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-occurance 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 statitcial 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 (± 1.53)	5.66 (± 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 (± 6.98)	4.2 (± 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 particpiants 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 occurrences (all)	2 / 61 (3.28%) 2	4 / 60 (6.67%) 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