Clinical trial results:
A Phase 1 Open-Label Study of the Pharmacokinetics of Tacrolimus Cream B 0.1% after Twice Daily Topical Administration in Adolescents (more than or equal to 12 to less than or equal to 17 years of age) with Psoriasis

Summary

EudraCT number	2006-002738-39
Trial protocol	LV
Global end of trial date	03 May 2007

Results information

Result version number	v1 (current)
This version publication date	01 April 2016
First version publication date	13 June 2015

Trial information

Trial identification

Sponsor protocol code	04-7-011

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma US, Inc.
Sponsor organisation address	1 Astellas Way, Northbrook, IL, United States, 60062
Public contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., Astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 May 2007
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 May 2007
Global end of trial reached?	Yes
Global end of trial date	03 May 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to determine the pharmacokinetics and safety of tacrolimus cream 0.1% in adolescents (≥ 12 to ≤ 17 years of age) with plaque psoriasis affecting ≥ 10% body surface area (BSA) (excluding the scalp) who were treated topically for 29 days (4 weeks).

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, ICH GCP Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki.

Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 December 2006
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	Latvia: 12
Country: Number of subjects enrolled	Bulgaria: 10
Worldwide total number of subjects	22
EEA total number of subjects	22

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)	22
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants aged 12 to 17 years with a diagnosis of plaque psoriasis affecting ≥ 10% BSA and a Physician's Static Global Assessment (PSGA) ≥ 3 were enrolled.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Tacrolimus cream 0.1%
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Tacrolimus cream 0.1%
Investigational medicinal product code	FK506
Other name	Tacrolimus cream B-0.1%
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

The investigator defined the areas for treatment at baseline (day 1) and each study visit. Tacrolimus cream 0.1% was applied topically as a thin coating on the specified treatment area twice daily for 28 days and once in the morning of day 29 (end of treatment/EOT). Applications were to occur at consistent times, approximately 12 hours apart. Participants were to wait at least 2 hours after application of study drug before bathing, showering, or heavy exercise. Any new non-scalp plaque lesions appearing after day 1 or existing plaques that increased in size were to be treated by the participant until clear plus an additional 7 days or until day 29, whichever came first. If the affected area decreased in size, the participant was to continue treatment of the area until day 29 or until the area was clear plus an additional 7 days, whichever came first.

Number of subjects in period 1	Tacrolimus cream 0.1%
Started	22
Completed	21
Not completed	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups	
Reporting group title	Tacrolimus cream 0.1%

Reporting group description: -

Reporting group values	Tacrolimus cream 0.1%	Total	
Number of subjects	22	22	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 15.3 ± 1.52	 -	
Gender categorical Units: Subjects			
Female	13	13	
Male	9	9	
BSA affected Units: percentage of BSA arithmetic mean standard deviation	 26 ± 14.42	 -	

End points

End points reporting groups

Reporting group title	Tacrolimus cream 0.1%

Reporting group description: -

Primary: Pharmacokinetic whole blood tacrolimus concentrations

End point title	Pharmacokinetic whole blood tacrolimus concentrations[1]

End point description:

The analysis population is the pharmacokinetic set, which consisted of all participants from the Safety Set whose profile data were adequate for the calculation of the primary pharmacokinetic parameters.

End point type	Primary

End point timeframe:

Day 29 (predose, hours 1, 2, 4, 6, 8, 12, 14 postdose) to Day 35 (postdose)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was written with no planned statistical analyses (statistical hypothesis testing) to be performed for any endpoints due to the simple design (i.e., one treatment group) and purpose of the study.

End point values	Tacrolimus cream 0.1%			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: ng/mL				
arithmetic mean (standard deviation)				
Predose (Day 29)	0.2443 (± 0.30465)			
Hour 1 (Day 29)	0.3367 (± 0.35458)			
Hour 2 (Day 29)	0.2444 (± 0.28315)			
Hour 4 (Day 29)	0.2529 (± 0.27985)			
Hour 6 (Day 29)	0.2434 (± 0.28806)			
Hour 8 (Day 29)	0.254 (± 0.27366)			
Hour 12 (Day 29)	0.237 (± 0.25764)			
Hour 14 (Day 29)	0.2546 (± 0.28267)			
Hour 24 (Day 30)	0.2479 (± 0.27247)			
Hour 48 (Day 31)	0.1942 (± 0.22829)			
Hour 72 (Day 32)	0.1518 (± 0.16487)			
Hour 96 (Day 33)	0.1159 (± 0.14319)			
Hour 120 (Day 34)	0.0744 (± 0.11124)			
Hour 144 (Day 25)	0.048 (± 0.08668)			

Statistical analyses

No statistical analyses for this end point

Primary: Maximum observed whole blood tacrolimus concentration (Cmax)

End point title	Maximum observed whole blood tacrolimus concentration (Cmax)[2]

End point description:

The analysis population is the pharmacokinetic set.

End point type	Primary

End point timeframe:

Days 29-35

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was written with no planned statistical analyses (statistical hypothesis testing) to be performed for any endpoints due to the simple design (i.e., one treatment group) and purpose of the study.

End point values	Tacrolimus cream 0.1%			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: ng/mL				
arithmetic mean (standard deviation)	0.383 (± 0.3653)			

Statistical analyses

No statistical analyses for this end point

Primary: Maximum observed whole blood tacrolimus concentration from t=0 hour (time of morning dosing) through 12 hours post dose (t=12 hour) (Cmax0-tau)

End point title	Maximum observed whole blood tacrolimus concentration from t=0 hour (time of morning dosing) through 12 hours post dose (t=12 hour) (Cmax0-tau)[3]

End point description:

The analysis population is the pharmacokinetic set.

End point type	Primary

End point timeframe:

Days 29-35

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was written with no planned statistical analyses (statistical hypothesis testing) to be performed for any endpoints due to the simple design (i.e., one treatment group) and purpose of

the study.

End point values	Tacrolimus cream 0.1%			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: ng/mL				
arithmetic mean (standard deviation)	0.375 (± 0.3632)			

Statistical analyses

No statistical analyses for this end point

Primary: Minimum observed whole blood tacrolimus concentration from t=0 hour (time of morning dosing) through 12 hours post dose (t=12 hour) (Cmin0-tau)

End point title	Minimum observed whole blood tacrolimus concentration from t=0 hour (time of morning dosing) through 12 hours post dose (t=12 hour) (Cmin0-tau)[4]

End point description:

The analysis population is the pharmacokinetic set.

End point type	Primary

End point timeframe:

Days 29-35

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was written with no planned statistical analyses (statistical hypothesis testing) to be performed for any endpoints due to the simple design (i.e., one treatment group) and purpose of the study.

End point values	Tacrolimus cream 0.1%			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: ng/mL				
arithmetic mean (standard deviation)	0.205 (± 0.2452)			

Statistical analyses

No statistical analyses for this end point

Primary: Time of the maximum whole blood tacrolimus concentration (tmax)

End point title	Time of the maximum whole blood tacrolimus concentration (tmax)[5]

End point description:

The analysis population is the pharmacokinetic set.

End point type	Primary

End point timeframe:

Days 29-35

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was written with no planned statistical analyses (statistical hypothesis testing) to be performed for any endpoints due to the simple design (i.e., one treatment group) and purpose of the study.

End point values	Tacrolimus cream 0.1%			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: hours				
median (full range (min-max))	3.5 (0 to 24)			

Statistical analyses

No statistical analyses for this end point

Primary: Average whole blood tacrolimus concentration over the morning dosing interval, i.e. from t=0 hour (time of morning dosing) through 12 hours post dose (t=12 hour) (Cavg0-tau)

End point title	Average whole blood tacrolimus concentration over the morning dosing interval, i.e. from t=0 hour (time of morning dosing) through 12 hours post dose (t=12 hour) (Cavg0-tau)[6]

End point description:

The analysis population is the pharmacokinetic set.

End point type	Primary

End point timeframe:

Days 29-35

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was written with no planned statistical analyses (statistical hypothesis testing) to be performed for any endpoints due to the simple design (i.e., one treatment group) and purpose of the study.

End point values	Tacrolimus cream 0.1%			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: ng/mL				
arithmetic mean (standard deviation)	0.334 (± 0.2664)			

Statistical analyses

No statistical analyses for this end point

Primary: Area under the whole blood tacrolimus concentration-time curve over the morning dosing interval; i.e., from t=0 hour (time of morning dosing) through 12 hours post dose (t=12 hour) (AUC0-tau)

End point title	Area under the whole blood tacrolimus concentration-time curve over the morning dosing interval; i.e., from t=0 hour (time of morning dosing) through 12 hours post dose (t=12 hour) (AUC0-tau)[7]

End point description:

The analysis population is the pharmacokinetic set.

End point type	Primary

End point timeframe:

Days 29-35

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was written with no planned statistical analyses (statistical hypothesis testing) to be performed for any endpoints due to the simple design (i.e., one treatment group) and purpose of the study.

End point values	Tacrolimus cream 0.1%			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: hr x ng/mL				
arithmetic mean (standard deviation)	4.01 (± 3.197)			

Statistical analyses

No statistical analyses for this end point

Primary: Safety as assessed by adverse events (AEs), clinical laboratory tests, vital signs, and physical examination

End point title	Safety as assessed by adverse events (AEs), clinical laboratory tests, vital signs, and physical examination[8]

End point description:

Safety is monitored by collecting AEs, which include abnormal laboratory tests, vital signs or physical examination data that were defined as an AE if the abnormality induced clinical signs or symptoms, required diagnostic evaluation, therapeutic intervention, interruption or discontinuation of study medication or was clinically significant in the investigator's opinion. A treatment-emergent adverse event (TEAE) was defined as an AE occurring from the first dose day of study drug to the last dose day of study drug with onset or worsening after the first study drug application.
The analysis population is the Safety Set, which consisted of all participants who were administered any amount of tacrolimus cream 0.1%.

End point type	Primary

End point timeframe:

From first dose of study drug up to 7 days after last dose of study drug

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was written with no planned statistical analyses (statistical hypothesis testing) to be performed for any endpoints due to the simple design (i.e., one treatment group) and purpose of the study.

End point values	Tacrolimus cream 0.1%			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: participants				
Any adverse event	5			
General disorders & administration site conditions	2			
Blood & lymphatic system disorders	1			
Infections & infestations	1			
Injury, poisoning & procedural complications	1			
Respiratory, thoracic & mediastinal disorders	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Tacrolimus predose concentration at the end of the previous dosing interval (Ctrough)

End point title	Tacrolimus predose concentration at the end of the previous dosing interval (Ctrough)

End point description:

The analysis population is the pharmacokinetic set.

End point type	Secondary

End point timeframe:

Days 1, 8, 15, 22 and 29

End point values	Tacrolimus cream 0.1%			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1	0 (± 0)			
Day 8	0.2317 (± 0.26139)			
Day 15	0.3179 (± 0.33797)			
Day 22	0.274 (± 0.33075)			
Day 29	0.2443 (± 0.30465)			

Statistical analyses

No statistical analyses for this end point

Secondary: Average whole blood tacrolimus concentration from t=0 hour (time of morning dosing) through 24 hours post dose (t=24 hour) (Cavg0-24)

End point title	Average whole blood tacrolimus concentration from t=0 hour (time of morning dosing) through 24 hours post dose (t=24 hour) (Cavg0-24)

End point description:

The analysis population is the pharmacokinetic set.

End point type	Secondary

End point timeframe:

Days 29-35

End point values	Tacrolimus cream 0.1%			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: ng/mL				
arithmetic mean (standard deviation)	0.331 (± 0.2672)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to last measurable concentration of the study drug (tlast)

End point title	Time to last measurable concentration of the study drug (tlast)

End point description:

The analysis population is the pharmacokinetic set.

End point type	Secondary

End point timeframe:

Days 29-35

End point values	Tacrolimus cream 0.1%			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: hours				
median (full range (min-max))	108 (1 to 144)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the whole blood tacrolimus concentration-time curve from t=0 hour (time of morning dosing) through 24 hours post dose (t=24 hour) (AUC0-24)

End point title	Area under the whole blood tacrolimus concentration-time curve from t=0 hour (time of morning dosing) through 24 hours post dose (t=24 hour) (AUC0-24)

End point description:

The analysis population is the pharmacokinetic set.

End point type	Secondary

End point timeframe:

Days 29-35

End point values	Tacrolimus cream 0.1%			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: hr x ng/mL				
arithmetic mean (standard deviation)	7.95 (± 6.412)			

Statistical analyses

No statistical analyses for this end point

Secondary: Peak-to-trough ratio over the 12 hours after the dose (PTRtau)

End point title	Peak-to-trough ratio over the 12 hours after the dose (PTRtau)

End point description:

The analysis population is the pharmacokinetic set.

End point type	Secondary

End point timeframe:

Days 29-35

End point values	Tacrolimus cream 0.1%			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: ratio				
arithmetic mean (standard deviation)	1.51 (± 0.333)			

Statistical analyses

No statistical analyses for this end point

Secondary: Difference in extreme concentrations (Cmax0-tau, Cmin0-tau) relative to the average concentration (Cavg0-tau) over the morning dosing interval (FLCTN0-tau)

End point title	Difference in extreme concentrations (Cmax0-tau, Cmin0-tau) relative to the average concentration (Cavg0-tau) over the morning dosing interval (FLCTN0-tau)

End point description:

The analysis population is the pharmacokinetic set.

End point type	Secondary

End point timeframe:

Days 29-35

End point values	Tacrolimus cream 0.1%			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: ng/mL				
arithmetic mean (standard deviation)	1.79 (± 3.101)			

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination rate constant (Kel)

End point title	Elimination rate constant (Kel)

End point description:

The analysis population is the pharmacokinetic set.

End point type	Secondary

End point timeframe:

Days 29-35

End point values	Tacrolimus cream 0.1%			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: 1/hour				
arithmetic mean (standard deviation)	0.0096 (± 0.00444)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the whole blood tacrolimus concentration-time curve from t=0 hour (time of morning dosing) through time of last measurable concentration of tacrolimus (AUClast)

End point title	Area under the whole blood tacrolimus concentration-time curve from t=0 hour (time of morning dosing) through time of last measurable concentration of tacrolimus (AUClast)

End point description:

The analysis population is the pharmacokinetic set.

End point type	Secondary

End point timeframe:

Days 29-35

End point values	Tacrolimus cream 0.1%			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: hr x ng/mL				
arithmetic mean (standard deviation)	21.95 (± 25.859)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the whole blood tacrolimus concentration-time curve from t=0 hour (time of morning dosing) extrapolated to infinity (AUC0-inf)

End point title	Area under the whole blood tacrolimus concentration-time curve from t=0 hour (time of morning dosing) extrapolated to infinity (AUC0-inf)

End point description:

The analysis population is the pharmacokinetic set.

Due to an insufficient number of measurable samples, AUC0-inf was assumed to be unreliable; hence, the value was not calculated.

End point type	Secondary

End point timeframe:

Days 29-35

End point values	Tacrolimus cream 0.1%			
Subject group type	Reporting group			
Number of subjects analysed	0[9]			
Units: hr x ng/mL				
arithmetic mean (standard deviation)	()			

Notes:

[9] - Insufficient number of measurable samples.

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal half life (t1/2)

End point title	Terminal half life (t1/2)

End point description:

The analysis population is the pharmacokinetic set.

End point type	Secondary

End point timeframe:

Days 29-35

End point values	Tacrolimus cream 0.1%			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: hours				
arithmetic mean (standard deviation)	95.61 (± 61.048)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 7 days after last dose of study drug

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	8.1

Reporting groups

Reporting group title	Tacrolimus cream 0.1%

Reporting group description: -

Serious adverse events	Tacrolimus cream 0.1%		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 22 (4.55%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Tacrolimus cream 0.1%		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 22 (18.18%)		
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
General disorders and administration site conditions			
Application site irritation			

subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Application site pruritus			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Infections and infestations			
Furuncle			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 June 2006	The original study protocol dated February 2, 2006 was amended once on June 14, 2006 (Latvia-specific) in order to provide required text per European Regulatory guidelines with respect to concomitant medication administration, adverse event reporting, study timelines and drug supplies, administrative and regulatory considerations.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported