Clinical trial results:
A randomized, double-blind, parallel group phase III multi-center trial to compare twice daily topical application of M518101, Daivonex® and vehicle in patients with plaque psoriasis

Summary

EudraCT number	2013-001632-21
Trial protocol	LT HU PL BG AT
Global end of trial date	07 January 2015

Results information

Result version number	v1 (current)
This version publication date	18 November 2021
First version publication date	18 November 2021

Trial information

Trial identification

Sponsor protocol code	M518101-EU04

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Maruho Co.,Ltd.
Sponsor organisation address	Kyoto R&D Center, 93, Awata-cho, Chudoji, Shimogyo-ku, Kyoto, Japan, 600-8815
Public contact	Clinical Trials Information, Maruho Co.,Ltd. Kyoto R&D Center, +81 (0)75-325-3279, ctinfo@mii.maruho.co.jp
Scientific contact	Clinical Trials Information, Maruho Co.,Ltd. Kyoto R&D Center, +81 (0)75-325-3279, ctinfo@mii.maruho.co.jp

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	27 April 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 January 2015
Global end of trial reached?	Yes
Global end of trial date	07 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The trial was designed with two sequentially assessed primary objectives as described in the EMA guideline (Points to consider on switching between superiority and non-inferiority. EMA, July 2000). For the first stage, the primary objective was to demonstrate that M518101 was non-inferior to Daivonex® in % reduction in mPASI and success rate based on IGA.
If non-inferiority was demonstrated, the analysis was to proceed to the second stage, which was to demonstrate that M518101 was more effective than Daivonex® in the same endpoints. In addition, superiority to Vehicle for both M518101 and Daivonex® were tested for the same endpoints.

Protection of trial subjects:

The study was completed in accordance with ICH guidelines. Compliance with this standard provides public assurance that the rights, safety and well-being of the study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki

Background therapy:

During the screening period subjects should have had adhered to their standard skin care regimen and may have used their standard emollients/moisturizers as symptoms required.

Evidence for comparator:

This study was designed consistent with European guidelines for psoriasis that allow for demonstration of non-inferiority to an active control as long as the treatment is also superior to vehicle. Scientifically, efficacy is most convincingly established by demonstrating superiority to a comparator (vehicle or active control).
Furthermore, the comparisons serve to establish that there are no clinically unacceptable differences in safety and tolerability compared with either a comparator drug or vehicle.
The comparator identified for this study on psoriasis (Daivonex® ointment, calcipotriol) or calcipotriene) is an established vitamin D3 ointment.
A vehicle arm was included to show the possible influence on psoriasis due to skin care effects of the vehicle formulation.

Actual start date of recruitment	31 October 2013
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	Poland: 322
Country: Number of subjects enrolled	Austria: 21
Country: Number of subjects enrolled	Bulgaria: 75
Country: Number of subjects enrolled	Germany: 52
Country: Number of subjects enrolled	Hungary: 91
Country: Number of subjects enrolled	Lithuania: 72
Country: Number of subjects enrolled	Romania: 62

Country: Number of subjects enrolled	Ukraine: 93
Worldwide total number of subjects	788
EEA total number of subjects	695

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)	737
From 65 to 84 years	51
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 53 centers in 8 countries (Poland, Germany, Hungary, Bulgaria, Romania, Lithuania, Ukraine, Austria) between 31 October 2013 (first subject first visit) to 07 January 2015 (last subject last visit).

Pre-assignment

Screening details:

A total of 1068 potential subjects were screened after signing an informed consent form, of whom 788 subjects were randomized to receive study treatment.

Period 1

Period 1 title	Comparative Treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Period1:M518101

Arm description:

Subjects were blindly randomized in M518101 BID, 8 weeks.

Arm type	Experimental
Investigational medicinal product name	M518101
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

M518101 BID application was performed during 8 weeks in Period 1.
Based on application guidance and depending on affected BSA (maximum 20%) it was calculated that each application required up to 5 g ointment. (up to 10 g ointment per day).

Arm title	Period1:Daivonex® ointment

Arm description:

Subjects were blindly randomized in Daivonex® ointment BID, 8 weeks.

Arm type	Active comparator
Investigational medicinal product name	Daivonex® ointment
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

Daivonex® ointment BID application was performed during 8 weeks in Period 1.
Based on application guidance and depending on affected BSA (maximum 20%) it was calculated that each application required up to 5 g ointment. (up to 10 g ointment per day).

Arm title	Period1:Vehicle

Arm description:

Subjects were blindly randomized in Vehicle BID, 8 weeks.

Arm type	Placebo

Investigational medicinal product name	Vehicle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

Vehicle BID application was performed during 8 weeks in Period 1.
Based on application guidance and depending on affected BSA (maximum 20%) it was calculated that each application required up to 5 g ointment. (up to 10 g ointment per day).

Number of subjects in period 1	Period1:M518101	Period1:Daivonex® ointment	Period1:Vehicle
Started	318	313	157
Completed	267	284	127
Not completed	51	29	30
Consent withdrawn by subject	20	12	17
Physician decision	1	-	-
QTcF measurements increased 60 msec from Baseline	1	1	-
Non-compliant use of the study drug	-	-	1
Adverse event, non-fatal	19	3	-
Other	1	2	1
Worsening of psoriasis	2	4	3
Lost to follow-up	5	3	4
Protocol deviation	2	4	4

Period 2

Period 2 title	Follow-Up Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Period2:M518101

Arm description:

Subjects who achieved >= mPASI50 improvement at WEEK 8 were eligible to enter the Vehicle BID of period2 up to maximum duration of 8 weeks.

Arm type	Experimental

Investigational medicinal product name	Vehicle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

Subjects who achieved >= mPASI50 improvement at WEEK 8 were eligible to enter the period2 up to a maximum duration of 8 weeks, and were supplied with vehicle and instructed to apply BID.

Arm title	Period2:Daivonex® ointment

Arm description:

Subjects who achieved >= mPASI50 improvement at WEEK 8 were eligible to enter the Vehicle BID of period2 up to maximum duration of 8 weeks.

Arm type	Active comparator
Investigational medicinal product name	Vehicle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

Subjects who achieved >= mPASI50 improvement at WEEK 8 were eligible to enter the period2 up to a maximum duration of 8 weeks, and were supplied with vehicle and instructed to apply BID.

Arm title	Period2:Vehicle

Arm description:

Subjects who achieved >= mPASI50 improvement at WEEK 8 were eligible to enter the Vehicle BID of period2 up to maximum duration of 8 weeks.

Arm type	Placebo
Investigational medicinal product name	Vehicle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

Subjects who achieved >= mPASI50 improvement at WEEK 8 were eligible to enter the period2 up to a maximum duration of 8 weeks, and were supplied with vehicle and instructed to apply BID.

Number of subjects in period 2[1]	Period2:M518101	Period2:Daivonex® ointment	Period2:Vehicle
Started	205	242	65
Completed	195	217	65
Not completed	10	25	0
Consent withdrawn by subject	5	15	-
Physician decision	1	3	-
Non-compliant use of the study drug	-	1	-
Adverse event, non-fatal	-	1	-
Other	2	1	-
Pregnancy	1	-	-
Worsening of psoriasis	-	1	-

Lost to follow-up	1	1	-
Protocol deviation	-	2	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Subjects who achieved ≥ mPASI50 (at least a 50% improvement in mPASI score) at WEEK 8 were eligible to participate in the follow-up phase.

Baseline characteristics

Reporting groups	
Reporting group title	Period1:M518101
Reporting group description:	
Subjects were blindly randomized in M518101 BID, 8 weeks.	
Reporting group title	Period1:Daivonex® ointment
Reporting group description:	
Subjects were blindly randomized in Daivonex® ointment BID, 8 weeks.	
Reporting group title	Period1:Vehicle
Reporting group description:	
Subjects were blindly randomized in Vehicle BID, 8 weeks.	

Reporting group values	Period1:M518101	Period1:Daivonex® ointment	Period1:Vehicle
Number of subjects	318	313	157
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	295	297	145
From 65-84 years	23	16	12
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	43.8	43.9	43.4
standard deviation	± 14.10	± 13.11	± 14.67
Gender categorical Units: Subjects			
Female	109	135	60
Male	209	178	97
Race Units: Subjects			
White/Caucasian	318	312	157
Other	0	1	0

Reporting group values	Total		
Number of subjects	788		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	737		
From 65-84 years	51		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	304		
Male	484		
Race			
Units: Subjects			
White/Caucasian	787		
Other	1		

End points

End points reporting groups

Reporting group title	Period1:M518101
Reporting group description:	
Subjects were blindly randomized in M518101 BID, 8 weeks.	
Reporting group title	Period1:Daivonex® ointment
Reporting group description:	
Subjects were blindly randomized in Daivonex® ointment BID, 8 weeks.	
Reporting group title	Period1:Vehicle
Reporting group description:	
Subjects were blindly randomized in Vehicle BID, 8 weeks.	
Reporting group title	Period2:M518101
Reporting group description:	
Subjects who achieved >= mPASI50 improvement at WEEK 8 were eligible to enter the Vehicle BID of period2 up to maximum duration of 8 weeks.	
Reporting group title	Period2:Daivonex® ointment
Reporting group description:	
Subjects who achieved >= mPASI50 improvement at WEEK 8 were eligible to enter the Vehicle BID of period2 up to maximum duration of 8 weeks.	
Reporting group title	Period2:Vehicle
Reporting group description:	
Subjects who achieved >= mPASI50 improvement at WEEK 8 were eligible to enter the Vehicle BID of period2 up to maximum duration of 8 weeks.	

Primary: The success rate based on IGA score at WEEK 8

End point title	The success rate based on IGA score at WEEK 8
End point description:	
The success rate was defined as the subject having ''absence'' of disease or ''very mild'' disease with at least a 2-grade improvement in the IGA at WEEK 8 when compared to Baseline.	
End point type	Primary
End point timeframe:	
week 8	

End point values	Period1:M518101	Period1:Daivonex® ointment	Period1:Vehicle	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	318	313	157	
Units: percentage of subjects				
number (not applicable)	46.5	57.2	21.7	

Statistical analyses

Statistical analysis title	M518101 vs Vehicle
Comparison groups	Period1:M518101 v Period1:Vehicle
Number of subjects included in analysis	475
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.279
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.091
upper limit	5.143

Statistical analysis title	M518101 vs Daivonex® ointment
Comparison groups	Period1:M518101 v Period1:Daivonex® ointment
Number of subjects included in analysis	631
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.007
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.474
upper limit	0.891

Primary: % reduction in mPASI at WEEK 8 compared to Baseline	
End point title	% reduction in mPASI at WEEK 8 compared to Baseline
End point description:	
End point type	Primary
End point timeframe:	
week 8	

End point values	Period1:M518101	Period1:Daivonex® ointment	Period1:Vehicle	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	270	286	128	
Units: percentage of units on a scale				
least squares mean (confidence interval 95%)	62.265 (58.242 to 66.287)	70.959 (66.969 to 74.948)	39.340 (33.580 to 45.100)	

Statistical analyses

Statistical analysis title	M518101 vs Vehicle
Comparison groups	Period1:M518101 v Period1:Vehicle
Number of subjects included in analysis	398
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	MMRM/ANCOVA Model
Parameter estimate	LS Mean Difference
Point estimate	22.925
Confidence interval	
level	95 %
sides	2-sided
lower limit	15.966
upper limit	29.884

Statistical analysis title	M518101 vs Daivonex® ointment
Comparison groups	Period1:M518101 v Period1:Daivonex® ointment
Number of subjects included in analysis	556
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.002 [1]
Method	MMRM/ANCOVA Model
Parameter estimate	LS Mean Difference
Point estimate	-8.694
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.276
upper limit	-3.112

Notes:

[1] - The hypothesis testing non-inferiority of M518101 vs Daivonex® ointment could not be rejected since the lower bound of the 95% CI of the LS mean difference in % reduction in mPASI (-14.276) was lower than the non- inferiority margin(-Δ1= -11%).

Secondary: mPASI50 rate at WEEK 8

End point title	mPASI50 rate at WEEK 8

End point description:

End point type	Secondary

End point timeframe:
week 8

End point values	Period1:M518101	Period1:Daivonex® ointment	Period1:Vehicle	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	318	313	157	
Units: percentage of subjects				
number (not applicable)	69.8	82.7	43.9	

Statistical analyses

No statistical analyses for this end point

Secondary: mPASI75 rate at WEEK 8

End point title	mPASI75 rate at WEEK 8

End point description:

End point type	Secondary

End point timeframe:
week 8

End point values	Period1:M518101	Period1:Daivonex® ointment	Period1:Vehicle	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	318	313	157	
Units: percentage of subjects				
number (not applicable)	39.9	56.2	21.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in PSI total score at WEEK 8 compared to Baseline

End point title	Change in PSI total score at WEEK 8 compared to Baseline

End point description:

End point type	Secondary
End point timeframe: week 8	

End point values	Period1:M518101	Period1:Daivonex® ointment	Period1:Vehicle	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	270	286	128	
Units: units on a scale				
arithmetic mean (standard deviation)	-9.9 (± 4.27)	-11.3 (± 3.64)	-7.2 (± 4.52)	

Statistical analyses

No statistical analyses for this end point

Secondary: % reduction in mPASI at WEEK 1 compared to Baseline

End point title	% reduction in mPASI at WEEK 1 compared to Baseline
End point description:	

End point type	Secondary
End point timeframe: week 1	

End point values	Period1:M518101	Period1:Daivonex® ointment	Period1:Vehicle	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	313	311	154	
Units: percentage of units on a scale				
least squares mean (confidence interval 95%)	23.522 (21.361 to 25.683)	24.504 (22.327 to 26.682)	15.877 (12.875 to 18.879)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Duration of response (time to relapse)

End point title	Duration of response (time to relapse)

End point description:

According to the EMA guideline relapse was defined when the maximal improvement from Baseline is reduced by > 50%.

End point type	Other pre-specified

End point timeframe:

The date at which the relapse occurred

End point values	Period2:M518101	Period2:Daivonex® ointment	Period2:Vehicle	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	204	242	65	
Units: days				
median (inter-quartile range (Q1-Q3))	57.0 (56.0 to 57.0)	57.0 (55.0 to 57.0)	57.0 (55.0 to 57.0)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in QOL-DLQI score from Baseline to WEEK 8

End point title	Change in QOL-DLQI score from Baseline to WEEK 8

End point description:

End point type	Other pre-specified

End point timeframe:

week 8

End point values	Period1:M518101	Period1:Daivonex® ointment	Period1:Vehicle	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	269	284	128	
Units: units on a scale				
least squares mean (confidence interval 95%)	-4.3 (-4.86 to -3.71)	-5.9 (-6.43 to -5.29)	-3.2 (-3.98 to -2.35)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time course change in mean % reduction in mPASI score

End point title	Time course change in mean % reduction in mPASI score

End point description:

End point type	Other pre-specified

End point timeframe:
week 1,2,4,6,8

End point values	Period1:M518101	Period1:Daivonex® ointment	Period1:Vehicle	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	313[2]	311[3]	154[4]	
Units: percentage of units on a scale				
least squares mean (confidence interval 95%)				
week1	23.522 (21.361 to 25.683)	24.504 (22.327 to 26.682)	15.877 (12.875 to 18.879)	
week2	39.667 (37.008 to 42.325)	41.925 (39.249 to 44.600)	27.221 (23.499 to 30.943)	
week4	50.366 (47.227 to 53.505)	55.685 (52.529 to 58.840)	31.302 (26.881 to 35.723)	
week6	58.289 (55.098 to 61.480)	65.916 (62.713 to 69.118)	37.518 (32.988 to 42.048)	
week8	62.265 (58.242 to 66.287)	70.959 (66.969 to 74.948)	39.340 (33.580 to 45.100)	

Notes:
[2] - week1:N=313, week2:N=306, week4:N=300, week6:N=289, week8:N=270
[3] - week1:N=311, week2:N=304, week4:N=299, week6:N=290, week8:N=286
[4] - week1:N=154, week2:N=151, week4:N=148, week6:N=136, week8:N=128

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time course change in PSI total score

End point title	Time course change in PSI total score

End point description:

End point type	Other pre-specified

End point timeframe:
week 1,2,4,6,8

End point values	Period1:M518101	Period1:Daivonex® ointment	Period1:Vehicle	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	270	286	128	
Units: units on a scale				
least squares mean (confidence interval 95%)				

week1	-4.3 (-4.62 to -3.97)	-4.2 (-4.51 to -3.85)	-2.5 (-2.99 to -2.07)	
week2	-6.6 (-7.00 to -6.29)	-6.9 (-7.29 to -6.57)	-4.6 (-5.09 to -4.09)	
week4	-7.9 (-8.31 to -7.55)	-8.9 (-9.26 to -8.50)	-5.6 (-6.12 to -5.06)	
week6	-9.0 (-9.42 to -8.66)	-10.1 (-10.53 to -9.76)	-6.3 (-6.82 to -5.75)	
week8	-9.5 (-9.99 to -9.10)	-11.0 (-11.40 to -10.52)	-6.8 (-7.42 to -6.15)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in BSA at WEEK 8 compared to the Baseline

End point title	Change in BSA at WEEK 8 compared to the Baseline
End point description:	
End point type	Other pre-specified
End point timeframe:	
week 8	

End point values	Period1:M518101	Period1:Daivonex® ointment	Period1:Vehicle	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	269	283	127	
Units: percentage				
least squares mean (confidence interval 95%)	-2.9 (-3.28 to -2.43)	-3.3 (-3.73 to -2.90)	-1.9 (-2.45 to -1.26)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time course change in mPASI rates (50% and 75%)

End point title	Time course change in mPASI rates (50% and 75%)
End point description:	
End point type	Other pre-specified
End point timeframe:	
week 1,2,4,6,8	

End point values	Period1:M518101	Period1:Daivonex® ointment	Period1:Vehicle	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	313[5]	311[6]	154[7]	
Units: percentage of units on a scale				
number (not applicable)				
mPASI50 response WEEK 1	10.1	8.9	5.1	
mPASI50 response WEEK 2	36.2	37.4	16.6	
mPASI50 response WEEK 4	55.7	65.5	26.1	
mPASI50 response WEEK 6	67.3	81.5	37.6	
mPASI50 response WEEK 8	69.8	82.7	43.9	
mPASI75 response WEEK 1	1.3	0.3	0.0	
mPASI75 response WEEK 2	5.7	5.4	0.6	
mPASI75 response WEEK 4	17.3	21.1	3.8	
mPASI75 response WEEK 6	28.9	38.7	11.5	
mPASI75 response WEEK 8	39.9	56.2	21.7	

Notes:

[5] - Week 1:N=313, Week 2:N=306, Week 4:N=300, Week 6:N=289, Week 8:N=270

[6] - Week 1:N=311, Week 2:N=304, Week 4:N=299, Week 6:N=290, Week 8:N=286

[7] - Week 1:N=154, Week 2:N=151, Week 4:N=148, Week 6:N=136, Week 8:N=128

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time course change in IGA success rate

End point title	Time course change in IGA success rate

End point description:

End point type	Other pre-specified

End point timeframe:

week 1,2,4,6,8

End point values	Period1:M518101	Period1:Daivonex® ointment	Period1:Vehicle	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	318	313	157	
Units: percentage of units on a score				
number (not applicable)				
week1	3.8	1.9	0	
week2	10.4	9.3	4.5	
week4	20.1	25.6	4.5	
week6	33.0	41.2	14.0	
week8	46.5	57.2	21.7	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
16 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	Period1:M518101
Reporting group description:	
Subjects were blindly randomized in M518101 BID, 8 weeks.	
Reporting group title	Period1:Daivonex® ointment
Reporting group description:	
Subjects were blindly randomized in Daivonex® ointment BID, 8 weeks.	
Reporting group title	Period1:Vehicle
Reporting group description:	
Subjects were blindly randomized in Vehicle BID, 8 weeks.	
Reporting group title	Period2:M518101
Reporting group description:	
Subjects who achieved >= mPASI50 improvement at WEEK 8 were eligible to enter the Vehicle BID of period2 up to maximum duration of 8 weeks.	
Reporting group title	Period2:Daivonex® ointment
Reporting group description:	
Subjects who achieved >= mPASI50 improvement at WEEK 8 were eligible to enter the Vehicle BID of period2 up to maximum duration of 8 weeks.	
Reporting group title	Period2:Vehicle
Reporting group description:	
Subjects who achieved >= mPASI50 improvement at WEEK 8 were eligible to enter the Vehicle BID of period2 up to maximum duration of 8 weeks.	

Serious adverse events	Period1:M518101	Period1:Daivonex® ointment	Period1:Vehicle
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 315 (0.63%)	1 / 312 (0.32%)	2 / 158 (1.27%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Fracture displacement			
subjects affected / exposed	0 / 315 (0.00%)	1 / 312 (0.32%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	0 / 315 (0.00%)	0 / 312 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congestive cardiomyopathy			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 315 (0.00%)	0 / 312 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 315 (0.32%)	0 / 312 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	0 / 315 (0.00%)	0 / 312 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Peritonsillar abscess			
subjects affected / exposed	1 / 315 (0.32%)	0 / 312 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Period2:M518101	Period2:Daivonex® ointment	Period2:Vehicle
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 204 (0.00%)	1 / 242 (0.41%)	0 / 66 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Fracture displacement			

subjects affected / exposed	0 / 204 (0.00%)	0 / 242 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 204 (0.00%)	0 / 242 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congestive cardiomyopathy			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 204 (0.00%)	1 / 242 (0.41%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 204 (0.00%)	0 / 242 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	0 / 204 (0.00%)	0 / 242 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Peritionsillar abscess			
subjects affected / exposed	0 / 204 (0.00%)	0 / 242 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Period1:M518101	Period1:Daivonex® ointment	Period1:Vehicle
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 315 (12.38%)	17 / 312 (5.45%)	6 / 158 (3.80%)
General disorders and administration site conditions			
Application site pain	Additional description: No data available to report for period2.		
subjects affected / exposed	7 / 315 (2.22%)	3 / 312 (0.96%)	1 / 158 (0.63%)
occurrences (all)	9	6	1
Application site pruritus	Additional description: No data available to report for period2.		
subjects affected / exposed	7 / 315 (2.22%)	2 / 312 (0.64%)	0 / 158 (0.00%)
occurrences (all)	8	4	0
Skin and subcutaneous tissue disorders			
Contact dermatitis	Additional description: No data available to report for period2.		
subjects affected / exposed	16 / 315 (5.08%)	3 / 312 (0.96%)	0 / 158 (0.00%)
occurrences (all)	19	3	0
Infections and infestations			
Nasopharyngitis	Additional description: No data available to report for period2.		
subjects affected / exposed	9 / 315 (2.86%)	9 / 312 (2.88%)	5 / 158 (3.16%)
occurrences (all)	9	10	6

Non-serious adverse events	Period2:M518101	Period2:Daivonex® ointment	Period2:Vehicle
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 204 (0.00%)	0 / 242 (0.00%)	0 / 66 (0.00%)
General disorders and administration site conditions			
Application site pain	Additional description: No data available to report for period2.		
subjects affected / exposed	0 / 204 (0.00%)	0 / 242 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Application site pruritus	Additional description: No data available to report for period2.		
subjects affected / exposed	0 / 204 (0.00%)	0 / 242 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Contact dermatitis	Additional description: No data available to report for period2.		
subjects affected / exposed	0 / 204 (0.00%)	0 / 242 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis	Additional description: No data available to report for period2.		
subjects affected / exposed	0 / 204 (0.00%)	0 / 242 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0

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