

**Clinical trial results:****An International, Multicenter, Randomized, Double-Blind, Parallel-Group Phase 2 Study Evaluating the Safety and Efficacy of Diacerein 1% Ointment Topical Formulation in Subjects with Epidermolysis Bullosa Simplex (EBS) [DELIVERS Study]****Summary**

EudraCT number	2016-004427-24
Trial protocol	DE AT NL GB FR
Global end of trial date	31 October 2018

Results information

Result version number	v1 (current)
This version publication date	30 October 2019
First version publication date	30 October 2019

Trial information**Trial identification**

Sponsor protocol code	CCP-020-301
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03154333
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 131 384

Notes:

Sponsors

Sponsor organisation name	Castle Creek Pharmaceuticals, LLC
Sponsor organisation address	6 Century Drive , Parsippany, NJ , United States, NJ 07054
Public contact	Dr. Mary Spellman, Castle Creek Pharmaceuticals, LLC , 001 8622860400, mspellman@castlecreekpharma.com
Scientific contact	Dr. Mary Spellman, Castle Creek Pharmaceuticals, LLC , 001 8622860400, mspellman@castlecreekpharma.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	17 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 October 2018
Global end of trial reached?	Yes
Global end of trial date	31 October 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to compare the efficacy of diacerein 1% ointment to control ointment when applied once daily for 8 weeks in subjects with epidermolysis bullosa simplex (EBS).

Protection of trial subjects:

The study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonization (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2017
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	Netherlands: 4
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Israel: 5
Country: Number of subjects enrolled	United States: 23
Worldwide total number of subjects	54
EEA total number of subjects	24

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)	37
Adolescents (12-17 years)	5
Adults (18-64 years)	12
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were screened for inclusion and exclusion criteria at Visit 1 (Week -6). Subjects must have had a genotypic confirmation of an EBS protocol-defined mutation through prior genetic testing or via a blood or saliva genetic assessment as part of the study.

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

Blinding implementation details:

This study used a double-blind design. The study drugs were indistinguishable in appearance, packaging, and labeling.

Arms

Are arms mutually exclusive?	Yes
Arm title	Diacerein 1%

Arm description:

At Visit 2 (Week 0), eligible subjects randomized in a 1:1 ratio to receive diacerein 1% ointment to all EBS lesions in the Assessment Area.

Arm type	Experimental
Investigational medicinal product name	Diacerein
Investigational medicinal product code	CCP-020
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

During the 8-week Treatment Period, Diacerein was administered from Visit 2 (Week 0) to Visit 6 (Week 8) once daily in the evening to EBS lesions in the Assessment Area (regardless of lesion resolution) and Treatment Area (until lesion(s) resolution). The subject/caregiver applied sufficient quantity of Diacerein to cover all EBS lesions and to approximately ¾ inch (2 cm) of uninvolved skin surrounding each lesion with a thin layer and gently rubbed it in.

Arm title	Control
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Arm description:

At Visit 2 (Week 0), eligible subjects randomized in a 1:1 ratio to receive control ointment to all EBS lesions in the Assessment Area.

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

Dosage and administration details:

During the 8-week Treatment Period, the control ointment was administered from Visit 2 (Week 0) to Visit 6 (Week 8) once daily in the evening to EBS lesions in the Assessment Area (regardless of lesion resolution) and Treatment Area (until lesion(s) resolution). The subject/caregiver applied sufficient quantity of the control ointment to cover all EBS lesions and to approximately ¾ inch (2 cm) of uninvolved skin surrounding each lesion with a thin layer and gently rubbed it in.

Number of subjects in period 1	Diacerein 1%	Control
Started	28	26
Completed	21	21
Not completed	7	5
Study terminated by Sponsor	6	5
Lost to follow-up	1	-

Baseline characteristics

Reporting groups

Reporting group title	Diacerein 1%
Reporting group description: At Visit 2 (Week 0), eligible subjects randomized in a 1:1 ratio to receive diacerein 1% ointment to all EBS lesions in the Assessment Area.	
Reporting group title	Control
Reporting group description: At Visit 2 (Week 0), eligible subjects randomized in a 1:1 ratio to receive control ointment to all EBS lesions in the Assessment Area.	

Reporting group values	Diacerein 1%	Control	Total
Number of subjects	28	26	54
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	19	18	37
Adolescents (12-17 years)	1	4	5
Adults (18-64 years)	8	4	12
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	14	16	30
Male	14	10	24

End points

End points reporting groups

Reporting group title	Diacerein 1%
Reporting group description: At Visit 2 (Week 0), eligible subjects randomized in a 1:1 ratio to receive diacerein 1% ointment to all EBS lesions in the Assessment Area.	
Reporting group title	Control
Reporting group description: At Visit 2 (Week 0), eligible subjects randomized in a 1:1 ratio to receive control ointment to all EBS lesions in the Assessment Area.	

Primary: Achievement $\geq 60\%$ reduction in BSA of EBS in the assessment area

End point title	Achievement $\geq 60\%$ reduction in BSA of EBS in the assessment area
End point description: The primary efficacy endpoint of this study was the proportion of subjects who achieved $\geq 60\%$ reduction in body surface area (BSA) of Epidermolysis Bullosa Simplex (EBS) lesions within the Assessment Area from Baseline to Week 8.	
End point type	Primary
End point timeframe: The primary efficacy endpoint was examined from Baseline/Visit 2 (Week 0) to Visit 6 (Week 8).	

End point values	Diacerein 1%	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	26		
Units: Subjects	16	14		

Statistical analyses

Statistical analysis title	Comparison in $\geq 60\%$ reduction in BSA of EBS
Comparison groups	Diacerein 1% v Control
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.9666
Method	Cochran-Mantel-Haenszel
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.62

Notes:

[1] - Subjects who achieved $\geq 60\%$ reduction in BSA of EBS lesions within the Assessment Area from Baseline to Week 8 for the diacerein 1% group compared to the control group for the ITT Population.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from Week 0 Day 1 through the study until the end.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Diacerein 1%
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Reporting group description: -

Reporting group title	Control
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Reporting group description: -

Serious adverse events	Diacerein 1%	Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 28 (0.00%)	2 / 26 (7.69%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Meniere's disease			
subjects affected / exposed	0 / 28 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Diacerein 1%	Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 28 (78.57%)	21 / 26 (80.77%)	
Injury, poisoning and procedural complications			

Fall subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	3 / 26 (11.54%) 4	
Skin abrasion subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	2 / 26 (7.69%) 2	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	3 / 26 (11.54%) 3	
General disorders and administration site conditions Application site pruritus subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0 2 / 28 (7.14%) 2	2 / 26 (7.69%) 2 0 / 26 (0.00%) 0	
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2	1 / 26 (3.85%) 1	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 4 2 / 28 (7.14%) 2 4 / 28 (14.29%) 5	0 / 26 (0.00%) 0 0 / 26 (0.00%) 0 1 / 26 (3.85%) 1	
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2	0 / 26 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	4 / 28 (14.29%) 4	1 / 26 (3.85%) 1	
Nasal congestion subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2	1 / 26 (3.85%) 1	
Skin and subcutaneous tissue disorders			
Blister subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	2 / 26 (7.69%) 2	
Pruritus subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 3	1 / 26 (3.85%) 1	
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 28 (14.29%) 4	2 / 26 (7.69%) 2	
Skin infection subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 4	3 / 26 (11.54%) 4	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	2 / 26 (7.69%) 3	
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2	2 / 26 (7.69%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 March 2017	Global Protocol Amendment 1, dated 17 March 2017. The key changes to the primary endpoint were as follows: <ul style="list-style-type: none">- Removal of the LSA and addition of the IGA at Visit 8 (Week 16).- Inclusion Criterion 1 was updated to reflect an increase in the subject's minimum age from 6 months to 4 years.- Inclusion Criterion 5 was revised to the minimum IGA score of 3.- PK sampling was removed from the protocol.- Genotyping criteria were expanded.- Sample size was recalculated.
08 June 2017	Global Protocol Amendment 2. The key changes were as follows: <ul style="list-style-type: none">- Clarification of BSA of an EBS lesion and LSA Area.- Inclusion Criterion 2, clarification of eligibility criteria.- Inclusion Criterion 3, clarification of eligibility criteria.- Treatment Area clarified (not to exceed 30% BSA).- Inclusion Criterion 5 and 6, clarification of eligibility criteria.- An IDMC added to conduct interim analysis.- Exclusion Criterion 11 clarification of eligibility criteria.- Exclusion Criterion 12 clarification of eligibility criteria.- PK was added to protocol.- Subject withdrawals clarified.- Clarified study procedures and safety reporting, where necessary.
02 January 2018	Global Protocol Amendment 3a. <ul style="list-style-type: none">- Clarification dose and treatment rationale.- Clarification risk and/or benefits to subjects.- Primary objective updated to include reduction in BSA of EBS lesions.- Secondary objective updated to include changes in IGA scores.- Primary endpoint updated.- Key secondary endpoint was added and other secondary endpoints were updated.- PK endpoints clarified.- eDiary instructions clarified and updated.- Number of sites were updated.- The list of permitted topical products and therapies was further updated.- Siblings of those enrolled were not allowed in the study, was removed.- Clarification on exclusion of subjects with controlled diabetes and HbA1c<6.5%.- Describing prohibited therapies was removed.- Instructions for treatment of EBS were clarified.- Laboratory tests updated.- Use of body charts to record the location of EBS lesion revised.- Definitions of occluded lesions clarified.- Pruritus and pain scales updated.- SAEs and AESI clarified.- Contraception methods clarified.- Safety methods updated to include ECG.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
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30 October 2018	Following the interim analysis on 40 randomized subjects, the IDMC made the recommendation to the Sponsor to terminate the study on the basis that the primary BSA endpoint was unlikely to achieve statistical significance. Per this recommendation, Castle Creek terminated the study but allowed patients to roll over into a separate open-label extension study.	-
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Notes:

Limitations and caveats

None reported