

Secondary: Total Skin Disease Activity Score (Sum of Scores for Erythema, Scaling/Hyperkeratosis, and Oedema/Infiltration) at Week 6.

End point title	Total Skin Disease Activity Score (Sum of Scores for Erythema, Scaling/Hyperkeratosis, and Oedema/Infiltration) at Week 6.

End point description:

End point type	Secondary

End point timeframe:

Week 6

End point values	Delgocitinib cream 20 mg/g	Delgocitinib cream vehicle		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22[11]	22[12]		
Units: Total Skin Disease Activity Score				
median (inter-quartile range (Q1-Q3))	2.5 (2 to 4)	2.5 (1 to 4)		

Notes:

[11] - Per protocol (PP) analysis set

[12] - Per protocol (PP) analysis set

Statistical analyses

Statistical analysis title	Total skin disease activity score at Week 6

Statistical analysis description:

22 subjects with 2 DLE lesions each (44 DLE lesions in total). Each subject had one DLE lesion treated with delgocitinib cream 20 mg/g and another DLE lesion treated with delgocitinib cream vehicle.

Total skin disease activity score is the sum of the scores for erythema, scaling/hyperkeratosis, and oedema/infiltration.

Total skin disease activity score ranges from 0 to 7 with lower score indicating better state.

Comparison groups	Delgocitinib cream 20 mg/g v Delgocitinib cream vehicle
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7862 [13]
Method	Wilcoxon signed rank test

Notes:

[13] - p-value of the Wilcoxon signed rank test.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline to Week 8	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0
Reporting groups	
Reporting group title	Randomised subjects

Reporting group description:

All subjects received delgocitinib cream 20 mg/g on one DLE target lesion and delgocitinib cream vehicle on another DLE target lesion twice daily for 6 weeks.
Delgocitinib cream 20 mg/g: Cream for topical application.
Delgocitinib cream vehicle: The cream vehicle is similar to the delgocitinib cream except that it does not contain any active ingredient.

Serious adverse events	Randomised subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (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	Randomised subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 27 (29.63%)		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
General disorders and administration site conditions			
Application site pain			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	2		
Application site pruritus			

subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Ear and labyrinth disorders Middle ear inflammation subjects affected / exposed occurrences (all)	 1 / 27 (3.70%) 1		
Gastrointestinal disorders Gastrointestinal disorder subjects affected / exposed occurrences (all)	 1 / 27 (3.70%) 1		
Skin and subcutaneous tissue disorders Cutaneous lupus erythematosus subjects affected / exposed occurrences (all) Rash erythematous subjects affected / exposed occurrences (all)	 1 / 27 (3.70%) 1 1 / 27 (3.70%) 1		
Musculoskeletal and connective tissue disorders Musculoskeletal pain subjects affected / exposed occurrences (all)	 1 / 27 (3.70%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 4 / 27 (14.81%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 May 2019	Amendment 1 (substantial, global, 15-May-2019): The protocol was amended to address comments mainly from the German authorities and ethics committee, who requested further specification of details about e.g. lab procedures, re-assessment of eligibility, and discontinuation of IMP, as well as correction of inconsistencies regarding wording of the primary endpoint and exclusion criteria.
22 October 2019	Amendment 2 (substantial, global, 22-Oct-2019): The protocol was amended to address recruitment issues. DLE is a rare disease, and the number of patients eligible for this trial was limited. The exclusion criteria concerning tobacco use and hepatitis B serology (exclusion criteria 17 and 26) were therefore modified to ease recruitment without compromising the safety of the subjects and the evaluation of trial results.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The trial was terminated prematurely due to slow recruitment, and due to an anticipation that recruitment would become further delayed due to the COVID-19 pandemic affecting recruitment activities.

Notes: