



## Clinical trial results:

**An intra-individual randomized controlled study to evaluate the efficacy and tolerance of the product RV4421A BS0042 in association with a moderately potent topical corticosteroid in adults with Atopic Dermatitis**

### Summary

EudraCT number	2014-002194-10
Trial protocol	DE
Global end of trial date	09 July 2015

### Results information

Result version number	v1 (current)
This version publication date	12 December 2018
First version publication date	12 December 2018

### Trial information

#### Trial identification

Sponsor protocol code	RV4421A2013147
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#### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	Pierre Fabre Dermo Cosmétique
Sponsor organisation address	45 place Abel Gance, Boulogne, France, 92654
Public contact	not applicable, proDERM GmbH, AHougardy@proDERM.de
Scientific contact	not applicable, proDERM GmbH, AHougardy@proDERM.de

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	24 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 July 2015
Global end of trial reached?	Yes
Global end of trial date	09 July 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective will be to evaluate the benefit of the association of the product RV4421A BS0042 with a moderately potent topical corticosteroid compared with the moderately potent topical corticosteroid alone, in improvement of Atopic Dermatitis in adults, measured by the reduction of L-SCORAD at Day 3 (D3).

Protection of trial subjects:

This study was performed in accordance with the principles stated in the Declaration of Helsinki (1964) and subsequent amendments, and in accordance with the EN ISO 14155 (2011) and national regulations.

The protocol and related documents (including the informed consent form) were submitted for approval to an independent Ethics Committees before the study set up, according to national regulations.

The first application of the associated product and test product was performed at investigational centre under the study personnel control in order to explain the way of use to the patient and to evaluate the immediate local tolerance.

Additionally to the test product (on one arm or leg), all patients received on both arms or legs an activetreatment by an appropriate, representative, widely used and in the European Union (EU) approved TCS for 10 days.

Background therapy:

No other therapy was used during the trial. The patient was allowed to apply any topical medication on face and body, except on both study arms or legs. For instance, topical treatments prescribed by the investigator for the other AD lesions than those on study arms or legs were allowed throughout the duration of the study.

During the 2nd period of the study (from D10 to D24), in case of worsening of lesions on one/both arm(s) or leg(s) leading to the need of a product application, the patient was authorized to apply any product on his/her suitable arm(s) or leg(s).

Evidence for comparator:

According to several guidelines for treatment of Atopic Dermatitis, potent steroids should be avoided and moderately potent Topical Corticosteroids (TCS) are recommended on areas where the skin is already thin, such as flexures. Desonide 0.1 % cream (LOCAPRED) has been chosen as TCS because it is one of the most prescribed TCS in France and it is commercialized in most of Europe.

Actual start date of recruitment	01 October 2014
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: 54
Worldwide total number of subjects	54
EEA total number of subjects	54

Notes:

<b>Subjects enrolled per age group</b>	
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)	54
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

This superiority clinical study was conducted as a European, multicentre, randomized, open-label, controlled, intra-individual(right/left arm/leg) trial on 54 adults with moderate to severe AD with symmetric lesions on arms or popliteal fossa. All patients were recruited in 4 centres in Germany

### Pre-assignment

Screening details:

The patients with a phototype > IV were not included in the study because of difficulties in assessing the local tolerance of the products on darker skin.

### Period 1

Period 1 title	First Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	First Group

Arm description:

Left arm/popliteal fossa: twice daily application of the product RV4421A BS0042 in association with once daily application of TCS on the AD lesions (10 days)

Right arm/ popliteal fossa: once daily application of TCS alone on the AD lesions

Arm type	Experimental
Investigational medicinal product name	RV4421A-BS0042
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use

Dosage and administration details:

The test product had to be applied twice daily (morning and evening) on lesions of only one study arm or popliteal fossa according to randomization, after the associated product, if applicable. One fingertip unit of test product had to be applied on only one arm or popliteal fossa, at each application. If the patient presented other lesions on the same arm or the same leg, he would also apply the test product on these lesions. The first application of test product was performed at the investigational centre.

Investigational medicinal product name	topical corticosteroid (TCS)
Investigational medicinal product code	Locapred 0.1%
Other name	
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use

Dosage and administration details:

The TCS was applied once daily (evening only) on lesions of both study arms or popliteal fossa, before the test product if applicable. Two fingertip units of TCS were applied per study arm or popliteal fossa, at each application. If the patient presented other lesions on the study arm(s) or leg(s), he also applied the associated product on these lesions. The first application of TCS was performed at the investigational centre.

<b>Arm title</b>	Second Group
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Arm description:

Left arm/ popliteal fossa: once daily application of TCS alone on the AD lesions

Right arm/ popliteal fossa: twice daily application of the product RV4421A BS0042 in association with once daily application of TCS on the AD lesions (10 days)

Arm type	Experimental
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Investigational medicinal product name	Topical corticosteroid
Investigational medicinal product code	Locapred 0.1%
Other name	
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use

Dosage and administration details:

The TCS was applied once daily (evening only) on lesions of both study arms or popliteal fossa, before the test product if applicable. Two fingertip units of TCS were applied per study arm or popliteal fossa, at each application. If the patient presented other lesions on the study arm(s) or leg(s), he also applied the associated product on these lesions. The first application of TCS was performed at the investigational centre.

Investigational medicinal product name	RV4421A-BS0042
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use

Dosage and administration details:

The test product had to be applied twice daily (morning and evening) on lesions of only one study arm or popliteal fossa according to randomization, after the associated product, if applicable. One fingertip unit of test product had to be applied on only one arm or popliteal fossa, at each application. If the patient presented other lesions on the same arm or the same leg, he would also apply the test product on these lesions. The first application of test product was performed at the investigational centre.

<b>Number of subjects in period 1</b>	First Group	Second Group
Started	26	28
Completed	23	24
Not completed	3	4
Lack of efficacy	3	4

**Period 2**

Period 2 title	Maintenance period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

**Arms**

Are arms mutually exclusive?	Yes
<b>Arm title</b>	First Group

Arm description:

Left arm: twice daily application of the product RV4421A BS0042 (2 weeks).  
Right arm: not any product application (2 weeks).

Arm type	Experimental
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Investigational medicinal product name	RV4421A-BS0042
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use

Dosage and administration details:

The test product had to be applied twice daily (morning and evening) on lesions of only one study arm or popliteal fossa according to randomization, after the associated product, if applicable. One fingertip unit of test product had to be applied on only one arm or popliteal fossa, at each application. If the patient presented other lesions on the same arm or the same leg, he would also apply the test product on these lesions. The first application of test product was performed at the investigational centre.

<b>Arm title</b>	Second Group
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Arm description:

Left arm: no product was applied during the maintenance phase in this arm (2 weeks)  
 Right arm: twice daily application of the product RV4421A BS0042 (2 weeks)

Arm type	Experimental
Investigational medicinal product name	RV4421A-BS0042
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use

Dosage and administration details:

The test product had to be applied twice daily (morning and evening) on lesions of only one study arm or popliteal fossa according to randomization, after the associated product, if applicable. One fingertip unit of test product had to be applied on only one arm or popliteal fossa, at each application. If the patient presented other lesions on the same arm or the same leg, he would also apply the test product on these lesions. The first application of test product was performed at the investigational centre.

<b>Number of subjects in period 2</b>	First Group	Second Group
Started	23	24
Completed	22	24
Not completed	1	0
Personal Reason	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	First Period
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Reporting group description:

Fifty four patients with moderate to severe AD were included in the study. Fifty four patients were evaluated at D3 and D10, and 46 patients completed the study at D24. Eight patients discontinued during the study (before D24): 7 patients were not included in the 2nd period and 1 patient was withdrawn for a personal reason during the 2nd period.

Reporting group values	First Period	Total	
Number of subjects	54	54	
Age categorical			
Units: Subjects			
Adults (18-64 years)	54	54	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
median	26.06		
standard deviation	± 12.11	-	
Gender categorical			
Units: Subjects			
Female	31	31	
Male	23	23	
Phototype			
Description of the phototype classified with the Fitzpatrick scale			
Units: Subjects			
Phototype I	1	1	
Phototype II	16	16	
Phototype III	26	26	
Phototype IV	11	11	
L-IGA Score (Locapred alone)			
The Local Investigator's Global Assessment (L-IGA) score was assessed by the investigator independently on both study elbow creases/arms or popliteal fossa on a 6-point scale ranged from 0 (clear) to 5 (very severe disease).			
Units: Subjects			
Moderate Disease	35	35	
Severe Disease	19	19	
L-IGA Score (RV4421 + Locapred)			
The Local Investigator's Global Assessment (L-IGA) score was assessed by the investigator independently on both study elbow creases/arms or popliteal fossa on a 6-point scale ranged from 0 (clear) to 5 (very severe disease).			
Units: Subjects			
Moderate disease	33	33	
Severe disease	21	21	

## End points

### End points reporting groups

Reporting group title	First Group
Reporting group description: Left arm/popliteal fossa: twice daily application of the product RV4421A BS0042 in association with once daily application of TCS on the AD lesions (10 days) Right arm/ popliteal fossa: once daily application of TCS alone on the AD lesions	
Reporting group title	Second Group
Reporting group description: Left arm/ popliteal fossa: once daily application of TCS alone on the AD lesions Right arm/ popliteal fossa: twice daily application of the product RV4421A BS0042 in association with once daily application of TCS on the AD lesions (10 days)	
Reporting group title	First Group
Reporting group description: Left arm: twice daily application of the product RV4421A BS0042 (2 weeks). Right arm: not any product application (2 weeks).	
Reporting group title	Second Group
Reporting group description: Left arm: no product was applied during the maintenance phase in this arm (2 weeks) Right arm: twice daily application of the product RV4421A BS0042 (2 weeks)	

### Primary: L-SCORAD

End point title	L-SCORAD
End point description: The LSCORAD is the sum of all SCORAD objective signs scores evaluated on a chosen target area. The SCORAD objective signs were: erythema, oedema/papulation, oozing/crusts, excoriation, lichenification and xerosis. For the primary efficacy criterion (L-SCORAD Index), if at least one evaluation was missing after the first evaluation of post product application, the LOCF method (Last Observation Carried Forward) was used to replace missing data.	
End point type	Primary
End point timeframe: The primary criterion was the L-SCORAD index assessed independently on both elbow creases/study arms or popliteal fossa by the investigator on a scale ranged from 0 to 18, at Visit 2 (D3).	

End point values	First Group	Second Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	28		
Units: not applicable				
number (not applicable)	26	28		

### Statistical analyses

Statistical analysis title	L-SCORAD
Comparison groups	First Group v Second Group

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005
Method	ANCOVA
Parameter estimate	F statistic
Confidence interval	
level	95 %
sides	2-sided

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

At inclusion, any concomitant disease was reported. At each further visit, the occurrence of AE was determined by the patient's spontaneous reporting, the investigator's non-leading questioning and his/her clinical/dermatological evaluation.

Adverse event reporting additional description:

The patient's assessment had at least to take into account the following functional signs: burning sensation, warm sensation, itching/pruritus, tightness, stinging/prickling. The investigator and patient's assessment had at least to take into account the following physical signs: redness/erythema swelling/oedema, desquamation, dryness, vesicles.

Assessment type	Systematic
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### Dictionary used

Dictionary name	Not applicable
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Dictionary version	NA
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### Reporting groups

Reporting group title	First + second Groups
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Reporting group description:

Throughout the whole study, 16 patients out of 54 included patients (72%) experienced at least one adverse event suspected to be related to the test product and associated products and reported a total of 30 AEs. Serious adverse events (SAE) were not reported during this study.

Serious adverse events	First + second Groups		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 54 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	First + second Groups		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 54 (29.63%)		
Skin and subcutaneous tissue disorders			
Burning sensation	Additional description: Burning sensation on application		
subjects affected / exposed	10 / 54 (18.52%)		
occurrences (all)	21		
Exacerbation of Atopic Dermatitis			
subjects affected / exposed	4 / 54 (7.41%)		
occurrences (all)	5		

Pruritus			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Pruritus sensation erythema			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 March 2015	<p>Modification of study areas:</p> <p><b>Arms</b> In order to facilitate recruitment without changing the target population, it has been decided to extend the target areas from the elbow creases to the arms (including wrists). Indeed, in adults, atopic Dermatitis (AD) often appears in the elbow creases, but lesions affect also forearms and wrists. Furthermore, in this study, each patient's arm followed randomly a specific treatment regimen (either topical corticosteroids (TCS) alone, or association of TCS with RV4421A BS0042) and all scores (including primary criterion) were assessed independently on both sides. We considered that lesions on arms (including on wrists), similar in terms of extent and severity, didn't need to be symmetrical in terms of specific location on arms. For example, a patient could be included if he presented similar target lesions on the left wrist and the right elbow crease without impacting the study results. In order to have comparable data between all included patients, inclusion criteria related to disease severity were not modified.</p> <p><b>Popliteal fossa</b> In order to make facilitate recruitment without changing the target population, it has been decided to extend the target areas not only on the arms, but also on the popliteal fossa. Popliteal fossa are areas commonly affected by inflammatory lesions in the adult population. Furthermore, AD often appears in these areas in a symmetrical distribution, perfectly adapted to an intra-individual study. According to several guidelines, moderately potent topical corticosteroids (TCS), like the one used in this study, are recommended for AD affecting the flexures. Both products are adapted to lesions affecting the popliteal fossa. We considered that a patient could be included if he presents similar lesions on the popliteal fossa without impacting the study results.</p>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported