Clinical trial results:
A multi-center, randomized, double-blind, three-arm, 16 week, adaptive phase III clinical study to investigate the efficacy and safety of LAS41008 vs LASW1835 and vs placebo in patients with moderate to severe plaque psoriasis

Summary

EudraCT number	2012-000055-13
Trial protocol	DE AT NL PL
Global end of trial date	19 October 2015

Results information

Result version number	v1 (current)
This version publication date	11 December 2016
First version publication date	11 December 2016

Trial information

Trial identification

Sponsor protocol code	M41008-1102

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	ALMIRALL S.A.
Sponsor organisation address	Laureà Miró 408-410, Sant Feliu de Llobregat (Barcelona), Spain, 08980
Public contact	Disclosure Central Team, ALMIRALL S.A., R&D@almirall.com
Scientific contact	Disclosure Central Team, ALMIRALL S.A., R&D@almirall.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	19 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 October 2015
Global end of trial reached?	Yes
Global end of trial date	19 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the study are:
Superiority of LAS41008 versus placebo based on the proportion of subjects achieving PASI 75 (a reduction of at least 75% in the Psoriasis Area and Severity Index) at Week 16
Superiority of LAS41008 versus placebo based on the proportion of subjects achieving a score of 'clear' or 'almost clear' in the Physician's Global Assessment (PGA) at Week 16
Non-inferiority of LAS41008 compared to LASW1835 (internal code for Fumaderm®) regarding PASI 75 at Week 16

Protection of trial subjects:

This study was conducted in accordance with the protocol, Good Clinical Practice (GCP), ICH (International Conference on Harmonization) guidelines, and the ethical principles set forth in the Declaration of Helsinki and its amendments (October 2008)

A favourable opinion of the relevant independent ethics committees was obtained prior to the start of the study and written informed consent was obtained from all patients prior to entry into the study. The investigator explained to each patient, orally and in writing (patient information sheet), the nature, significance, risks and implications of the trial

Background therapy: -

Evidence for comparator:

Fumaderm® is a prescription only medicine currently approved only in Germany, where it is the most commonly prescribed oral therapy for the treatment of psoriasis

Several publications and other prescribing evidence indicate that Fumaderm® is used by specialist dermatology centers under local legal arrangements in a number of other countries throughout Europe

Actual start date of recruitment	07 January 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	Poland: 321
Country: Number of subjects enrolled	Austria: 65
Country: Number of subjects enrolled	Germany: 302
Worldwide total number of subjects	699
EEA total number of subjects	699

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)	637
From 65 to 84 years	61
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This study was conducted in a total of 57 sites, 7 in Austria, 36 in Germany, 12 in Poland, and 2 in the Netherlands

The first patient visit was in January 2013 and the last patient visit was October 2015

Pre-assignment

Screening details:

A total of 839 patients were screened and 704 patients were randomised
Wash-out periods were 2 weeks (corticosteroids, vitamin A or D analogues, anthracene derivatives, tar and salicylic acid preparations), 1 month (conventional systemic antipsoriatic drugs and phototherapy), 3 months (antipsoriatic biologics) or 6 months (cytostatics)

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	LAS41008

Arm description: -

Arm type	Experimental
Investigational medicinal product name	LAS41008
Investigational medicinal product code	
Other name	Dimethyl fumarate
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the first three weeks of the treatment period, patients received up to 3 x 1 tablet containing 30 mg LAS41008 (30 mg/day in Week 1, 60 mg/day in Week 2 and 90 mg/day in Week 3)
During the subsequent 13 weeks (Week 4 until Week 16), patients received up to 3 x 2 tablets each containing 120 mg LAS41008 leading to a maximum of 720 mg/day (120 mg/day in Week 4, 240 mg/day in Week 5, 360 mg/day in Week 6, 480 mg/day in Week 7, 600 mg/day in Week 8, 720 mg/day in Week 9 onwards)
In case of individual intolerability of the increased dosage, the patient was to receive the last tolerated dose, which was then to be maintained until the end of the treatment period
If treatment success (patient achieved a score of 'clear' or 'almost clear' in the PGA or >90% improvement in PASI from baseline) was reached before administration of the maximum dose of 720 mg/day, no further dose increase was necessary and the dosage was to be steadily reduced to an individual maintenance dose

Arm title	Fumaderm®

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Fumaderm®
Investigational medicinal product code	
Other name	Dimethyl fumarate
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the first three weeks of the treatment period, patients received up to 3 x 1 tablet containing 30

mg Fumaderm® (30 mg/day in Week 1, 60 mg/day in Week 2 and 90 mg/day in Week 3)
During the subsequent 13 weeks (Week 4 until Week 16), patients received up to 3 x 2 tablets each containing 120 mg Fumaderm® leading to a maximum of 720 mg/day (120 mg/day in Week 4, 240 mg/day in Week 5, 360 mg/day in Week 6, 480 mg/day in Week 7, 600 mg/day in Week 8, 720 mg/day in Week 9 onwards)
In case of individual intolerability of the increased dosage, the patient was to receive the last tolerated dose, which was then to be maintained until the end of the treatment period
If treatment success (patient achieved a score of 'clear' or 'almost clear' in the PGA or >90% improvement in PASI from baseline) was reached before administration of the maximum dose of 720 mg/day, no further dose increase was necessary and the dosage was to be steadily reduced to an individual maintenance dose

Arm title	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the first three weeks of the treatment period, patients received up to 3 x 1 placebo and during the subsequent 13 weeks (Week 4 until Week 16), patients received up to 3 x 2 placebo tablets

Number of subjects in period 1	LAS41008	Fumaderm®	Placebo
Started	279	283	137
Completed treatment period	176	176	98
Completed	42	51	17
Not completed	237	232	120
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	40	40	29
Adverse event, non-fatal	66	70	6
Not specified	56	38	19
Lost to follow-up	23	26	17
Protocol deviation	6	8	1
Lack of efficacy	46	49	48

Baseline characteristics

Reporting groups	
Reporting group title	LAS41008
Reporting group description: -	
Reporting group title	Fumaderm®
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	LAS41008	Fumaderm®	Placebo
Number of subjects	279	283	137
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 44 ± 15.24	 45 ± 13.84	 44 ± 14.26
Gender categorical Units: Subjects			
Female	105	98	44
Male	174	185	93

Reporting group values	Total		
Number of subjects	699		
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 -	 	
Gender categorical Units: Subjects			
Female	247		
Male	452		

End points

End points reporting groups

Reporting group title	LAS41008
Reporting group description: -	
Reporting group title	Fumaderm®
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Proportion of patients achieving Psoriasis Area and Severity Index (PASI) 75 at Week 16

End point title	Proportion of patients achieving Psoriasis Area and Severity Index (PASI) 75 at Week 16

End point description:

PASI 75 is a reduction of at least 75% in the Psoriasis Area and Severity Index (PASI)
The PASI requires the assessment of erythema (E), infiltration (I), desquamation (D), and body surface area involvement (A) over 4 body regions: head (h), trunk (t), upper (u) and lower (l) extremities
Degree of severity (per body region) for each variable:
0 = no symptom
1 = slight
2 = moderate
3 = marked
4 = very marked
Surface area involved (per body region):
1 = <10%
2 = 10-29%
3 = 30-49%
4 = 50-69%
5 = 70-89%
6 = 90-100%

End point type	Primary

End point timeframe:

Week 16 of treatment

End point values	LAS41008	Fumaderm®	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	267	273	131	
Units: Percentage				
number (not applicable)	37.5	40.3	15.3	

Statistical analyses

Statistical analysis title	LAS41008 vs Placebo

Statistical analysis description:

P values are derived from the Wald test for risk differences and a combination (p value Stage 1 x p value Stage 2) of the p-values from Stage 1 (from study start to the time of the interim analysis) and Stage 2 (period comprising the remaining treatment period and the first 2 months of follow up for all

subjects continuing in the study) according to the Bauer & Köhne procedure
Co-primary endpoints were non-adjusted
The last observation carried forward (LOCF) method was used for missing data

Comparison groups	Placebo v LAS41008
Number of subjects included in analysis	398
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Wald test
Parameter estimate	Mean difference (net)
Point estimate	0.222
Confidence interval	
level	Other: 99.24 %
sides	2-sided
lower limit	0.107
upper limit	0.337

Notes:

[1] - p value is significant if <0.0038

Statistical analysis title	LAS-41008 vs Fumaderm®

Statistical analysis description:

P values are derived from the Wald test for risk differences and a combination (p value Stage 1 x p value Stage 2) of the p-values from Stage 1 (from study start to the time of the interim analysis) and Stage 2 (period comprising the remaining treatment period and the first 2 months of follow up for all subjects continuing in the study) according to the Bauer & Köhne procedure
Co-primary endpoints were non-adjusted
The last observation carried forward (LOCF) method was used for missing data

Comparison groups	Fumaderm® v LAS41008
Number of subjects included in analysis	540
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0003 [2]
Method	Wald test
Parameter estimate	Mean difference (net)
Point estimate	-0.028
Confidence interval	
level	Other: 99.24 %
sides	2-sided
lower limit	-0.14
upper limit	0.084

Notes:

[2] - p value is significant if <0.0038

Primary: Proportion of patients achieving a score of 'clear' or 'almost clear' in the Physician's Global Assessment at Week 16

End point title	Proportion of patients achieving a score of 'clear' or 'almost clear' in the Physician's Global Assessment at Week 16

End point description:

The Physician's Global Assessment (PGA) is scored as:
0 = clear (no signs of psoriasis (post-inflammatory hyperpigmentation may be present))
1 = almost clear (intermediate between mild and clear)
2 = mild (slight plaque elevation, scaling and/or erythema)
3 = moderate (moderate plaque elevation, scaling and/or erythema)
4 = moderate to severe (marked plaque elevation, scaling and/or erythema)

5 = severe (very marked plaque elevation, scaling and/or erythema)

End point type	Primary

End point timeframe:

Week 16 of treatment

End point values	LAS41008	Fumaderm®	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	267	273	131	
Units: Percentage				
number (not applicable)	33	37.4	13	

Statistical analyses

Statistical analysis title	LAS41008 vs Placebo

Statistical analysis description:

P values are derived from the Wald test for risk differences and a combination (p value Stage 1 x p value Stage 2) of p-values from Stage 1 (from study start to the time of the interim analysis) and Stage 2 (period comprising the remaining treatment period and the first 2 months of follow up for all subjects continuing in the study) according to the Bauer & Köhne procedure
Co-primary endpoints were non-adjusted
The last observation carried forward (LOCF) method was used for missing data

Comparison groups	Placebo v LAS41008
Number of subjects included in analysis	398
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Wald test
Parameter estimate	Median difference (net)
Point estimate	0.2
Confidence interval	
level	Other: 99.24 %
sides	2-sided
lower limit	0.09
upper limit	0.31

Notes:

[3] - p value is significant if <0.0038

Secondary: Proportion of patients achieving Psoriasis Area and Severity Index (PASI) 75 at Week 3 and 8

End point title	Proportion of patients achieving Psoriasis Area and Severity Index (PASI) 75 at Week 3 and 8

End point description:

PASI 75 is a reduction of at least 75% in the Psoriasis Area and Severity Index (PASI)
The PASI requires the assessment of erythema (E), infiltration (I), desquamation (D), and body surface area involvement (A) over 4 body regions: head (h), trunk (t), upper (u) and lower (l) extremities
Degree of severity (per body region) for each variable:
0 = no symptom
1 = slight
2 = moderate

3 = marked
4 = very marked
Surface area involved (per body region):
1 = <10%
2 = 10-29%
3 = 30-49%
4 = 50-69%
5 = 70-89%
6 = 90-100%

End point type	Secondary

End point timeframe:

Week 3 and 8 of treatment

End point values	LAS41008	Fumaderm®	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	267	273	131	
Units: Percentage				
number (not applicable)				
Week 3	1.1	0.4	0	
Week 8	7.5	8.4	5.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients achieving Psoriasis Area and Severity Index (PASI) 50 and PASI 90 at Week 3, 8, and 16

End point title	Proportion of patients achieving Psoriasis Area and Severity Index (PASI) 50 and PASI 90 at Week 3, 8, and 16

End point description:

PASI 50 is a reduction of at least 50% in the Psoriasis Area and Severity Index (PASI); PASI 90 is a reduction of at least 90% in the PASI
The PASI requires the assessment of erythema (E), infiltration (I), desquamation (D), and body surface area involvement (A) over 4 body regions: head (h), trunk (t), upper (u) and lower (l) extremities
Degree of severity (per body region) for each variable:
0 = no symptom
1 = slight
2 = moderate
3 = marked
4 = very marked
Surface area involved (per body region):
1 = <10%
2 = 10-29%
3 = 30-49%
4 = 50-69%
5 = 70-89%
6 = 90-100%

End point type	Secondary

End point timeframe:

Week 3, 8, and 16 of treatment

End point values	LAS41008	Fumaderm®	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	267	273	131	
Units: Percentage				
number (not applicable)				
PASI 50 Week 3	5.6	5.9	2.3	
PASI 50 Week 8	26.6	31.9	17.6	
PASI 50 Week 16	53.6	61.9	29	
PASI 90 Week 3	0	0	0	
PASI 90 Week 8	1.5	1.5	0	
PASI 90 Week 16	18.4	22.3	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients achieving a score of 'clear' or 'almost clear' in the Physician's Global Assessment at Week 3 and 8

End point title	Proportion of patients achieving a score of 'clear' or 'almost clear' in the Physician's Global Assessment at Week 3 and 8

End point description:

The Physician's Global Assessment (PGA) is scored as:
0 = clear (no signs of psoriasis (post-inflammatory hyperpigmentation may be present))
1 = almost clear (intermediate between mild and clear)
2 = mild (slight plaque elevation, scaling and/or erythema)
3 = moderate (moderate plaque elevation, scaling and/or erythema)
4 = moderate to severe (marked plaque elevation, scaling and/or erythema)
5 = severe (very marked plaque elevation, scaling and/or erythema)

End point type	Secondary

End point timeframe:

Week 3 and 8 of treatment

End point values	LAS41008	Fumaderm®	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	267	273	131	
Units: Percentage				
number (not applicable)				
Week 3	0.4	0	0	
Week 8	5.6	7	2.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute values and percent change from baseline in Psoriasis Area and Severity Index (PASI) at Week 3, 8, 16, and 2 months treatment-free

End point title	Absolute values and percent change from baseline in Psoriasis Area and Severity Index (PASI) at Week 3, 8, 16, and 2 months treatment-free

End point description:

The PASI requires the assessment of erythema (E), infiltration (I), desquamation (D), and body surface area involvement (A) over 4 body regions: head (h), trunk (t), upper (u) and lower (l) extremities
Degree of severity (per body region) for each variable:
0 = no symptom
1 = slight
2 = moderate
3 = marked
4 = very marked
Surface area involved (per body region):
1 = <10%
2 = 10-29%
3 = 30-49%
4 = 50-69%
5 = 70-89%
6 = 90-100%

End point type	Secondary

End point timeframe:

Week 3, 8 and 16 of treatment and 2 months treatment-free

End point values	LAS41008	Fumaderm®	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	267	273	131	
Units: Score				
arithmetic mean (standard deviation)				
Week 3 (absolute values)	14.4 (± 6.42)	14.5 (± 7.38)	14.8 (± 5.53)	
Week 8 (absolute values)	11 (± 5.78)	11.2 (± 8.04)	12.9 (± 6.57)	
Week 16 (absolute values)	7.8 (± 6.8)	7.8 (± 8.73)	11.9 (± 7.25)	
2 months treatment-free (absolute values)	8.1 (± 6.74)	8.3 (± 8.78)	11.8 (± 7.55)	
Week 3 (percent change)	-11.8 (± 24.19)	-12.3 (± 22.14)	-8.2 (± 18.11)	
Week 8 (percent change)	-30.9 (± 33.36)	-33.1 (± 31.77)	-20 (± 31.2)	
Week 16 (percent change)	-50.8 (± 41.78)	-54.1 (± 39.94)	-27 (± 37.62)	
2 months treatment-free (percent change)	-48.5 (± 41.72)	-51.6 (± 39.87)	-27.5 (± 39.28)	

Statistical analyses

No statistical analyses for this end point

Secondary: Physician's Global Assessment score at Week 3

End point title	Physician's Global Assessment score at Week 3

End point description:

The Physician's Global Assessment (PGA) is scored as:
0 = clear (no signs of psoriasis (post-inflammatory hyperpigmentation may be present))
1 = almost clear (intermediate between mild and clear)
2 = mild (slight plaque elevation, scaling and/or erythema)
3 = moderate (moderate plaque elevation, scaling and/or erythema)
4 = moderate to severe (marked plaque elevation, scaling and/or erythema)
5 = severe (very marked plaque elevation, scaling and/or erythema)

End point type	Secondary

End point timeframe:

Week 3 of treatment

End point values	LAS41008	Fumaderm®	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	267	273	131	
Units: Percent of patients				
number (not applicable)				
PGA Score 0	0	0	0	
PGA Score 1	0.4	0	0	
PGA Score 2	10.1	11.7	10.7	
PGA Score 3	62.5	60.8	55.7	
PGA Score 4	22.1	24.2	32.1	
PGA Score 5	4.9	3.3	1.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Physician's Global Assessment score at Week 8

End point title	Physician's Global Assessment score at Week 8

End point description:

The Physician's Global Assessment (PGA) is scored as:
0 = clear (no signs of psoriasis (post-inflammatory hyperpigmentation may be present))
1 = almost clear (intermediate between mild and clear)
2 = mild (slight plaque elevation, scaling and/or erythema)
3 = moderate (moderate plaque elevation, scaling and/or erythema)
4 = moderate to severe (marked plaque elevation, scaling and/or erythema)
5 = severe (very marked plaque elevation, scaling and/or erythema)

End point type	Secondary

End point timeframe:

Week 8 of treatment

End point values	LAS41008	Fumaderm®	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	267	273	131	
Units: Percent of patients				
number (not applicable)				
PGA Score 0	0.4	0	0	
PGA Score 1	5.2	7	2.3	
PGA Score 2	31.1	35.2	27.5	
PGA Score 3	48.7	43.6	45	
PGA Score 4	12.4	12.1	23.7	
PGA Score 5	2.2	2.2	1.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Physician's Global Assessment score at Week 16

End point title	Physician's Global Assessment score at Week 16

End point description:

The Physician's Global Assessment (PGA) is scored as:
0 = clear (no signs of psoriasis (post-inflammatory hyperpigmentation may be present))
1 = almost clear (intermediate between mild and clear)
2 = mild (slight plaque elevation, scaling and/or erythema)
3 = moderate (moderate plaque elevation, scaling and/or erythema)
4 = moderate to severe (marked plaque elevation, scaling and/or erythema)
5 = severe (very marked plaque elevation, scaling and/or erythema)

End point type	Secondary

End point timeframe:

Week 16 of treatment

End point values	LAS41008	Fumaderm®	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	267	273	131	
Units: Percent of patients				
number (not applicable)				
PGA Score 0	6.4	7.7	0.8	
PGA Score 1	26.6	29.7	12.2	
PGA Score 2	23.2	25.6	20.6	
PGA Score 3	33.7	26.7	42.7	
PGA Score 4	8.6	8.1	20.6	
PGA Score 5	1.5	2.2	3.1	

Statistical analyses

No statistical analyses for this end point

Secondary: Physician's Global Assessment score 2 months treatment-free

End point title	Physician's Global Assessment score 2 months treatment-free

End point description:

The Physician's Global Assessment (PGA) is scored as:
0 = clear (no signs of psoriasis (post-inflammatory hyperpigmentation may be present))
1 = almost clear (intermediate between mild and clear)
2 = mild (slight plaque elevation, scaling and/or erythema)
3 = moderate (moderate plaque elevation, scaling and/or erythema)
4 = moderate to severe (marked plaque elevation, scaling and/or erythema)
5 = severe (very marked plaque elevation, scaling and/or erythema)

End point type	Secondary

End point timeframe:

2 months treatment-free

End point values	LAS41008	Fumaderm®	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	267	273	131	
Units: Percent of patients				
number (not applicable)				
PGA Score 0	6	7	0	
PGA Score 1	21	23.4	15.3	
PGA Score 2	28.8	28.6	18.3	
PGA Score 3	33	28.6	44.3	
PGA Score 4	9.4	9.9	20.6	
PGA Score 5	1.9	2.6	1.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean % change from baseline in % body surface area (BSA) affected

End point title	Mean % change from baseline in % body surface area (BSA) affected

End point description:

End point type	Secondary

End point timeframe:

Week 3, 8, 16 of treatment and 2 months treatment-free

End point values	LAS41008	Fumaderm®	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	267	273	131	
Units: Percent of BSA				
arithmetic mean (standard deviation)				
Week 3	-0.5 (± 5.02)	-0.5 (± 3.63)	-0.7 (± 4.73)	
Week 8	-4.1 (± 7.56)	-3.5 (± 6.2)	-2.3 (± 7.59)	
Week 16	-13.2 (± 12.07)	-11.3 (± 10.25)	-4.9 (± 10.76)	
2 months treatment-free	-13.5 (± 11.52)	-12.7 (± 10.67)	-7.2 (± 13.22)	

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment success rate

End point title	Treatment success rate

End point description:

Treatment success was defined as patients achieving either a 'clear' or 'almost clear score in the Physician's Global Assessment (PGA) score and/or Psoriasis Area and Severity Index (PASI) 90

End point type	Secondary

End point timeframe:

Week 3, 8, 16 of treatment and 2 months treatment-free

End point values	LAS41008	Fumaderm®	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	267	273	131	
Units: Percent of patients				
number (not applicable)				
Week 3	0.4	0	0	
Week 8	5.6	7	2.3	
Week 16	33.3	38.1	13	
2 months treatment-free	27.5	32.6	15.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Remission rate

End point title	Remission rate

End point description:

The remission rate was defined as a score of 'clear' in the Physician's Global Assessment (PGA) score

End point type	Secondary

End point timeframe:

Week 3, Week 8, Week 16 of treatment and 2 months treatment-free

End point values	LAS41008	Fumaderm®	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	267	273	131	
Units: Percent				
number (not applicable)				
Week 3	0	0	0	
Week 8	0.4	0	0	
Week 16	6.4	7.7	0.8	
2 months treatment-free	6	7	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean time to relapse within 2 months of stopping therapy

End point title	Mean time to relapse within 2 months of stopping therapy

End point description:

Relapse was defined as the event when the achieved maximal improvement from baseline was subsequently reduced by ≥50% based on the Psoriasis Area and Severity Index (PASI)

End point type	Secondary

End point timeframe:

Up to 2 months after stopping therapy

End point values	LAS41008	Fumaderm®	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16[4]	17[5]	16[6]	
Units: Days				
arithmetic mean (standard error)	66.8 (± 0.74)	65 (± 0.72)	59.6 (± 1.65)	

Notes:

[4] - 16/175 patients in the LAS41008 group had a relapse

[5] - 17/179 patients in the Fumaderm® group had a relapse

[6] - 16/68 patients in the placebo group had a relapse

Statistical analyses

No statistical analyses for this end point

Secondary: Time to rebound within 2 months of stopping therapy

End point title	Time to rebound within 2 months of stopping therapy

End point description:

Rebound was defined as worsening of psoriasis over baseline value (Psoriasis Area and Severity Index [PASI]≥125%) or new pustular, erythrodermic or more inflammatory psoriasis occurring within 2 months of stopping therapy

End point type	Secondary

End point timeframe:

Up to 2 months after stopping therapy

End point values	LAS41008	Fumaderm®	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[7]	4[8]	7[9]	
Units: Days				
arithmetic mean (standard error)	63.7 (± 0.4)	64.6 (± 0.36)	62.3 (± 1.12)	

Notes:

[7] - 2/177 patients in the LAS41008 group had a rebound

[8] - 4/183 patients in the Fumaderm® group had a rebound

[9] - 7/75 patients in the placebo group had a rebound

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Benefit Index (PBI) at Week 16 and 2 months treatment-free

End point title	Patient Benefit Index (PBI) at Week 16 and 2 months treatment-free

End point description:

The Patient Benefit Index (PBI) was calculated based on the Patient Need Questionnaire (PNQ) assessed at the start of treatment and on the Patient Benefit Questionnaire (PBQ) assessed after 16 weeks of treatment and during the follow-up period

In the PNQ, patients were asked to indicate how important they considered 25 different treatment goals on a five-point scale from 'not at all' to 'very'
In the PBQ, patients were asked if the study treatment had helped them to achieve these goals

The PBI was calculated by averaging the preference-weighed results of all items

End point type	Secondary

End point timeframe:

Week 16 of treatment and 2 months treatment-free

End point values	LAS41008	Fumaderm®	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	254	260	119	
Units: Score				
arithmetic mean (standard deviation)				
Week 16	2.1 (± 1.25)	2.1 (± 1.24)	1.3 (± 1.1)	
2 months treatment-free	2.4 (± 1.05)	2.4 (± 1.02)	1.5 (± 1.17)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute values and percent change from baseline in Psoriasis Area and Severity Index (PASI) at 6 and 12 months treatment-free

End point title	Absolute values and percent change from baseline in Psoriasis Area and Severity Index (PASI) at 6 and 12 months treatment-free

End point description:

The PASI requires the assessment of erythema (E), infiltration (I), desquamation (D), and body surface area involvement (A) over 4 body regions: head (h), trunk (t), upper (u) and lower (l) extremities
Degree of severity (per body region) for each variable:
0 = no symptom
1 = slight
2 = moderate
3 = marked
4 = very marked
Surface area involved (per body region):
1 = <10%
2 = 10-29%
3 = 30-49%
4 = 50-69%
5 = 70-89%
6 = 90-100%

End point type	Secondary

End point timeframe:

6 and 12 months treatment-free

End point values	LAS41008	Fumaderm®	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	267	273	131	
Units: Score				
arithmetic mean (standard deviation)				
6 months treatment-free (absolute values)	9 (± 6.61)	9.4 (± 8.65)	12 (± 7.36)	
12 months treatment-free (absolute values)	9.4 (± 6.68)	9.5 (± 8.57)	11.8 (± 7.47)	
6 months treatment-free (percent change)	-42.7 (± 41.38)	-44.2 (± 40.6)	-25.2 (± 39.46)	
12 months treatment-free (percent change)	-40.6 (± 41.93)	-43.6 (± 39.19)	-27.5 (± 39.91)	

Statistical analyses

No statistical analyses for this end point

Secondary: Physician's Global Assessment score 6 months treatment-free

End point title	Physician's Global Assessment score 6 months treatment-free

End point description:

The Physician's Global Assessment (PGA) is scored as:
0 = clear (no signs of psoriasis (post-inflammatory hyperpigmentation may be present))
1 = almost clear (intermediate between mild and clear)
2 = mild (slight plaque elevation, scaling and/or erythema)
3 = moderate (moderate plaque elevation, scaling and/or erythema)
4 = moderate to severe (marked plaque elevation, scaling and/or erythema)
5 = severe (very marked plaque elevation, scaling and/or erythema)

End point type	Secondary

End point timeframe:

6 months treatment-free

End point values	LAS41008	Fumaderm®	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	267	273	131	
Units: Percent of patients				
number (not applicable)				
PGA Score 0	3.4	2.9	0	
PGA Score 1	16.9	17.2	10.7	
PGA Score 2	27.3	32.6	22.9	
PGA Score 3	40.1	33.3	43.5	
PGA Score 4	10.1	11.4	21.4	
PGA Score 5	2.2	2.6	1.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Physician's Global Assessment score 12 months treatment-free

End point title	Physician's Global Assessment score 12 months treatment-free

End point description:

The Physician's Global Assessment (PGA) is scored as:
0 = clear (no signs of psoriasis (post-inflammatory hyperpigmentation may be present))
1 = almost clear (intermediate between mild and clear)
2 = mild (slight plaque elevation, scaling and/or erythema)
3 = moderate (moderate plaque elevation, scaling and/or erythema)
4 = moderate to severe (marked plaque elevation, scaling and/or erythema)
5 = severe (very marked plaque elevation, scaling and/or erythema)

End point type	Secondary

End point timeframe:

12 months treatment-free

End point values	LAS41008	Fumaderm®	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	267	273	131	
Units: Percent of patients				
number (not applicable)				
PGA Score 0	2.6	3.7	0	
PGA Score 1	15.4	16.8	9.2	
PGA Score 2	27.3	29.7	26.7	
PGA Score 3	40.8	35.5	41.2	
PGA Score 4	11.6	11.7	21.4	
PGA Score 5	2.2	2.6	1.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean % change from baseline in % body surface area (BSA) affected at 6 and 12 months treatment-free

End point title	Mean % change from baseline in % body surface area (BSA) affected at 6 and 12 months treatment-free

End point description:

End point type	Secondary

End point timeframe:

6 and 12 months treatment-free

End point values	LAS41008	Fumaderm®	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	267	273	131	
Units: Percent of BSA				
arithmetic mean (standard deviation)				
6 months treatment-free	-11.4 (± 11.57)	-9 (± 11.75)	-9.2 (± 13.58)	
12 months treatment-free	-10.2 (± 15.44)	-11 (± 8.65)	-9.2 (± 7.59)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean time to relapse including data up to 12 months treatment-free

End point title	Mean time to relapse including data up to 12 months treatment-free

End point description:

Relapse was defined as the event when the achieved maximal improvement from baseline was

subsequently reduced by ≥50% based on PASI

End point type	Secondary

End point timeframe:

Up to 12 months treatment-free

End point values	LAS41008	Fumaderm®	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54[10]	66[11]	40[12]	
Units: Days				
arithmetic mean (standard error)	377.3 (± 13.04)	354.9 (± 11.99)	226.4 (± 9.54)	

Notes:

[10] - 54/267 patients in the LAS41008 group had a relapse

[11] - 66/273 patients in the Fumaderm® group had a relapse

[12] - 40/131 patients in the placebo group had a relapse

Statistical analyses

No statistical analyses for this end point

Secondary: Dermatology Life Quality Index (DLQI) score

End point title	Dermatology Life Quality Index (DLQI) score

End point description:

The Dermatology Life Quality Index (DLQI) is a patient-reported outcome that also includes assessment of improvement in symptoms such as pruritus
The questionnaire comprises 10 questions (eg, over the last week, how itchy, sore, painful or stinging has your skin been?) relating to symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment
The scoring of each question was as follows:
0 = not at all
1 = a little
2 = a lot
3 = very much
The DLQI was calculated by summing the score for each question, resulting in a maximum of 30 and a minimum of 0

End point type	Secondary

End point timeframe:

Week 16 of treatment and 2, 6 and 12 months treatment-free

End point values	LAS41008	Fumaderm®	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	267	273	131	
Units: Score				
arithmetic mean (standard deviation)				
Week 16	5.4 (± 6.07)	6.1 (± 7.18)	8.5 (± 6.88)	
2 months treatment-free	4.8 (± 5.57)	5.4 (± 6.12)	7.8 (± 5.98)	
6 months treatment-free	5.8 (± 6.66)	6.6 (± 5.77)	7.6 (± 6.33)	
12 months treatment-free	7.8 (± 6.63)	8 (± 6.55)	7 (± 5.96)	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients achieving Psoriasis Area and Severity Index (PASI) 75 at Week 16 by intake of potentially nephrotoxic medicines

End point title	Proportion of patients achieving Psoriasis Area and Severity Index (PASI) 75 at Week 16 by intake of potentially nephrotoxic medicines

End point description:

PASI 75 is a reduction of at least 75% in the Psoriasis Area and Severity Index (PASI)
The PASI requires the assessment of erythema (E), infiltration (I), desquamation (D), and body surface area involvement (A) over 4 body regions: head (h), trunk (t), upper (u) and lower (l) extremities
Degree of severity (per body region) for each variable:
0 = no symptom
1 = slight
2 = moderate
3 = marked
4 = very marked
Surface area involved (per body region):
1 = <10%
2 = 10-29%
3 = 30-49%
4 = 50-69%
5 = 70-89%
6 = 90-100%

End point type	Secondary

End point timeframe:

Week 16 of treatment

End point values	LAS41008	Fumaderm®	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	267	273	131	
Units: Percentage				
number (not applicable)				
Patients using potentially nephrotoxic medicine	39	28	11.8	
Not using potentially nephrotoxic medicine	37.2	43	15.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients achieving Psoriasis Area and Severity Index

(PASI) 75 at Week 16 by age group

End point title	Proportion of patients achieving Psoriasis Area and Severity Index (PASI) 75 at Week 16 by age group

End point description:

PASI 75 is a reduction of at least 75% in the Psoriasis Area and Severity Index (PASI)
The PASI requires the assessment of erythema (E), infiltration (I), desquamation (D), and body surface area involvement (A) over 4 body regions: head (h), trunk (t), upper (u) and lower (l) extremities
Degree of severity (per body region) for each variable:
0 = no symptom
1 = slight
2 = moderate
3 = marked
4 = very marked
Surface area involved (per body region):
1 = <10%
2 = 10-29%
3 = 30-49%
4 = 50-69%
5 = 70-89%
6 = 90-100%

End point type	Secondary

End point timeframe:

Week 16 of treatment

End point values	LAS41008	Fumaderm®	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	267	273	131	
Units: Percentage				
number (not applicable)				
≤35 years	34.4	48.6	20.6	
35 to ≤55 years	36.8	37.3	13.2	
>55 years	42.6	37.7	13.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients achieving a score of 'clear' or 'almost clear' in the Physician's Global Assessment at Week 16 by intake of potentially nephrotoxic medicines

End point title	Proportion of patients achieving a score of 'clear' or 'almost clear' in the Physician's Global Assessment at Week 16 by intake of potentially nephrotoxic medicines

End point description:

The Physician's Global Assessment (PGA) is scored as:
0 = clear (no signs of psoriasis (post-inflammatory hyperpigmentation may be present))
1 = almost clear (intermediate between mild and clear)
2 = mild (slight plaque elevation, scaling and/or erythema)
3 = moderate (moderate plaque elevation, scaling and/or erythema)
4 = moderate to severe (marked plaque elevation, scaling and/or erythema)
5 = severe (very marked plaque elevation, scaling and/or erythema)

End point type	Secondary

End point timeframe:

Week 16 of treatment

End point values	LAS41008	Fumaderm®	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	267	273	131	
Units: Percentage				
number (not applicable)				
Patients using potentially nephrotoxic medicine	34.1	22	5.9	
Not using potentially nephrotoxic medicine	32.7	40.8	14	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients achieving a score of 'clear' or 'almost clear' in the Physician's Global Assessment at Week 16 by age group

End point title	Proportion of patients achieving a score of 'clear' or 'almost clear' in the Physician's Global Assessment at Week 16 by age group

End point description:

The Physician's Global Assessment (PGA) is scored as:
0 = clear (no signs of psoriasis (post-inflammatory hyperpigmentation may be present))
1 = almost clear (intermediate between mild and clear)
2 = mild (slight plaque elevation, scaling and/or erythema)
3 = moderate (moderate plaque elevation, scaling and/or erythema)
4 = moderate to severe (marked plaque elevation, scaling and/or erythema)
5 = severe (very marked plaque elevation, scaling and/or erythema)

End point type	Secondary

End point timeframe:

Week 16 of treatment

End point values	LAS41008	Fumaderm®	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	267	273	131	
Units: Percentage				
number (not applicable)				
Aged ≤35 years	29	48.6	20.6	
Aged >35 to ≤55 years	34	34.5	10.3	
Aged >55 years	36.8	31.1	10.3	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
During the 16 week (± 3 days) treatment period and 12 months (± 10 days) follow-up period	
Adverse event reporting additional description:	
Serious adverse events with onset >30 days after end of treatment were not classified as serious treatment-emergent adverse events	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups	
Reporting group title	LAS41008
Reporting group description:	
Safety analysis set (SAS) defined as all patients who were randomised and received at least one dose of the investigational medicinal product	
Reporting group title	Fumaderm®
Reporting group description:	
Safety analysis set (SAS) defined as all patients who were randomised and received at least one dose of the investigational medicinal product	
Reporting group title	Placebo
Reporting group description:	
Safety analysis set (SAS) defined as all patients who were randomised and received at least one dose of the investigational medicinal product	

Serious adverse events	LAS41008	Fumaderm®	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 279 (3.23%)	8 / 283 (2.83%)	5 / 137 (3.65%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	1 / 279 (0.36%)	0 / 283 (0.00%)	0 / 137 (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
Vascular disorders			
Peripheral artery stenosis			
subjects affected / exposed	0 / 279 (0.00%)	0 / 283 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	2 / 279 (0.72%)	0 / 283 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 279 (0.00%)	0 / 283 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 279 (0.00%)	1 / 283 (0.35%)	0 / 137 (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
Myocardial infarction			
subjects affected / exposed	0 / 279 (0.00%)	1 / 283 (0.35%)	0 / 137 (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
Subendocardial ischaemia			
subjects affected / exposed	0 / 279 (0.00%)	1 / 283 (0.35%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Surgical and medical procedures			
Spinal fusion surgery			
subjects affected / exposed	0 / 279 (0.00%)	1 / 283 (0.35%)	0 / 137 (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
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	0 / 279 (0.00%)	1 / 283 (0.35%)	0 / 137 (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
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 279 (0.36%)	0 / 283 (0.00%)	0 / 137 (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

Pregnancy, puerperium and perinatal conditions			
Ectopic pregnancy			
subjects affected / exposed	1 / 279 (0.36%)	0 / 283 (0.00%)	0 / 137 (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
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 279 (0.36%)	0 / 283 (0.00%)	0 / 137 (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
Gastrointestinal disorders			
Duodenal ulcer			
subjects affected / exposed	1 / 279 (0.36%)	0 / 283 (0.00%)	0 / 137 (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
Gastritis erosive			
subjects affected / exposed	0 / 279 (0.00%)	1 / 283 (0.35%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroduodenitis			
subjects affected / exposed	0 / 279 (0.00%)	1 / 283 (0.35%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia, obstructive			
subjects affected / exposed	0 / 279 (0.00%)	1 / 283 (0.35%)	0 / 137 (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
Psychiatric disorders			
Alcohol abuse			
subjects affected / exposed	1 / 279 (0.36%)	0 / 283 (0.00%)	0 / 137 (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
Bipolar disorder			

subjects affected / exposed	0 / 279 (0.00%)	0 / 283 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	1 / 279 (0.36%)	0 / 283 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 279 (0.00%)	0 / 283 (0.00%)	1 / 137 (0.73%)
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			
Erysipelas			
subjects affected / exposed	0 / 279 (0.00%)	0 / 283 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	LAS41008	Fumaderm®	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	201 / 279 (72.04%)	203 / 283 (71.73%)	60 / 137 (43.80%)
Vascular disorders			
Flushing			
subjects affected / exposed	51 / 279 (18.28%)	44 / 283 (15.55%)	2 / 137 (1.46%)
occurrences (all)	124	90	2
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	25 / 279 (8.96%)	28 / 283 (9.89%)	0 / 137 (0.00%)
occurrences (all)	26	31	0
Eosinophilia			
subjects affected / exposed	25 / 279 (8.96%)	15 / 283 (5.30%)	0 / 137 (0.00%)
occurrences (all)	26	15	0
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	103 / 279 (36.92%)	109 / 283 (38.52%)	20 / 137 (14.60%)
occurrences (all)	151	175	25
Abdominal pain upper			
subjects affected / exposed	56 / 279 (20.07%)	59 / 283 (20.85%)	10 / 137 (7.30%)
occurrences (all)	72	83	10
Abdominal pain			
subjects affected / exposed	54 / 279 (19.35%)	43 / 283 (15.19%)	6 / 137 (4.38%)
occurrences (all)	103	70	8
Nausea			
subjects affected / exposed	30 / 279 (10.75%)	24 / 283 (8.48%)	5 / 137 (3.65%)
occurrences (all)	42	37	5
Flatulence			
subjects affected / exposed	15 / 279 (5.38%)	16 / 283 (5.65%)	7 / 137 (5.11%)
occurrences (all)	18	16	7
Vomiting			
subjects affected / exposed	12 / 279 (4.30%)	17 / 283 (6.01%)	2 / 137 (1.46%)
occurrences (all)	14	18	3
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	24 / 279 (8.60%)	28 / 283 (9.89%)	15 / 137 (10.95%)
occurrences (all)	42	37	16
Erythema			
subjects affected / exposed	26 / 279 (9.32%)	22 / 283 (7.77%)	3 / 137 (2.19%)
occurrences (all)	68	32	3
Skin burning sensation			
subjects affected / exposed	21 / 279 (7.53%)	18 / 283 (6.36%)	3 / 137 (2.19%)
occurrences (all)	49	32	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 October 2012	Concomitant therapy with cytostatics and medications with known harmful influences on the kidneys was prohibited A severe decline in the leukocyte (WBC) count – particularly with parameters below 3000/µL, or other pathological blood count changes or a creatinine increase above normal, were added as examples of adverse events that would constitute possible reasons for premature withdrawal of subjects It was added that during the first three weeks of treatment no dose reductions were possible
07 February 2013	It was clarified that patients could be included with prior therapy with systemic drugs for psoriasis that was discontinued due to an adverse event or insufficient effect It was clarified that male patients except vasectomized males (instead of previously including vasectomized males) had to use contraceptive measures BSA assessments at each follow-up visit were added PGA assessment at screening was added It was clarified that during the first week of treatment with the maintenance dose (week 4) no dose reduction was possible It was clarified that the sponsor reserved the right to modify or terminate the study at any time in agreement with the involved Ethics Committees and Competent Authorities
15 May 2013	Patients taking medications with known harmful influence on the kidneys were now to be included (and not, as previously described, excluded from the study) and a new secondary objective was added to assess safety and efficacy of LAS41008 and Fumaderm® in this subgroup of patients An analysis of the safety and efficacy of LAS41008 and Fumaderm® when administered concomitantly with medicines known to have potential nephrotoxic effects, e.g. angiotensin-converting enzyme, angiotensin II inhibitors and statins was added A more detailed definition of severe renal impairment was added and a more detailed definition of abnormal liver enzymes was added The risk benefit assessment was updated
03 November 2014	Clarification that a full integrated clinical study report was to be written after all patients had completed the 2 month follow up examination and that the 6 month and 12 month follow-up data was to be included in an updated study report after all patients had completed the 12 month follow-up

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported