Clinical trial results:
Double-blind, randomised clinical study comparing efficacy and safety of Ciclopirox Olamine Cream 10 mg/g (Test) vs. Batrafen® Cream (Reference) vs. Vehicle in patients with skin mycoses

Summary

EudraCT number	2018-001633-41
Trial protocol	DE
Global end of trial date	08 June 2021

Results information

Result version number	v1 (current)
This version publication date	08 June 2022
First version publication date	08 June 2022

Trial information

Trial identification

Sponsor protocol code	18-01/Cic-C

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Dermapharm AG
Sponsor organisation address	Lil-Dagover-Ring 7, Gruenwald, Germany, 82031
Public contact	Clinical Research Department, Dermapharm AG, +49 89641860, Clinicaltrials.Dermapharm@dermapharm.com
Scientific contact	Clinical Research Department, Dermapharm AG, +49 89641860, Clinicaltrials.Dermapharm@dermapharm.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	20 April 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 June 2021
Global end of trial reached?	Yes
Global end of trial date	08 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluation of the efficiacy and safety of a new creme containing 10 mg/g Ciclopirox Olamine vs. the originator Batrafen® Cream (Reference) vs. vehicle in patients with skin mycoses

Protection of trial subjects:

There were no specific measures necessary.

Background therapy:

There was no background therapy.

Evidence for comparator:

The comparator contains the same ingredients in the same concentration as the test product and has a marketing license for the study indication.

Actual start date of recruitment	18 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	Germany: 403
Worldwide total number of subjects	403
EEA total number of subjects	403

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)	296
From 65 to 84 years	105
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

14 study centers in Germany; first patient first visit: 05 August 2019; last patient last visit: 08 June 2021

Pre-assignment

Screening details:

Main criteria for inclusion:
Women and men ≥ 18 years of age; Diagnosis of skin mycosis confirmed by a positive microscopic native preparation in 30% potassium hydroxide (KOH); sum score of the parameters pruritus, burning/stinging, erythema, fissuring/cracking, scaling, and maceration up to a total score value of ≥ 6 (equal to moderate severity)

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	Investigator, Monitor, Data analyst, Subject

Blinding implementation details:

The tubes containing the study medications were neutral white. The attached labels were identical for all three preparations. All three study medications were indistinguishable in terms of appearance. The random code was transferred to the data base not before the following actions were completed: data base closure, finalisation of the SAP, a Blind Data Review (BDR) and the agreement between sponsor and study statistician
upon the definition of the analysis data sets (fixed in a BDR Report).

Arms

Are arms mutually exclusive?	Yes
Arm title	Cic-C

Arm description:

Test product

Arm type	Experimental
Investigational medicinal product name	Ciclopirox Olamin Cream 10 mg/g
Investigational medicinal product code	D01AE14
Other name	
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use

Dosage and administration details:

Application twice daily as a thin layer on the affected area

Arm title	Batrafen

Arm description:

Reference product

Arm type	Active comparator
Investigational medicinal product name	Batrafen Cream 10 mg/g
Investigational medicinal product code	D01AE14
Other name	
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use

Dosage and administration details:

Application twice daily as a thin layer on the affected area

Arm title	Vehicle

Arm description:	
Vehicle of test product	
Arm type	Placebo
Investigational medicinal product name	Vehicle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use

Dosage and administration details:

Application twice daily as a thin layer on the affected area.

Number of subjects in period 1	Cic-C	Batrafen	Vehicle
Started	129	141	133
Completed	120	129	117
Not completed	9	12	16
Consent withdrawn by subject	1	-	1
Covid-related	1	2	2
Adverse event, non-fatal	1	1	-
Technical-logistic reasons	2	3	5
Poor tolerability	-	1	-
Lost to follow-up	3	4	3
Lack of efficacy	1	1	5

Baseline characteristics

Reporting groups

Reporting group title	Treatment Period

Reporting group description: -

Reporting group values	Treatment Period	Total	
Number of subjects	403	403	
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)	296	296	
From 65-84 years	105	105	
85 years and over	2	2	
Gender categorical Units: Subjects			
Female	133	133	
Male	270	270	

Subject analysis sets

Subject analysis set title	Safety data set
Subject analysis set type	Safety analysis

Subject analysis set description:

Includes all randomised patients who had administered the study medication at least once and who provided at least one safety related outcome.

Subject analysis set title	FAS
Subject analysis set type	Full analysis

Subject analysis set description:

Consists of all patients as randomised who received study medication at least once and have an assessment of the primary efficacy variable.

Subject analysis set title	PP
Subject analysis set type	Per protocol

Subject analysis set description:

Comprises all patients of the FAS who did not exhibit any major protocol violations.

Reporting group values	Safety data set	FAS	PP
Number of subjects	394	390	370
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)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	289	286	273
From 65-84 years	103	102	95
85 years and over	2	2	2
Gender categorical Units: Subjects			
Female	127	126	121
Male	267	264	249

End points

End points reporting groups

Reporting group title	Cic-C
Reporting group description:	
Test product	
Reporting group title	Batrafen
Reporting group description:	
Reference product	
Reporting group title	Vehicle
Reporting group description:	
Vehicle of test product	
Subject analysis set title	Safety data set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Includes all randomised patients who had administered the study medication at least once and who provided at least one safety related outcome.	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
Consists of all patients as randomised who received study medication at least once and have an assessment of the primary efficacy variable.	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description:	
Comprises all patients of the FAS who did not exhibit any major protocol violations.	

Primary: Clinical treatment success

End point title	Clinical treatment success
End point description:	
The primary efficacy variable is clinical treatment success at the end-of-treatment examination at visit V4 (LOCF, i.e. last observation under treatment carried forward). Clinical treatment success was defined as 'yes' if the sum score of clinical parameters ≤ 2 AND all individual clinical score values ≤ 1 AND the mycological result was negative AND no further need for antimycotical treatment existed.	
End point type	Primary
End point timeframe:	
Start of treatment (visit 1) to EOT (visit 4) with 3 weeks treatment.	

End point values	Cic-C	Batrafen	Vehicle	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119	129	131	
Units: Percentage	45	66	46	

Statistical analyses

Statistical analysis title	Analysis of efficacy

Statistical analysis description:

The primary objective of this study was to show therapeutic equivalence of the test preparation Cic-C compared to the approved reference Batrafen with respect to the primary efficacy variable. Therapeutic equivalence was statistically proven if the two-sided 95% confidence interval for πCic-C - πBatrafen was completely contained within [-20%, 20%].

Comparison groups	Batrafen v Cic-C
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Mean difference (final values)
Point estimate	-13.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.42
upper limit	-0.28

Statistical analysis title	Superiority of Test over Vehicle

Statistical analysis description:

In order to verify assay sensitivity of the study, superiority of the two active preparations over the vehicle was tested by means of two-sided significance tests (Fisher’s exact tests) with α = 5%. The primary test of superiority was carried out for the FAS data set.

Comparison groups	Cic-C v Vehicle
Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6053
Method	Fisher exact

Statistical analysis title	Superiority of Reference over Vehicle

Statistical analysis description:

In order to verify assay sensitivity of the study, superiority of the two active preparations over the vehicle was tested by means of two-sided significance tests (Fisher’s exact tests) with α = 5%. The primary test of superiority was carried out for the FAS data set.

Comparison groups	Batrafen v Vehicle
Number of subjects included in analysis	260
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0132
Method	Fisher exact

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From the inclusion visit (V 1, day 0) to the final visit (V5, day 35, 2 weeks after EOT).	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	Cic-C
Reporting group description: Test product	
Reporting group title	Batrafen
Reporting group description: Reference product	
Reporting group title	Vehicle
Reporting group description: Vehicle of test product	

Serious adverse events	Cic-C	Batrafen	Vehicle
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 126 (0.79%)	1 / 137 (0.73%)	1 / 131 (0.76%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Weight decreased			
subjects affected / exposed	1 / 126 (0.79%)	0 / 137 (0.00%)	0 / 131 (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
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 126 (0.79%)	0 / 137 (0.00%)	0 / 131 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 126 (0.00%)	1 / 137 (0.73%)	0 / 131 (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

Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 126 (0.00%)	0 / 137 (0.00%)	1 / 131 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	Cic-C	Batrafen	Vehicle
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 126 (14.29%)	13 / 137 (9.49%)	20 / 131 (15.27%)
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 137 (0.00%)	0 / 131 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Application site dryness			
subjects affected / exposed	1 / 126 (0.79%)	0 / 137 (0.00%)	0 / 131 (0.00%)
occurrences (all)	1	0	0
Application site erythema			
subjects affected / exposed	1 / 126 (0.79%)	0 / 137 (0.00%)	0 / 131 (0.00%)
occurrences (all)	1	0	0
Application site pain			
subjects affected / exposed	0 / 126 (0.00%)	2 / 137 (1.46%)	1 / 131 (0.76%)
occurrences (all)	0	2	1
Application site paraesthesia			
subjects affected / exposed	1 / 126 (0.79%)	0 / 137 (0.00%)	0 / 131 (0.00%)
occurrences (all)	1	0	0
Application site pruritus			
subjects affected / exposed	1 / 126 (0.79%)	0 / 137 (0.00%)	0 / 131 (0.00%)
occurrences (all)	1	0	0
Feeling hot			
subjects affected / exposed	1 / 126 (0.79%)	0 / 137 (0.00%)	0 / 131 (0.00%)
occurrences (all)	1	0	0
Peripheral swelling			

subjects affected / exposed	1 / 126 (0.79%)	0 / 137 (0.00%)	0 / 131 (0.00%)
occurrences (all)	1	0	0
Swelling			
subjects affected / exposed	0 / 126 (0.00%)	1 / 137 (0.73%)	0 / 131 (0.00%)
occurrences (all)	0	1	0
Xerosis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 137 (0.00%)	1 / 131 (0.76%)
occurrences (all)	0	0	1
Immune system disorders			
Allergy to chemicals			
subjects affected / exposed	0 / 126 (0.00%)	1 / 137 (0.73%)	0 / 131 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Menstrual disorder			
subjects affected / exposed	0 / 126 (0.00%)	0 / 137 (0.00%)	1 / 131 (0.76%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Nasal polyps			
subjects affected / exposed	0 / 126 (0.00%)	1 / 137 (0.73%)	0 / 131 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	1 / 126 (0.79%)	0 / 137 (0.00%)	1 / 131 (0.76%)
occurrences (all)	1	0	1
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	0 / 126 (0.00%)	0 / 137 (0.00%)	1 / 131 (0.76%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Skin laceration			
subjects affected / exposed	1 / 126 (0.79%)	0 / 137 (0.00%)	0 / 131 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Burning sensation			
subjects affected / exposed	0 / 126 (0.00%)	1 / 137 (0.73%)	0 / 131 (0.00%)
occurrences (all)	0	1	0
Headache			

subjects affected / exposed	2 / 126 (1.59%)	1 / 137 (0.73%)	2 / 131 (1.53%)
occurrences (all)	2	1	2
Paraesthesia			
subjects affected / exposed	1 / 126 (0.79%)	2 / 137 (1.46%)	0 / 131 (0.00%)
occurrences (all)	1	2	0
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 126 (0.00%)	1 / 137 (0.73%)	0 / 131 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 126 (0.00%)	2 / 137 (1.46%)	0 / 131 (0.00%)
occurrences (all)	0	2	0
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	1 / 126 (0.79%)	0 / 137 (0.00%)	0 / 131 (0.00%)
occurrences (all)	1	0	0
Dry skin			
subjects affected / exposed	0 / 126 (0.00%)	0 / 137 (0.00%)	1 / 131 (0.76%)
occurrences (all)	0	0	1
Eczema			
subjects affected / exposed	2 / 126 (1.59%)	0 / 137 (0.00%)	0 / 131 (0.00%)
occurrences (all)	2	0	0
Erythema			
subjects affected / exposed	1 / 126 (0.79%)	1 / 137 (0.73%)	0 / 131 (0.00%)
occurrences (all)	1	1	0
Intertrigo			
subjects affected / exposed	1 / 126 (0.79%)	0 / 137 (0.00%)	0 / 131 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	0 / 126 (0.00%)	1 / 137 (0.73%)	0 / 131 (0.00%)
occurrences (all)	0	1	0
Psoriasis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 137 (0.00%)	1 / 131 (0.76%)
occurrences (all)	0	0	1
Rosacea			

subjects affected / exposed	0 / 126 (0.00%)	0 / 137 (0.00%)	1 / 131 (0.76%)
occurrences (all)	0	0	1
Skin exfoliation			
subjects affected / exposed	0 / 126 (0.00%)	1 / 137 (0.73%)	0 / 131 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 126 (0.79%)	0 / 137 (0.00%)	0 / 131 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 137 (0.00%)	0 / 131 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	2 / 126 (1.59%)	2 / 137 (1.46%)	1 / 131 (0.76%)
occurrences (all)	2	2	1
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 126 (0.79%)	0 / 137 (0.00%)	0 / 131 (0.00%)
occurrences (all)	1	0	0
Epididymitis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 137 (0.00%)	0 / 131 (0.00%)
occurrences (all)	1	0	0
Fungal infection			
subjects affected / exposed	0 / 126 (0.00%)	0 / 137 (0.00%)	2 / 131 (1.53%)
occurrences (all)	0	0	3
Fungal skin infection			
subjects affected / exposed	0 / 126 (0.00%)	0 / 137 (0.00%)	1 / 131 (0.76%)
occurrences (all)	0	0	2
Groin abscess			
subjects affected / exposed	0 / 126 (0.00%)	0 / 137 (0.00%)	1 / 131 (0.76%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 137 (0.00%)	4 / 131 (3.05%)
occurrences (all)	1	0	4
Pulpitis dental			

subjects affected / exposed	0 / 126 (0.00%)	0 / 137 (0.00%)	1 / 131 (0.76%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 126 (0.00%)	1 / 137 (0.73%)	1 / 131 (0.76%)
occurrences (all)	0	1	1
Tinea pedis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 137 (0.00%)	0 / 131 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	0 / 126 (0.00%)	1 / 137 (0.73%)	0 / 131 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	1 / 126 (0.79%)	0 / 137 (0.00%)	0 / 131 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None reported

Notes: