



Clinical trial results:

Proactive Treatment With [0.03%] Tacrolimus Ointment in Children With Moderate/Severe Atopic Dermatitis: A Randomized, Multicenter, Open-label Study.

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2015-001040-11 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 30 November 2013 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 26 February 2016 |
| First version publication date | 18 July 2015 |

Trial information

Trial identification

| | |
|-----------------------|-----------------|
| Sponsor protocol code | ACN-PRT-AD-12-1 |
|-----------------------|-----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01745159 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Astellas Pharma (China) Co., Ltd |
| Sponsor organisation address | No. 8 Jianguomenwai Avenue, Chaoyang District, Beijing , China, |
| Public contact | Clinical Trial Disclosure , Astellas Pharma (China), Astellas.resultsdisclosure@astellas.com |
| Scientific contact | Clinical Trial Disclosure , Astellas Pharma (China), Astellas.resultsdisclosure@astellas.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? | Yes |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 30 November 2013 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 30 November 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 November 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Main objective of the trial was to assess if proactive, 2 times-weekly application of 0.03% tacrolimus ointment can extend remission time to relapse and reduce the incidence of disease exacerbation (DE) in paediatric patients over a period of 6 months.

Protection of trial subjects:

This study complies with the Helsinki ethics guidelines for human medical research and was executed in accordance with the China Food and Drug Administration's (CFDA) GCP ethical requirements and applicable laws and regulations.

Background therapy: -

Evidence for comparator:

Atopic dermatitis (AD) is a hereditary immunologic abnormality associated with chronic, inflammatory, recurring skin disease characterized by intense pruritus and dry skin. Recent research has shown that normal skin in atopic dermatitis (AD) patients contains subclinical inflammation, so continued anti-inflammatory therapy is necessary to prevent disease exacerbation. Tacrolimus ointment (brand name: Protopic®) is a macrolide calcineurin inhibitor, and several studies have demonstrated efficacy in treating AD. Several long-term studies have confirmed that intermittent maintenance therapy with tacrolimus twice weekly can decrease the number of disease exacerbations and prolong the interval between exacerbations.

| | |
|---|-------------------|
| Actual start date of recruitment | 13 September 2012 |
| 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 | China: 171 |
| Worldwide total number of subjects | 171 |
| EEA total number of subjects | 0 |

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) | 160 |
| Adolescents (12-17 years) | 11 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Males and females, ages 2 to 15 years with moderate to severe atopic dermatitis (AD).

Pre-assignment

Screening details:

At the start of period 1, 171 patients were screened and approved to enter the study. All patients received 0.03% topical tacrolimus ointment twice daily for 2-6 weeks. At the end of period 1, 125 patients completed treatment and had (investigator general assessment) IGA ≤ 2 . They were randomized in period 2, out of 125 patients 121 completed the study

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Tacrolimus 0.03% [Twice Daily] |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|-----------|---------------------------|
| Arm title | Tacrolimus ointment 0.03% |
|-----------|---------------------------|

Arm description:

All moderate to severe atopic dermatitis patients who met eligibility criteria received conventional therapy of 0.03% Tacrolimus ointment twice daily for up to 6 weeks. At the end of period 1, those who achieved IGA ≤ 2 were entered into Period 2 and randomized 1:1 into the experimental group or control arm for the efficacy and safety observation.

| | |
|--|---------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tacrolimus ointment 0.03% |
| Investigational medicinal product code | |
| Other name | Protopic |
| Pharmaceutical forms | Ointment |
| Routes of administration | Topical use |

Dosage and administration details:

All patients applied 0.03% tacrolimus ointment to affected areas topically twice daily for up to 6 weeks. Thin layer of tacrolimus ointment was used to cover skin lesion by gentle daubing. The area applied with ointment should not have been bandaged. Patients were asked not to take the shower soon after the application, and no skin washing instruction was provided prior to application. Tacrolimus ointment was provided in tubes of 10 grams.

| Number of subjects in period 1 | Tacrolimus ointment 0.03% |
|--|---------------------------|
| Started | 171 |
| Completed | 125 |
| Not completed | 46 |
| Consent withdrawn by subject | 1 |
| Treatment termination as per investigator advice | 3 |
| Other | 12 |
| Serious protocol deviation as per investigator | 2 |
| Lost to follow-up | 8 |

| | |
|--|----|
| '[IGA > 2] Period 1 - after 6 weeks of treatment ' | 20 |
|--|----|

| | |
|--|---|
| Period 2 | |
| Period 2 title | Tacrolimus 0.03% [Twice Weekly]v Control |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |
| Arms | |
| Are arms mutually exclusive? | Yes |
| Arm title | Tacrolimus 0.03% [Twice a week-Mon & Thu] |
| Arm description: | |
| In the experimental group in period 2 tacrolimus ointment 0.03% was applied topically twice a week on Mondays and Thursdays. If disease exacerbation occurred patients were switched to conventional therapy and were followed-up for 6 months. | |
| Arm type | Experimental |
| Investigational medicinal product name | Tacrolimus 0.03% [Twice a Week] |
| Investigational medicinal product code | |
| Other name | Protopic |
| Pharmaceutical forms | Ointment |
| Routes of administration | Topical use |
| Dosage and administration details: | |
| All patients applied 0.03% tacrolimus ointment to affected areas topically twice weekly on Monday and Thursday for up to 6 weeks. Thin layer of tacrolimus ointment was used to cover the skin lesion by gentle daubing. The applied area was free of any bandages. Patients were asked not to take the shower soon after the application, and no instruction was provided for skin washing prior to application. Tacrolimus ointment was provided in tubes of 10 grams. | |
| Arm title | Control Group |
| Arm description: | |
| In the control group no treatment was administered in period 2 unless there was disease exacerbation. Patients who experienced disease exacerbation received conventional treatment and were followed-up for a period of 6 months. | |
| Arm type | Control Group |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 2 | Tacrolimus 0.03% [Twice a week-Mon & Thu] | Control Group |
|--|---|---------------|
| Started | 62 | 63 |
| Completed | 45 | 47 |
| Not completed | 17 | 16 |
| Treatment termination as per investigator advice | 1 | 1 |

| | | |
|---|---|---|
| IGA≤2 Period 1 end&re-occurrence of IGA>2 in 7 Days | - | 1 |
| IGA>2 after 6 weeks of treatment with Tacrolimus | 5 | 3 |
| Other | 5 | 8 |
| Lost to follow-up | 6 | 3 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------------------------|
| Reporting group title | Tacrolimus 0.03% [Twice Daily] |
|-----------------------|--------------------------------|

Reporting group description: -

| Reporting group values | Tacrolimus 0.03% [Twice Daily] | Total | |
|---|-----------------------------------|-------|--|
| Number of subjects | 171 | 171 | |
| 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) | 160 | 160 | |
| Adolescents (12-17 years) | 11 | 11 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous Units: years | | | |
| arithmetic mean | 6.61 | - | |
| standard deviation | ± 3.05 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 78 | 78 | |
| Male | 93 | 93 | |
| Ethnicity Units: Subjects | | | |
| Han Chinese | 164 | 164 | |
| Other | 7 | 7 | |
| Height Units: centimeters | | | |
| arithmetic mean | 121.54 | - | |
| standard deviation | ± 21.91 | - | |
| Weight Units: kilogram(s) | | | |
| arithmetic mean | 26.2 | - | |
| standard deviation | ± 11.22 | - | |
| BMI Units: kilogram(s)/square meter | | | |
| arithmetic mean | 17.21 | - | |
| standard deviation | ± 3.45 | - | |

End points

End points reporting groups

| | |
|-----------------------|---------------------------|
| Reporting group title | Tacrolimus ointment 0.03% |
|-----------------------|---------------------------|

Reporting group description:

All moderate to severe atopic dermatitis patients who met eligibility criteria received conventional therapy of 0.03% Tacrolimus ointment twice daily for up to 6 weeks. At the end of period 1, those who achieved IGA ≤ 2 were entered into Period 2 and randomized 1:1 into the experimental group or control arm for the efficacy and safety observation.

| | |
|-----------------------|---|
| Reporting group title | Tacrolimus 0.03% [Twice a week-Mon & Thu] |
|-----------------------|---|

Reporting group description:

In the experimental group in period 2 tacrolimus ointment 0.03% was applied topically twice a week on Mondays and Thursdays. If disease exacerbation occurred patients were switched to conventional therapy and were followed-up for 6 months.

| | |
|-----------------------|---------------|
| Reporting group title | Control Group |
|-----------------------|---------------|

Reporting group description:

In the control group no treatment was administered in period 2 unless there was disease exacerbation. Patients who experienced disease exacerbation received conventional treatment and were followed-up for a period of 6 months.

| | |
|----------------------------|-------------------------|
| Subject analysis set title | Full Analysis Set (FAS) |
|----------------------------|-------------------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

The Full Analysis Set (FAS) included patients who have received randomized assignment, at least 1 dose of study medication, and at least 1 efficacy assessment. The FAS was used as the major set for efficacy analysis of this study.

| | |
|----------------------------|---------------------------|
| Subject analysis set title | Safety Analysis Set (SAF) |
|----------------------------|---------------------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

The SAF included patients who have received randomized assignment, at least 1 dose of study medication, and at least 1 safety assessment. The SAF was used as the major set for safety analysis of this study.

| | |
|----------------------------|------------------------|
| Subject analysis set title | Per Protocol Set (PPS) |
|----------------------------|------------------------|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

Per Protocol Set (PPS) is a FAS subset and includes patients from FAS who have no serious protocol deviation, and who are compliant (the actual dosage used is 80%-120% of the planned dosage) and do not have missing data of primary efficacy measures. In this study, PPS was used as the secondary population for efficacy analysis, since patients who withdraw due to a lack of response were also included. Number of patients were censored, from the time to first disease exacerbation, and analyzed with the survival analysis. Time to first disease exacerbation, and the outcome was either (first) disease exacerbation or censored (or deleted) data. The time to first disease exacerbation was defined as the number of days between the end of treatment in stage 1 and the time to first disease exacerbation (i.e. the time to first disease exacerbation [days] = the date of first disease exacerbation - the date of the end of treatment).

Primary: Time to first disease exacerbation (FAS)

| | |
|-----------------|--|
| End point title | Time to first disease exacerbation (FAS) |
|-----------------|--|

End point description:

Disease exacerbation was defined as IGA >2 . The time to first disease exacerbation was the number of days between the end of treatment in stage 1 and the time to first disease exacerbation, i.e. the time to first disease exacerbation (days) = the date of first disease exacerbation - the date of the end of treatment in stage 1+1. The number of censored cases in time to first disease exacerbation was 35 for the Tacrolimus arm and 15 for the Control arm in the Full Analysis Set.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Week 2 - Month 6 [+(-) 7days]

| | | | | |
|--------------------------------------|--|--------------------|--|--|
| End point values | Tacrolimus 0.03% [Twice a week-Mon & Thu] | Control Group | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 25 | 46 | | |
| Units: Number | | | | |
| arithmetic mean (standard deviation) | 46.88 (± 37.71) | 28.83 (± 32.33) | | |

Statistical analyses

| | |
|-----------------------------------|---------------------------------|
| Statistical analysis title | Cox regression analysis / Group |
|-----------------------------------|---------------------------------|

Statistical analysis description:

Cox Regression Analysis includes patients with disease exacerbation as well as the censored patients. Total number of patients who have entered period 2 was 121, this was a number of patients that was subject to survival analysis.

| | |
|---|---|
| Comparison groups | Tacrolimus 0.03% [Twice a week-Mon & Thu] v Control Group |
| Number of subjects included in analysis | 71 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| P-value | < 0.0001 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.35 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.214 |
| upper limit | 0.573 |

Notes:

[1] - A Cox regression model was adopted using the stepwise regression method to incorporate factors such as group, gender, age, disease severity, EASI score, VAS score, and IGA score upon entry into stage 2, and the overall response to the treatment in stage 1 into the regression model.

| | |
|-----------------------------------|--|
| Statistical analysis title | Cox regression analysis / Gender [Male & Female] |
|-----------------------------------|--|

Statistical analysis description:

Cox Regression Analysis includes patients with disease exacerbation as well as the censored patients. Total number of patients who have entered period 2 was 121, this was a number of patients that was subject to survival analysis. Furthermore this statistical analysis compares Females to Males.

| | |
|---|---|
| Comparison groups | Tacrolimus 0.03% [Twice a week-Mon & Thu] v Control Group |
| Number of subjects included in analysis | 71 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[2] |
| P-value | < 0.0329 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.665 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.042 |
| upper limit | 2.66 |

Notes:

[2] - A Cox regression model was adopted using the stepwise regression method to incorporate factors such as group, gender, age, disease severity, EASI score, VAS score, and IGA score upon entry into stage 2, and the overall response to the treatment in stage 1 into the regression model.

| | |
|---|---|
| Statistical analysis title | The time to first disease exacerbation |
| Comparison groups | Tacrolimus 0.03% [Twice a week-Mon & Thu] v Control Group |
| Number of subjects included in analysis | 71 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.02 |
| Method | Rank Sum Test |

| | |
|--|---|
| Statistical analysis title | Time to first disease exacerbation [Log Rank] |
| Statistical analysis description: | |
| Total number of patients used for this analysis was 121. | |
| Comparison groups | Tacrolimus 0.03% [Twice a week-Mon & Thu] v Control Group |
| Number of subjects included in analysis | 71 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 |
| Method | Logrank |

Secondary: The number of disease exacerbations in period 2 (FAS)

| | |
|--|---|
| End point title | The number of disease exacerbations in period 2 (FAS) |
| End point description: | |
| Exacerbation is documented if the inter-exacerbation interval is < 7 days. Only patients with disease exacerbation were analyzed. Patients with no disease exacerbation were excluded from the analysis. The number of patient-time disease exacerbations in stage 2 = the total number of disease exacerbations in stage 2 or the total observation time (patient-months) in stage 2. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 2 to Month 6 [+(-) 7 days] | |

| | | | | |
|--------------------------------------|---|-----------------|--|--|
| End point values | Tacrolimus 0.03% [Twice a week-Mon & Thu] | Control Group | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 | 61 | | |
| Units: Number | | | | |
| arithmetic mean (standard deviation) | 0.52 (± 0.68) | 1.41 (± 1.23) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Number of disease exacerbations Stage 2 (FAS) |
| Comparison groups | Tacrolimus 0.03% [Twice a week-Mon & Thu] v Control Group |
| Number of subjects included in analysis | 121 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 |
| Method | Group T-test |

Secondary: The disease severity EASI score at disease exacerbation in period 2 (FAS)

| | |
|-----------------|---|
| End point title | The disease severity EASI score at disease exacerbation in period 2 (FAS) |
|-----------------|---|

End point description:

EASI is an overall score calculated based on the severity and the area of skin lesions at each section, as well as age group (≥ 8 and < 8 years of age) and the area of each section as a percentage of the total body surface area. It is calculated as follows: 1) Clinical symptom evaluation which can be divided into 4 categories: erythema, papules/swelling, scratches/epidermal excoriations, lichenification. Each clinical manifestation has a severity score on a scale of 0-3. 0 = none, 1 = mild, 2 = moderate, 3 = severe. 2) Clinical surface area involvement score: Body is divided into 4 areas: head/neck (H), upper limb (UL), trunk (T), lower limb (LL). Upper limb includes outer armpit and hands. In calculating the size of skin area covered by lesions, the patient's palm is taken as an approximation of 1% of the body. 3) The proportion of skin surface area occupied by lesions in each location is assigned a number on a scale of 0-6.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 2 to Month 6 (+(-) 7 Days)

| | | | | |
|--------------------------------------|---|-----------------|--|--|
| End point values | Tacrolimus 0.03% [Twice a week-Mon & Thu] | Control Group | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 25 | 46 | | |
| Units: Number on a Scale | | | | |
| arithmetic mean (standard deviation) | 10.88 (± 9.42) | 9.72 (± 10.43) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | EASI score disease exacerbation stage 2 (FAS) |
| Comparison groups | Tacrolimus 0.03% [Twice a week-Mon & Thu] v Control Group |
| Number of subjects included in analysis | 71 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.3927 |
| Method | Rank Sum Test |

Secondary: The IGA (Investigator General Assessment) score at disease exacerbation in period 2 (FAS)

| | |
|-------------------------------|---|
| End point title | The IGA (Investigator General Assessment) score at disease exacerbation in period 2 (FAS) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Week 2- Month 6 (+(-) 7 Days) | |

| | | | | |
|--------------------------------------|---|-----------------|--|--|
| End point values | Tacrolimus 0.03% [Twice a week-Mon & Thu] | Control Group | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 25 | 46 | | |
| Units: Number | | | | |
| arithmetic mean (standard deviation) | 3.16 (± 0.37) | 3.22 (± 0.51) | | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | IGA score at 1st disease exacerbation Stage 2(FAS) |
| Statistical analysis description: | |
| The investigator general assessment (IGA) score at the first disease exacerbation in stage 2 for inter-group comparison (FAS). | |
| Comparison groups | Tacrolimus 0.03% [Twice a week-Mon & Thu] v Control Group |

| | |
|---|---------------|
| Number of subjects included in analysis | 71 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.8315 |
| Method | Rank Sum Test |

Secondary: The duration of disease exacerbation in period 2 (FAS)

| | |
|---|--|
| End point title | The duration of disease exacerbation in period 2 (FAS) |
| End point description: The duration of the first disease exacerbation (days) = (the end date of the first disease exacerbation – the start date of the first disease exacerbation +1). In case of multiple disease exacerbations in stage 2, the duration of each disease exacerbation is added. In case of disease exacerbation at the end of observation period, then the end date of disease exacerbation at the end of the observation period is used for calculation. | |
| End point type | Secondary |
| End point timeframe: Week 2 - Month 6 (+(-) 7 Days) | |

| | | | | |
|--------------------------------------|--|--------------------|--|--|
| End point values | Tacrolimus 0.03% [Twice a week-Mon & Thu] | Control Group | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 25 | 46 | | |
| Units: Number | | | | |
| arithmetic mean (standard deviation) | 33.64 (± 26.32) | 48.76 (± 30.79) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Disease exacerbation stage 2 intergroup (FAS) |
| Comparison groups | Tacrolimus 0.03% [Twice a week-Mon & Thu] v Control Group |
| Number of subjects included in analysis | 71 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0662 |
| Method | Rank Sum Test |

Secondary: The itching score at disease exacerbation in period 2 (FAS)

| | |
|---|---|
| End point title | The itching score at disease exacerbation in period 2 (FAS) |
| End point description: Patients score their itching on a 10 cm visual analogue scale (VAS). The post-treatment and pre-treatment scores are compared. If the difference follows a normal distribution, a paired t test is performed; if the difference does not follow a normal distribution, a Wilcoxon signed-rank test is | |

performed.

| | |
|--------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 2- Months 6 (+(-) 7 days) | |

| | | | | |
|--------------------------------------|--|--------------------|--|--|
| End point values | Tacrolimus 0.03% [Twice a week-Mon & Thu] | Control Group | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 25 | 46 | | |
| Units: Number | | | | |
| arithmetic mean (standard deviation) | 5.84 (\pm 1.53) | 5.66 (\pm 1.96) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | The itching (VAS) score Period 2 (FAS) |
| Comparison groups | Tacrolimus 0.03% [Twice a week-Mon & Thu] v Control Group |
| Number of subjects included in analysis | 71 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.9469 |
| Method | Rank Sum Test |

Secondary: The overall dosage of tacrolimus in period 2 (FAS)

| | |
|------------------------------|--|
| End point title | The overall dosage of tacrolimus in period 2 (FAS) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Week 2- Month 6 (+(-) 7days) | |

| | | | | |
|--------------------------------------|--|-------------------|--|--|
| End point values | Tacrolimus 0.03% [Twice a week-Mon & Thu] | Control Group | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 | 61 | | |
| Units: Number | | | | |
| arithmetic mean (standard deviation) | 8 (\pm 6.98) | 4.2 (\pm 6.88) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | The overall dosage of tacrolimus in period 2 (FAS) |
| Comparison groups | Tacrolimus 0.03% [Twice a week-Mon & Thu] v Control Group |
| Number of subjects included in analysis | 121 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0031 |
| Method | Paired t-test |

Secondary: The overall response rate in period 1 (FAS)

| | |
|------------------------|---|
| End point title | The overall response rate in period 1 (FAS) |
| End point description: | The overall response rate is the sum of the cure rate and effective rate. period 1 overall rate of improvement (%)=(pre-treatment EASI - post-treatment EASI)/pre-treatment EASI×100.00; pre-treatment refers to the screening period (day 0), post-treatment refers to the period 1 end time; post-treatment EASI assessment information was not obtained for 5 patients The overall improvement is rated according to a 4-point efficacy scale: cure: overall improvement ≥90%; effective: 60%-<90%; improved: 20%-<60%; ineffective: <20%. |
| End point type | Secondary |
| End point timeframe: | Week 2- 6 Months (+(-) 7 days) |

| | | | | |
|--------------------------------------|---------------------------|--|--|--|
| End point values | Tacrolimus ointment 0.03% | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 166 | | | |
| Units: Number | | | | |
| arithmetic mean (standard deviation) | 69.04 (± 37.22) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were recorded from the start of the study up until the End of Treatment. In case of disease exacerbation participants were followed up to 6 months.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------------|
| Reporting group title | Period 2 - Control Group |
|-----------------------|--------------------------|

| | |
|------------------------------|---|
| Reporting group description: | - |
|------------------------------|---|

| | |
|-----------------------|--|
| Reporting group title | Period 2 - 0.03% Tacrolimus [2 times a week] |
|-----------------------|--|

| | |
|------------------------------|---|
| Reporting group description: | - |
|------------------------------|---|

| Serious adverse events | Period 2 - Control Group | Period 2 - 0.03% Tacrolimus [2 times a week] | |
|---|--------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 60 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |

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

| Non-serious adverse events | Period 2 - Control Group | Period 2 - 0.03% Tacrolimus [2 times a week] | |
|---|--------------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 16 / 61 (26.23%) | 16 / 60 (26.67%) | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 4 / 61 (6.56%) | 1 / 60 (1.67%) | |
| occurrences (all) | 4 | 1 | |
| Upper respiratory tract | | | |
| subjects affected / exposed | 5 / 61 (8.20%) | 1 / 60 (1.67%) | |
| occurrences (all) | 6 | 1 | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| Impetigo | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 4 / 60 (6.67%) | |
| occurrences (all) | 2 | 4 | |

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

None reported