Clinical trial results:
Randomised, double-blind, bilateral comparison of two emollients in patients with dry skin.

Summary

EudraCT number	2014-001026-16
Trial protocol	GB
Global end of trial date	12 June 2015

Results information

Result version number	v1 (current)
This version publication date	08 March 2017
First version publication date	08 March 2017

Trial information

Trial identification

Sponsor protocol code	DELP-05

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Dermal Laboratories Limited
Sponsor organisation address	Tatmore Place, Gosmore, Hitchin, United Kingdom, SG4 7QR
Public contact	Clinical Trials Administrator, Dermal Laboratories Limited, 0044 1462458866, clinical@dermal.co.uk
Scientific contact	Clinical Trials Administrator, Dermal Laboratories Limited, 0044 1462458866, clinical@dermal.co.uk

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	23 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 June 2015
Global end of trial reached?	Yes
Global end of trial date	12 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare (bilaterally) Doublebase Dayleve Gel and Zerobase Emollient Cream, two moisturisers currently marketed in the UK, in terms of their cumulative effects on skin moisturisation levels (determined by corneometry), when applied twice daily by atopic eczema patients to their lower legs over 5 consecutive days. The secondary objective was to compare (bilaterally) the cosmetic acceptability of the two products. Each patient applied both study products: one to their left leg and the other to their right leg. The allocation of study products to left or right leg was randomised.

Protection of trial subjects:

This was a low risk trial as the products tested are currently marketed in the UK and being used in accordance with their indication/ labelling instructions and current clinical practice. The main risk to participants was posed by them undergoing a 1 week washout period as part of the screening process; whereby they were asked not to apply any moisturisers to their lower legs only. This was mitigated by allowing the patients to carry on using their regular moisturisers/ treatments for managing their dry skin and eczema, apart from on their lower legs. In addition, only patients without active eczema flares on their lower legs were entered into the washout. Patients were also given the contact details of the study centre in case they had any concerns during this period, and in the unlikely event of their condition deteriorating, the Investigator would have immediately discontinued their participation in the study.

Background therapy:

The use of the trial products was restricted to the patients' lower legs only. Elsewhere, they were allowed to carry on applying their usual topical treatments and moisturisers to manage their skin condition.

Evidence for comparator:

The NICE Clinical Guideline for the management of atopic eczema advocates the frequent, widespread and liberal use of skin moisturisers, reapplied frequently throughout the day (even if the eczema is clear). However, this is not always practical and many patients are only able to apply their prescribed moisturisers in the morning and in the evening. This study was conducted to provide comparative evidence of the ability of moisturisers to improve and maintain skin hydration, when applied only twice daily. Therefore, both products selected for testing in this trial are popular moisturisers currently prescribed in the UK for the management of dry skin conditions such as atopic eczema.

Actual start date of recruitment	28 April 2015
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	United Kingdom: 18
Worldwide total number of subjects	18
EEA total number of subjects	18

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)	17
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Potential participants were primarily identified from a review of the study centre's patient volunteer database. In addition, a study poster was used in order to publicise the study to the wider community.

Pre-assignment

Screening details:

24 potential participants were consented and screened, 3 failed screening prior to washout. 21 patients commenced the one week washout period, of whom 18 were eligible for the study after completing the washout period and were randomised to 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, Data analyst, Assessor

Blinding implementation details:

For blinding purposes, the two products were repackaged into identical tubes and labelled with identical labels with the exception of the assigned patient number and right/ left lower leg allocation. Every patient number was unique and was related to the randomisation code pre-assigned by the statistician. In addition, the assessor was not allowed to witness the product application performed every morning (by the patient) at the study centre, nor see the actual content of the tubes.

Arms

Are arms mutually exclusive?	No
Arm title	DELP Gel treated legs

Arm description:

Each patient applied both treatments, one to each left or right lower leg (randomised treatment allocation).

Arm type	Experimental
Investigational medicinal product name	DELP Gel
Investigational medicinal product code	PR1
Other name	Doublebase Dayleve (PL 00173/0199)
Pharmaceutical forms	Gel
Routes of administration	Cutaneous use

Dosage and administration details:

The product was applied topically by the patient, twice daily - once in the morning (at the study centre) between 8 and 10 am and once in the evening (at home) between 8 and 10 pm; for 5 days. Patients were instructed in their treatment diary to apply enough of each product to treat the assigned lower leg (from the ankle to the knee). As a guide, an amount of about 1 inch of product squeezed from the tube, or a blob about the size of a 20p piece, was instructed. This unit dose is consistent with the normal use of the products and current clinical practice.

Arm title	ZBC treated legs

Arm description:

Each patient applied both treatments, one to each left or right lower leg (randomised treatment allocation).

Arm type	Active comparator
Investigational medicinal product name	ZBC
Investigational medicinal product code	PR2
Other name	Zerobase Emollient Cream
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use

Dosage and administration details:

The product was applied topically by the patient, twice daily - once in the morning (at the study centre) between 8 and 10 am and once in the evening (at home) between 8 and 10 pm; for 5 days. Patients were instructed in their treatment diary to apply enough of each product to treat the assigned lower leg (from the ankle to the knee). As a guide, an amount of about 1 inch of product squeezed from the tube, or a blob about the size of a 20p piece, was instructed. This unit dose is consistent with the normal use of the products and current clinical practice.

Number of subjects in period 1	DELP Gel treated legs	ZBC treated legs
Started	18	18
Completed	18	18

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description:

All randomised patients.

Reporting group values	Overall trial	Total	
Number of subjects	18	18	
Age categorical			
All randomised patients. Only patients between 16 and 65 years of age were eligible for this study.			
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)	17	17	
From 65-84 years	1	1	
85 years and over	0	0	
Gender categorical			
Only female subjects eligible for this study.			
Units: Subjects			
Female	18	18	
Ethnic group Units: Subjects			
Caucasian	16	16	
Other	2	2	
Solar skin type Units: Subjects			
1 (White, very fair, always burns)	0	0	
2 (White, fair, usually burns)	6	6	
3 (Cream white, sometimes mild burn)	10	10	
4 (Brown, typically mediterranean, rarely burns)	1	1	
5 (Dark brown, mid eastern, very rarely burns)	1	1	
6 (Black, never burns)	0	0	

Subject analysis sets

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set was defined as all randomised subjects provided that they had a baseline measurement of corneometry. Since all randomised patients had a baseline measurement of corneometry the Full Analysis Set and the Safety Analysis Set were the same and included all

randomised patients. The Full Analysis Set was used for the ITT analysis.

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

Subject analysis set description:

The Safety Analysis Set comprised of all randomised patients who used at least one of the study products. All safety analyses were based on the Safety Analysis Set.

Reporting group values	Full analysis set	Safety analysis set	
Number of subjects	18	18	
Age categorical			
All randomised patients. Only patients between 16 and 65 years of age were eligible for this study.			
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)	17	17	
From 65-84 years	1	1	
85 years and over	0	0	
Gender categorical			
Only female subjects eligible for this study.			
Units: Subjects			
Female	18	18	
Ethnic group Units: Subjects			
Caucasian	16	16	
Other	2	2	
Solar skin type Units: Subjects			
1 (White, very fair, always burns)	0	0	
2 (White, fair, usually burns)	6	6	
3 (Cream white, sometimes mild burn)	10	10	
4 (Brown, typically mediterranean, rarely burns)	1	1	
5 (Dark brown, mid eastern, very rarely burns)	1	1	
6 (Black, never burns)	0	0	

End points

End points reporting groups

Reporting group title	DELP Gel treated legs

Reporting group description:

Each patient applied both treatments, one to each left or right lower leg (randomised treatment allocation).

Reporting group title	ZBC treated legs

Reporting group description:

Each patient applied both treatments, one to each left or right lower leg (randomised treatment allocation).

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set was defined as all randomised subjects provided that they had a baseline measurement of corneometry. Since all randomised patients had a baseline measurement of corneometry the Full Analysis Set and the Safety Analysis Set were the same and included all randomised patients. The Full Analysis Set was used for the ITT analysis.

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

Subject analysis set description:

The Safety Analysis Set comprised of all randomised patients who used at least one of the study products. All safety analyses were based on the Safety Analysis Set.

Primary: DELP Gel vs ZBC: AUC change from baseline over 5 days

End point title	DELP Gel vs ZBC: AUC change from baseline over 5 days

End point description:

The primary endpoint was the area under the curve (AUC) of the change from baseline (i.e. Day 1 pre-treatment) of the skin corneometry measurements collected for each leg over a 5 day period for DELP compared to that for ZBC. AUC was calculated using the Trapezoidal rule from the mean of triplicate measurements and using the actual time recorded on the CRF for the corneometry measurements rather than the scheduled time.

End point type	Primary

End point timeframe:

Corneometry readings were obtained three times a day at approx. 4 hour intervals: first measurement in the morning around 9 am before product application, followed by the second measurement at around 1 pm and the third measurement at around 5 pm.

End point values	DELP Gel treated legs	ZBC treated legs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[1]	18[2]		
Units: Corneometry units				
arithmetic mean (standard deviation)	1797 (± 672.2)	177 (± 438.3)		

Notes:

[1] - Bilateral design - all 18 patients applied DELP Gel to one leg and ZBC to the other.

[2] - Bilateral design - all 18 patients applied DELP Gel to one leg and ZBC to the other.

Statistical analyses

Statistical analysis title	Treatment effect DELP Gel vs ZBC

Statistical analysis description:

The primary endpoint was analysed using a mixed model taking into account the within-patient design, with patient as a random effect and leg, randomised group and treatment as fixed effects and with baseline corneometry measurement as a covariate. The number of patients included in this analysis was 18 (not 36), as this was a within-patient, bilateral comparison study (each patient received both treatments, one to each leg). The Full Analysis Set was used for this ITT analysis.

Comparison groups	DELP Gel treated legs v ZBC treated legs
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001 [4]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1601
Confidence interval	
level	95 %
sides	2-sided
lower limit	1277
upper limit	1924
Variability estimate	Standard error of the mean
Dispersion value	151.7

Notes:

[3] - The number of patients included in this analysis was 18 (not 36), as this was a within-patient, bilateral comparison study (each patient received both treatments, one to each leg). The parameter estimate is the least squares mean treatment difference for the AUC change from baseline corneometry readings over the 5 day period.
[4] - Significant at 5% level (2-sided).

Secondary: DELP Gel vs ZBC: Change from baseline to first corneometry measurement on day 5

End point title	DELP Gel vs ZBC: Change from baseline to first corneometry measurement on day 5

End point description:

Secondary endpoints were the comparison between DELP Gel and ZBC in the change from baseline to the first corneometry measurement obtained on each of days 2 to 5. Since this is actually four secondary endpoints, a hierarchical testing regime, starting from day 5 through to day 2, was used to preserve the overall significance level. This is the day 5 secondary endpoint.

End point type	Secondary

End point timeframe:

Corneometry readings for this endpoint were obtained on the first measurement in the morning (around 9 am) of days 1 (baseline) and 5; before the first morning application on the day.

End point values	DELP Gel treated legs	ZBC treated legs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[5]	18[6]		
Units: Corneometry units				
arithmetic mean (standard deviation)	13.3 (± 9.62)	0.5 (± 4.53)		

Notes:

[5] - Bilateral design - all 18 patients applied DELP Gel to one leg and ZBC to the other.

[6] - Bilateral design - all 18 patients applied DELP Gel to one leg and ZBC to the other.

Statistical analyses

Statistical analysis title	Treatment effect DELP Gel vs ZBC

Statistical analysis description:

This secondary endpoint was analysed using a mixed model taking into account the within-patient design, with patient as a random effect and leg, randomised group and treatment as fixed effects and with baseline corneometry measurement as a covariate. The number of patients included in each analysis was 18 (not 36), as this was a within-patient, bilateral comparison study (each patient received both treatments, one to each leg). The Full Analysis Set was used for this ITT analysis.

Comparison groups	DELP Gel treated legs v ZBC treated legs
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.0001 [8]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	12.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.4
upper limit	16.8
Variability estimate	Standard error of the mean
Dispersion value	1.97

Notes:

[7] - The number of patients included in this analysis was 18 (not 36), as this was a within-patient, bilateral comparison study (each patient received both treatments, one to each leg). Parameter estimate is least squares mean treatment difference for the change from baseline to the first corneometry reading on day 5.
[8] - A hierarchical testing regime was used, starting from day 5 through to day 2, to preserve the overall significance level (significant at 5% level, 2-sided).

Secondary: DELP Gel vs ZBC: Change from baseline to first corneometry measurement on day 4

End point title	DELP Gel vs ZBC: Change from baseline to first corneometry measurement on day 4

End point description:

Secondary endpoints were the comparison between DELP Gel and ZBC in the change from baseline to the first corneometry measurement obtained on each of days 2 to 5. Since this is actually four secondary endpoints, a hierarchical testing regime, starting from day 5 through to day 2, was used to preserve the overall significance level. This is the day 4 secondary endpoint.

End point type	Secondary

End point timeframe:

Corneometry readings for this endpoint were obtained on the first measurement in the morning (around 9 am) of days 1 (baseline) and 4; before the first morning application on the day.

End point values	DELP Gel treated legs	ZBC treated legs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[9]	18[10]		
Units: Corneometry units				
arithmetic mean (standard deviation)	17.9 (± 9.79)	1.3 (± 5.85)		

Notes:

[9] - Bilateral design - all 18 patients applied DELP Gel to one leg and ZBC to the other.

[10] - Bilateral design - all 18 patients applied DELP Gel to one leg and ZBC to the other.

Statistical analyses

Statistical analysis title	Treatment effect DELP Gel vs ZBC

Statistical analysis description:

This secondary endpoint was analysed using a mixed model taking into account the within-patient design, with patient as a random effect and leg, randomised group and treatment as fixed effects and with baseline corneometry measurement as a covariate. The number of patients included in each analysis was 18 (not 36), as this was a within-patient, bilateral comparison study (each patient received both treatments, one to each leg). The Full Analysis Set was used for this ITT analysis.

Comparison groups	DELP Gel treated legs v ZBC treated legs
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	< 0.0001 [12]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	16.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.3
upper limit	20.4
Variability estimate	Standard error of the mean
Dispersion value	1.89

Notes:

[11] - The number of patients included in this analysis was 18 (not 36), as this was a within-patient, bilateral comparison study (each patient received both treatments, one to each leg). Parameter estimate is least squares mean treatment difference for the change from baseline to the first corneometry reading on day 4.

[12] - A hierarchical testing regime was used, starting from day 5 through to day 2, to preserve the overall significance level (significant at 5% level, 2-sided).

Secondary: DELP Gel vs ZBC: Change from baseline to first corneometry measurement on day 3

End point title	DELP Gel vs ZBC: Change from baseline to first corneometry measurement on day 3

End point description:

Secondary endpoints were the comparison between DELP Gel and ZBC in the change from baseline to the first corneometry measurement obtained on each of days 2 to 5. Since this is actually four secondary endpoints, a hierarchical testing regime, starting from day 5 through to day 2, was used to preserve the overall significance level. This is the day 3 secondary endpoint.

End point type	Secondary

End point timeframe:

Corneometry readings for this endpoint were obtained on the first measurement in the morning (around 9 am) of days 1 (baseline) and 3; before the first morning application on the day.

End point values	DELP Gel treated legs	ZBC treated legs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[13]	18[14]		
Units: corneometry units				
arithmetic mean (standard deviation)	10.9 (± 8.34)	-0.4 (± 4.83)		

Notes:

[13] - Bilateral design - all 18 patients applied DELP Gel to one leg and ZBC to the other.

[14] - Bilateral design - all 18 patients applied DELP Gel to one leg and ZBC to the other.

Statistical analyses

Statistical analysis title	Treatment effect DELP Gel vs ZBC

Statistical analysis description:

This secondary endpoint was analysed using a mixed model taking into account the within-patient design, with patient as a random effect and leg, randomised group and treatment as fixed effects and with baseline corneometry measurement as a covariate. The number of patients included in each analysis was 18 (not 36), as this was a within-patient, bilateral comparison study (each patient received both treatments, one to each leg). The Full Analysis Set was used for this ITT analysis.

Comparison groups	DELP Gel treated legs v ZBC treated legs
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	< 0.0001 [16]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	11
Confidence interval	
level	95 %
sides	2-sided
lower limit	7
upper limit	15
Variability estimate	Standard error of the mean
Dispersion value	1.88

Notes:

[15] - The number of patients included in this analysis was 18 (not 36), as this was a within-patient, bilateral comparison study (each patient received both treatments, one to each leg). Parameter estimate is least squares mean treatment difference for the change from baseline to the first corneometry reading on day 3.

[16] - A hierarchical testing regime was used, starting from day 5 through to day 2, to preserve the overall significance level (significant at 5% level, 2-sided).

Secondary: DELP Gel vs ZBC: Change from baseline to first corneometry measurement on day 2

End point title	DELP Gel vs ZBC: Change from baseline to first corneometry measurement on day 2

End point description:

Secondary endpoints were the comparison between DELP Gel and ZBC in the change from baseline to the first corneometry measurement obtained on each of days 2 to 5. Since this is actually four secondary endpoints, a hierarchical testing regime, starting from day 5 through to day 2, was used to preserve the overall significance level. This is the day 2 secondary endpoint.

End point type	Secondary

End point timeframe:

Corneometry readings for this endpoint were obtained on the first measurement in the morning (around 9 am) of days 1 (baseline) and 2; before the first morning application on the day.

End point values	DELP Gel treated legs	ZBC treated legs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[17]	17[18]		
Units: Corneometry units				
arithmetic mean (standard deviation)	10.6 (± 5.99)	1.2 (± 3.14)		

Notes:

[17] - All 18 patients applied DELP Gel to one leg and ZBC to the other. 17 patients had data for day 2.

[18] - All 18 patients applied DELP Gel to one leg and ZBC to the other. 17 patients had data for day 2.

Statistical analyses

Statistical analysis title	Treatment effect DELP Gel vs ZBC

Statistical analysis description:

This secondary endpoint was analysed using a mixed model taking into account the within-patient design, with patient as a random effect and leg, randomised group and treatment as fixed effects and with baseline corneometry measurement as a covariate. The number of patients included in each analysis was 17 (not 34), as this was a within-patient, bilateral comparison study (each patient received both treatments, one to each leg). The Full Analysis Set was used for this ITT analysis.

Comparison groups	DELP Gel treated legs v ZBC treated legs
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	< 0.0001 [20]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	9.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.6
upper limit	12.8
Variability estimate	Standard error of the mean
Dispersion value	1.68

Notes:

[19] - The number of patients included in this analysis was 17 (not 34), as this was a within-patient, bilateral comparison study (each patient received both treatments, one to each leg). Parameter estimate is least squares mean treatment difference for the change from baseline to the first corneometry reading on day 2.

[20] - A hierarchical testing regime was used, starting from day 5 through to day 2, to preserve the overall significance level (significant at 5% level, 2-sided).

Secondary: Patient reported outcomes: overall product acceptance

End point title	Patient reported outcomes: overall product acceptance

End point description:

Patients were asked to rate the overall acceptability of the treatments on their left and right legs on a five point scale (Dislike Strongly to Like Strongly). The overall acceptability endpoint was the proportion of patients ticking either ‘Like Strongly’ or ‘Like Slightly’ for DELP Gel vs. ZBC. Patients who ticked 'Dislike Strongly', 'Dislike Slightly' or 'Neither Like nor Dislike' are labelled as "Not ticked 'Like Strongly’ or ‘Like Slightly’" in the results presented below.

End point type	Secondary

End point timeframe:

Questionnaire completed by the patients at the end of the 5 day treatment period.

End point values	DELP Gel treated legs	ZBC treated legs		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[21]	18[22]		
Units: Number of patients				
Ticked 'Like Strongly' or 'Like Slightly'	13	9		
Not ticked 'Like Strongly' or 'Like Slightly'	5	9		

Notes:

[21] - Bilateral design - all 18 patients applied DELP Gel to one leg and ZBC to the other.

[22] - Bilateral design - all 18 patients applied DELP Gel to one leg and ZBC to the other.

Statistical analyses

Statistical analysis title	DELP Gel vs ZBC

Statistical analysis description:

The secondary efficacy analysis variable of overall acceptability was the proportion of patients ticking either "Like Strongly" or "Like Slightly". This was compared for the two study products, within subjects, using Prescott's test which is similar to McNemar's test but allows for an effect of leg.

Comparison groups	ZBC treated legs v DELP Gel treated legs
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.61
Method	Prescott's test
Parameter estimate	Risk difference (RD)
Point estimate	0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.62

Notes:

[23] - The number of patients included in each analysis was 18 (not 36), as this was a within-patient, bilateral comparison study (each patient received both treatments, one to each leg). The Full Analysis Set was used for this ITT analysis.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded throughout the five day treatment period. Any ongoing AEs were followed up until resolved, the condition stabilised, was otherwise explained, or the patient was lost to follow up.

Adverse event reporting additional description:

No intrusive safety monitoring procedures were used due to the accepted safety profile of the products. All AEs were recorded in the adverse events section of the CRF. AEs recorded by the patient in the treatment diary were subsequently entered into the CRF.

Assessment type	Systematic

Dictionary used

Dictionary name	As reported in CRF
Dictionary version	N/A

Reporting groups

Reporting group title	All randomised patients

Reporting group description:

The Safety Analysis Set comprised of all randomised patients who used at least one of the study products, this was actually all randomised patients. All safety analyses were based on the Safety Analysis Set.

Serious adverse events	All randomised patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (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	All randomised patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 18 (27.78%)		
General disorders and administration site conditions			
Headache	Additional description: Two headaches resolved at time of reporting. One headache resolved at follow up.		
subjects affected / exposed	3 / 18 (16.67%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract infection	Additional description: Resolved at follow up.		

subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Renal and urinary disorders			
Urinary tract infection	Additional description: Resolved at follow up.		
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 June 2015	A minor amendment of the protocol was implemented after the clinical phase of the study had been completed, to correct a typo in the sample size justification, and to clarify one of the secondary endpoints. This amendment did not materially change the protocol or statistical analysis, however it was deemed appropriate to manage it as substantial amendment given its relation to the scientific value of the study. Note that this minor amendment was instigated subsequent to the End of Trial notification, and so it was not formally acknowledged by the regulatory authority (date of letter, and implementation of amendment : 07/09/2016).

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.

None declared.

Notes: