Clinical trial results:
A 2:1 randomized, double-blinded, placebo-controlled study to evaluate the efficacy and safety of Fumaderm® in young patients aged 10 to 17 years with moderate to severe psoriasis vulgaris (KIFUderm study).

Summary

EudraCT number	2012-000035-82
Trial protocol	DE
Global end of trial date	20 September 2016

Results information

Result version number	v1 (current)
This version publication date	05 April 2017
First version publication date	05 April 2017

Trial information

Trial identification

Sponsor protocol code	027-008

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Biogen GmbH
Sponsor organisation address	Carl-Zeiss-Ring 6, Ismaning, Germany, 85737
Public contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com
Scientific contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 September 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to assess the efficacy and safety of Fumaderm® treatment in patients aged 10 to 17 after 20 weeks compared to placebo.

Protection of trial subjects:

As paediatric subjects do not possess legal right capacity and ability to enter into agreements, fully informed consent was obtained from the parents/legal guardian(s). Subjects and their parents/legal guardians were given adequate time to review the information in the informed consent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study. Through the informed consent process each subject was made aware of the purpose of the study, the procedures, the benefits and risks of the study, the discomforts and the precautions taken. Any side effects or other health issues occurring during the study were followed up by the study doctor. Subjects were able to stop taking part in the study at any time without giving any reason.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 December 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 135
Worldwide total number of subjects	135
EEA total number of subjects	135

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)	23
Adolescents (12-17 years)	112
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 22 study centres in Germany from 20-December 2012 (first patient randomised) to 20 September 2016 (last patient out).

Pre-assignment

Screening details:

In total, 163 patients were screened, resulting in the randomisation of 135 patients, of whom 134 patients received the investigational treatment at least once.
Eligible patients were randomised 2:1 at visit 1 to receive either Fumaderm® Initial / Fumaderm® or matching placebo. All patients received basic therapy for skin care (Basiscreme DAC).

Period 1

Period 1 title	Double-blind Treatment Phase (20 weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Fumaderm/Fumaderm

Arm description:

Participants first received Fumaderm Initial for three weeks, titrating up from one tablet/day in the first week of the study (week 0) to three tablets/day in week 2. Participants were then switched to Fumaderm, and were up-titrated from one tablet/day in the fourth week of the study (week 3) to three tablets/day in week 5. Participants continued to receive 3 tablets/day until week 19, unless they met protocol-specified criteria allowing further up-titration to 4 tablets/day from week 12 onwards.

Arm type	Experimental
Investigational medicinal product name	Fumaderm® Initial
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received one tablet per day in week 0, two tablets per day in week 1 and three tablets per day in week 2 of the study. Each tablet consists of dimethyl fumarate 30 mg, calcium ethyl fumarate 67 mg, magnesium ethyl fumarate 5 mg, and zinc ethyl fumarate 3 mg.

Investigational medicinal product name	Fumaderm®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received one tablet per day in week 3, two tablets per day in week 4 and three tablets per day from week 5 to week 19. After week 12, patients could have been up-titrated to 4 tablets per day if they met criteria defined in the protocol. Each tablet consists of dimethyl fumarate 120 mg, calcium ethyl fumarate 87 mg, magnesium ethyl fumarate 5 mg, and zinc ethyl fumarate 3 mg.

Arm title	Placebo/Fumaderm

Arm description:

Participants received matching placebo tablets for 20 weeks.

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:

Participants received matching placebo tablets.

Number of subjects in period 1	Fumaderm/Fumaderm	Placebo/Fumaderm
Started	91	44
Received Study Drug	91	43
Completed	75	26
Not completed	16	18
Consent withdrawn by subject	3	3
Adverse event, non-fatal	5	2
Other	1	2
Pregnancy	1	-
Lost to follow-up	-	4
Lack of efficacy	6	6
Protocol deviation	-	1

Period 2

Period 2 title	Open-label Treatment Phase (20 weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Fumaderm/Fumaderm

Arm description:

Participants continued to receive Fumaderm at the same dose they had received at the end of the first 20 weeks for another 20 weeks.

Arm type	Experimental
Investigational medicinal product name	Fumaderm®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received three tablets per day for 20 weeks. Each tablet consists of dimethyl fumarate 120 mg, calcium ethyl fumarate 87 mg, magnesium ethyl fumarate 5 mg, and zinc ethyl fumarate 3 mg.

Arm title	Placebo/Fumaderm

Arm description:

At week 20 participants switched from placebo to receive Fumaderm Initial for three weeks, starting at one tablet/day in week 20 and titrating up to three tablets/day in week 22. Participants were then switched to receive Fumaderm, starting at one tablet/day in week 23 and titrating up to three tablets/day in week 25. Participants continued to received 3 tablets/day until week 40, unless they met protocol-specified criteria allowing up-titration to 4 tablets/day from week 32 onwards.

Arm type	Experimental
Investigational medicinal product name	Fumaderm®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received one tablet per day in week 23, two tablets per day in week 24 and three tablets per day from week 25 to week 40. After week 32, patients could have been up-titrated to 4 tablets per day if they met criteria defined in the protocol. Each tablet consists of dimethyl fumarate 120 mg, calcium ethyl fumarate 87 mg, magnesium ethyl fumarate 5 mg, and zinc ethyl fumarate 3 mg.

Investigational medicinal product name	Fumaderm® Initial
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received one tablet per day in week 20, two tablets per day in week 21 and three tablets per day in week 22 during the open-label phase of the study. Each tablet consists of dimethyl fumarate 30 mg, calcium ethyl fumarate 67 mg, magnesium ethyl fumarate 5 mg, and zinc ethyl fumarate 3 mg.

Number of subjects in period 2[1]	Fumaderm/Fumaderm	Placebo/Fumaderm
Started	73	24
Completed	40	8
Not completed	33	16
Consent withdrawn by subject	18	9
Adverse event, non-fatal	3	2
Other	4	3
Lost to follow-up	-	1
Lack of efficacy	7	1
Protocol deviation	1	-

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: Four participants completed the double-blind treatment phase but did not start the open-label treatment phase.

Baseline characteristics

Reporting groups	
Reporting group title	Fumaderm/Fumaderm
Reporting group description:	
Participants first received Fumaderm Initial for three weeks, titrating up from one tablet/day in the first week of the study (week 0) to three tablets/day in week 2. Participants were then switched to Fumaderm, and were up-titrated from one tablet/day in the fourth week of the study (week 3) to three tablets/day in week 5. Participants continued to receive 3 tablets/day until week 19, unless they met protocol-specified criteria allowing further up-titration to 4 tablets/day from week 12 onwards.	
Reporting group title	Placebo/Fumaderm
Reporting group description:	
Participants received matching placebo tablets for 20 weeks.	

Reporting group values	Fumaderm/Fumaderm	Placebo/Fumaderm	Total
Number of subjects	91	44	135
Age categorical Units: Subjects			
Children (2-11 years)	14	9	23
Adolescents (12-17 years)	77	35	112
Age continuous			
Data are reported for the full analysis set population, which included 91 and 43 participants in each treatment group respectively.			
Units: years			
arithmetic mean	14.2	13.9	
standard deviation	± 2.12	± 2.41	-
Gender categorical Units: Subjects			
Female	40	20	60
Male	51	24	75
Race Units: Subjects			
White	86	43	129
Black	0	0	0
Asian	1	1	2
Other	4	0	4
Duration of Psoriasis			
Data are reported for the full analysis set population, which included 91 and 43 participants in each treatment group respectively.			
Units: years			
arithmetic mean	4.84	4.71	
standard deviation	± 4.08	± 3.58	-
Psoriasis Area and Severity Index (PASI) Score			
The Psoriasis Area and Severity Index (PASI) score is a combination of the intensity of psoriasis, assessed by the erythema (reddening), induration (plaque thickness) and desquamation (scaling) on a scale from none (0) to very severe (4), together with the involved skin area rated on a scale from 0 to 6 performed at four body areas, the head, arms, trunk, and legs. The total PASI score ranges from 0 (clear skin) to 72 (most severe psoriasis). Data are reported for the full analysis set population, which included 91 and 43 participants in each treatment group respectively.			
Units: units on a scale			

arithmetic mean	16.77	16.04	
standard deviation	± 7.534	± 7.293	-
Physician Global Assessment (PGA) Score			
The physician’s global assessment (PGA) describes the severity of psoriasis using 7 categories: Score 0 = Clear (no signs of psoriasis (post-inflammatory hyperpigmentation may be present)); Score 1 = Almost clear; Score 2 = Mild; Score 3 = Mild to moderate; Score 4 = Moderate; Score 5 = Moderate to severe; Score 6 = Severe. Data are reported for the full analysis set population, which included 91 and 43 participants in each treatment group respectively.			
Units: units on a scale			
arithmetic mean	4.4	4.3	
standard deviation	± 0.83	± 0.77	-

End points

End points reporting groups

Reporting group title	Fumaderm/Fumaderm
Reporting group description:	
Participants first received Fumaderm Initial for three weeks, titrating up from one tablet/day in the first week of the study (week 0) to three tablets/day in week 2. Participants were then switched to Fumaderm, and were up-titrated from one tablet/day in the fourth week of the study (week 3) to three tablets/day in week 5. Participants continued to receive 3 tablets/day until week 19, unless they met protocol-specified criteria allowing further up-titration to 4 tablets/day from week 12 onwards.	
Reporting group title	Placebo/Fumaderm
Reporting group description:	
Participants received matching placebo tablets for 20 weeks.	
Reporting group title	Fumaderm/Fumaderm
Reporting group description:	
Participants continued to receive Fumaderm at the same dose they had received at the end of the first 20 weeks for another 20 weeks.	
Reporting group title	Placebo/Fumaderm
Reporting group description:	
At week 20 participants switched from placebo to receive Fumaderm Initial for three weeks, starting at one tablet/day in week 20 and titrating up to three tablets/day in week 22. Participants were then switched to receive Fumaderm, starting at one tablet/day in week 23 and titrating up to three tablets/day in week 25. Participants continued to received 3 tablets/day until week 40, unless they met protocol-specified criteria allowing up-titration to 4 tablets/day from week 32 onwards.	

Primary: Proportion of Participants with a 75% Improvement in PASI Score from Baseline (PASI 75) at Week 20

End point title	Proportion of Participants with a 75% Improvement in PASI Score from Baseline (PASI 75) at Week 20
End point description:	
The Psoriasis Area and Severity Index (PASI) score is a combination of the intensity of psoriasis, assessed by the erythema (reddening), induration (plaque thickness) and desquamation (scaling) on a scale from none (0), mild (1), moderate (2), severe (3) or very severe (4), together with the involved skin area rated on a scale from 0 to 6 performed at four body areas, the head, arms, trunk, and legs. The total PASI score ranges from 0 (clear skin) to 72 (most severe psoriasis). The full analysis set was used for this analysis; last observation carried forward imputation was used for participants with missing data.	
End point type	Primary
End point timeframe:	
Baseline and week 20	

End point values	Fumaderm/Fumaderm	Placebo/Fumaderm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	43		
Units: proportion of participants				
number (confidence interval 95%)	0.55 (0.44 to 0.65)	0.19 (0.08 to 0.33)		

Statistical analyses

Statistical analysis title	Primary Analysis

Statistical analysis description:

The PASI 75 responder rate at week 20 was compared using Fisher's exact test at a study-wise two-sided type I error rate of α = 0.0253. 95% confidence intervals (CI) for the rate were calculated according to Clopper & Pearson. Due to testing of two primary endpoints (PASI and PGA) the significance levels for the single tests was adjusted to restrict the familywise error rate to 0.05.

Comparison groups	Placebo/Fumaderm v Fumaderm/Fumaderm
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact
Parameter estimate	Difference in Responder Rates
Point estimate	0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.53

Primary: Proportion of Participants with a Physician's Global Assessment of Clear or Almost Clear at Week 20

End point title	Proportion of Participants with a Physician's Global Assessment of Clear or Almost Clear at Week 20

End point description:

The physician's global assessment (PGA) describes the severity of psoriasis according to the following 7 categories:
Score 0 = Clear (no signs of psoriasis (post-inflammatory hyperpigmentation may be present); Score 1 = Almost clear (intermediate between mild and clear); Score 2 = Mild (slight plaque elevation, scaling, and / or erythema); Score 3 = Mild to moderate (intermediate between moderate and mild); Score 4 = Moderate (moderate plaque elevation, scaling, and / or erythema); Score 5 = Moderate to severe (marked plaque elevation, scaling, and / or erythema); Score 6 = Severe (very marked plaque elevation, scaling, and / or erythema).
The full analysis set was used for this analysis; last observation carried forward imputation was used for participants with missing data.

End point type	Primary

End point timeframe:

Week 20

End point values	Fumaderm/Fumaderm	Placebo/Fumaderm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	43		
Units: proportion of participants				
number (confidence interval 95%)	0.42 (0.32 to 0.53)	0.07 (0.01 to 0.19)		

Statistical analyses

Statistical analysis title	Primary Analysis

Statistical analysis description:

The PGA responder rate at week 20 was compared using Fisher's exact test at a study-wise two-sided type I error rate of α = 0.0253. 95% confidence intervals (CI) for the rate were calculated according to Clopper & Pearson. Due to testing of two primary endpoints (PASI and PGA) the significance levels for the single tests was adjusted to restrict the familywise error rate to 0.05.

Comparison groups	Placebo/Fumaderm v Fumaderm/Fumaderm
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact
Parameter estimate	Difference in Responder Rates
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	0.49

Secondary: Mean PASI Scores Over Time

End point title	Mean PASI Scores Over Time

End point description:

The Psoriasis Area and Severity Index (PASI) score is a combination of the intensity of psoriasis, assessed by the erythema (reddening), induration (plaque thickness) and desquamation (scaling) on a scale from none (0), mild (1), moderate (2), severe (3) or very severe (4), together with the involved skin area rated on a scale from 0 to 6 performed at four body areas, the head, arms, trunk, and legs. The total PASI score ranges from 0 (clear skin) to 72 (most severe psoriasis).
This analysis was performed using the full analysis set population with non-missing data at each time point. Participants in the Fumaderm/Fumaderm treatment group did not have study visits at weeks 26, 28, 30 and 36; "99999" indicates not applicable.

End point type	Secondary

End point timeframe:

Baseline and weeks 2, 4, 6, 8, 10, 12, 16, 20, 22, 24, 26, 28, 30, 32, 36, 40, 46, 52, and 60

End point values	Fumaderm/Fumaderm	Placebo/Fumaderm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	43		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (N = 91, 43)	16.77 (± 7.534)	16.04 (± 7.293)		
Week 2 (N = 89, 42)	15.11 (± 7.844)	15.43 (± 9.326)		
Week 4 (83, 41)	12.41 (± 7.131)	14.91 (± 11.147)		
Week 6 (N = 82, 36)	9.92 (± 6.627)	13.48 (± 11.071)		
Week 8 (N = 75, 34)	8.08 (± 6.125)	12.31 (± 8.761)		
Week 10 (N = 74, 29)	6.74 (± 4.783)	10.68 (± 9.732)		
Week 12 (N = 76, 28)	5.61 (± 4.473)	10 (± 10.872)		
Week 16 (N = 77, 26)	4.34 (± 4.303)	9.3 (± 11.697)		
Week 20 (N = 75, 26)	3.5 (± 3.792)	9.15 (± 11.731)		
Week 22 (N = 71, 23)	3.14 (± 3.627)	9.46 (± 12.433)		
Week 24 (N = 71, 22)	2.68 (± 3.006)	8.07 (± 10.005)		
Week 26 (N = 0, 22)	99999 (± 99999)	6.97 (± 9.916)		
Week 28 (N = 0, 21)	99999 (± 99999)	6.3 (± 8.171)		
Week 30 (N = 0, 20)	99999 (± 99999)	6.45 (± 9.267)		
Week 32 (N = 66, 21)	2.35 (± 2.53)	5.8 (± 8.022)		
Week 36 (N = 0, 19)	99999 (± 99999)	3.04 (± 2.505)		
Week 40 (N = 59, 15)	2.98 (± 3.242)	2.49 (± 1.918)		
Week 46 (N = 46, 10)	3.37 (± 3.259)	3.52 (± 3.524)		
Week 52 (N = 42, 9)	4.82 (± 4.851)	3.44 (± 5.014)		
Week 60 (N = 40, 8)	5.16 (± 5.215)	3.55 (± 3.851)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with a PASI 50 Response Over Time

End point title	Percentage of Participants with a PASI 50 Response Over Time

End point description:

The Psoriasis Area and Severity Index (PASI) score is a combination of the intensity of psoriasis, assessed by the erythema (reddening), induration (plaque thickness) and desquamation (scaling) on a scale from none (0), mild (1), moderate (2), severe (3) or very severe (4), together with the involved skin area rated on a scale from 0 to 6 performed at four body areas, the head, arms, trunk, and legs. The total PASI score ranges from 0 (clear skin) to 72 (most severe psoriasis).
A PASI 50 response is defined as the percentage of participants achieving at least a 50% reduction (improvement) in PASI score from baseline.
The full analysis set was used for this analysis; participants with missing data were counted as non-responders. Participants in the Fumaderm/Fumaderm treatment group did not have study visits at

weeks 26, 28, 30 and 36; "99999" indicates not applicable.

End point type	Secondary

End point timeframe:

Baseline and weeks 2, 4, 6, 8, 10, 12, 16, 20, 22, 24, 26, 28, 30, 32, 36, 40, 46, 52, and 60

End point values	Fumaderm/Fumaderm	Placebo/Fumaderm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	43		
Units: percentage of participants				
number (not applicable)				
Week 2	3.3	2.3		
Week 4	14.3	7		
Week 6	26.4	9.3		
Week 8	42.9	18.6		
Week 10	45.1	27.9		
Week 12	57.1	30.2		
Week 16	68.1	25.6		
Week 20	67	23.3		
Week 22	68.1	2.3		
Week 24	70.3	2.3		
Week 26	99999	11.6		
Week 28	99999	9.3		
Week 30	99999	18.6		
Week 32	68.1	23.3		
Week 36	99999	25.6		
Week 40	57.1	25.6		
Week 46	46.2	11.6		
Week 52	38.5	11.6		
Week 60	34.1	9.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with a PASI 75 Response Over Time

End point title	Percentage of Participants with a PASI 75 Response Over Time

End point description:

The Psoriasis Area and Severity Index (PASI) score is a combination of the intensity of psoriasis, assessed by the erythema (reddening), induration (plaque thickness) and desquamation (scaling) on a scale from none (0), mild (1), moderate (2), severe (3) or very severe (4), together with the involved skin area rated on a scale from 0 to 6 performed at four body areas, the head, arms, trunk, and legs. The total PASI score ranges from 0 (clear skin) to 72 (most severe psoriasis).
A PASI 75 response is defined as the percentage of participants achieving at least a 75% reduction (improvement) in PASI score from baseline.
The full analysis set was used for this analysis; participants with missing data were counted as non-responders. Participants in the Fumaderm/Fumaderm treatment group did not have study visits at weeks 26, 28, 30 and 36; "99999" indicates not applicable.

End point type	Secondary

End point timeframe:

Baseline and weeks 2, 4, 6, 8, 10, 12, 16, 20, 22, 24, 26, 28, 30, 32, 36, 40, 46, 52, and 60

End point values	Fumaderm/Fumaderm	Placebo/Fumaderm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	43		
Units: percentage of participants				
number (not applicable)				
Week 2	1.1	0		
Week 4	4.4	0		
Week 6	9.9	0		
Week 8	18.7	4.7		
Week 10	25.3	2.3		
Week 12	35.2	14		
Week 16	45.1	14		
Week 20	52.7	18.6		
Week 22	52.7	2.3		
Week 24	54.9	2.3		
Week 26	99999	4.7		
Week 28	99999	4.7		
Week 30	99999	4.7		
Week 32	59.3	4.7		
Week 36	99999	14		
Week 40	46.2	11.6		
Week 46	31.9	9.3		
Week 52	23.1	7		
Week 60	22	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with a PASI 90 Response Over Time

End point title	Percentage of Participants with a PASI 90 Response Over Time

End point description:

The Psoriasis Area and Severity Index (PASI) score is a combination of the intensity of psoriasis, assessed by the erythema (reddening), induration (plaque thickness) and desquamation (scaling) on a scale from none (0), mild (1), moderate (2), severe (3) or very severe (4), together with the involved skin area rated on a scale from 0 to 6 performed at four body areas, the head, arms, trunk, and legs. The total PASI score ranges from 0 (clear skin) to 72 (most severe psoriasis).
A PASI 90 response is defined as the percentage of participants achieving at least a 90% reduction (improvement) in PASI score from baseline.
The full analysis set was used for this analysis; participants with missing data were counted as non-responders. Participants in the Fumaderm/Fumaderm treatment group did not have study visits at weeks 26, 28, 30 and 36; "99999" indicates not applicable.

End point type	Secondary

End point timeframe:

Baseline and weeks 2, 4, 6, 8, 10, 12, 16, 20, 22, 24, 26, 28, 30, 32, 36, 40, 46, 52, and 60

End point values	Fumaderm/Fumaderm	Placebo/Fumaderm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	43		
Units: percentage of participants				
number (not applicable)				
Week 2	0	0		
Week 4	1.1	0		
Week 6	3.3	0		
Week 8	5.5	0		
Week 10	8.8	2.3		
Week 12	16.5	2.3		
Week 16	26.4	9.3		
Week 20	31.9	4.7		
Week 22	35.2	0		
Week 24	38.5	0		
Week 26	99999	0		
Week 28	99999	0		
Week 30	99999	0		
Week 32	31.9	0		
Week 36	99999	2.3		
Week 40	30.8	2.3		
Week 46	18.7	2.3		
Week 52	15.4	2.3		
Week 60	14.3	4.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with a Physician’s Global Assessment of Clear or Almost Clear Over Time

End point title	Percentage of Participants with a Physician’s Global Assessment of Clear or Almost Clear Over Time

End point description:

The physician’s global assessment (PGA) describes the severity of psoriasis according to the following 7 categories:
Score 0 = Clear (no signs of psoriasis (post-inflammatory hyperpigmentation may be present); Score 1 = Almost clear (intermediate between mild and clear); Score 2 = Mild (slight plaque elevation, scaling, and / or erythema); Score 3 = Mild to moderate (intermediate between moderate and mild); Score 4 = Moderate (moderate plaque elevation, scaling, and / or erythema); Score 5 = Moderate to severe (marked plaque elevation, scaling, and / or erythema); Score 6 = Severe (very marked plaque elevation, scaling, and / or erythema).
The full analysis set was used for this analysis; participants with missing data were counted as non-responders. Participants in the Fumaderm/Fumaderm treatment group did not have study visits at weeks 26, 28, 30 and 36; "99999" indicates not applicable.

End point type	Secondary

End point timeframe:

Weeks 2, 4, 6, 8, 10, 12, 16, and 20

End point values	Fumaderm/Fumaderm	Placebo/Fumaderm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	43		
Units: percentage of participants				
number (not applicable)				
Week 2	1.1	0		
Week 4	3.3	0		
Week 6	5.5	0		
Week 8	9.9	0		
Week 10	17.6	2.3		
Week 12	23.1	7		
Week 16	34.1	7		
Week 20	41.8	7		
Week 22	38.5	4.7		
Week 24	45.1	4.7		
Week 26	99999	7		
Week 28	99999	9.3		
Week 30	99999	16.3		
Week 32	44	18.6		
Week 36	99999	14		
Week 40	33	14		
Week 46	23.1	14		
Week 52	14.3	14		
Week 60	11	11.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Children's Dermatology Life Quality Index Scores Over Time

End point title	Mean Children's Dermatology Life Quality Index Scores Over Time

End point description:

The Children's Dermatology Life Quality Index (CDLQI) was completed by study participants who were younger than 17 years old at screening. The questionnaire consists of 10 questions addressing disease-related quality of life over the last week. Each question is answered on a scale from 0 (not at all) to 3 (very much). The total score is calculated by summing the scores from each question and ranges from 0 to 30; the higher the score, the more quality of life is impaired.
This analysis was performed using the full analysis set population aged 10-16 with non-missing data at each time point. Participants in the Fumaderm/Fumaderm treatment group did not have study visits at weeks 26, 28, 30 and 36; "99999" indicates not applicable.

End point type	Secondary

End point timeframe:

Baseline and weeks 2, 4, 6, 8, 10, 12, 16, 20, 22, 24, 26, 28, 30, 32, 36, 40, 46, 52, and 60

End point values	Fumaderm/Fumaderm	Placebo/Fumaderm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76[1]	34[2]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (N = 76, 34)	9.89 (± 6.636)	9.59 (± 7.007)		
Week 2 (N = 74, 34)	8.42 (± 6.387)	8.79 (± 7.277)		
Week 4 (N = 71, 33)	7.87 (± 6.622)	7.73 (± 6.043)		
Week 6 (N = 70, 29)	6.94 (± 6.225)	8 (± 6.285)		
Week 8 (N = 63, 27)	5.89 (± 6.07)	6.52 (± 5.944)		
Week 10 (N = 63, 24)	4.22 (± 4.794)	6.29 (± 5.812)		
Week 12 (N = 65, 21)	3.74 (± 4.331)	6.48 (± 5.501)		
Week 16 (N = 65, 21)	3.52 (± 4.213)	6.62 (± 5.757)		
Week 20 (N = 64, 21)	2.89 (± 4.056)	6.95 (± 5.643)		
Week 22 (N = 59, 19)	2.58 (± 3.692)	7 (± 7.055)		
Week 24 (N = 61, 18)	2.28 (± 3.513)	5.28 (± 5.571)		
Week 26 (N = 0, 18)	99999 (± 99999)	4.33 (± 5.145)		
Week 28 (N = 0, 17)	99999 (± 99999)	4.41 (± 4.345)		
Week 30 (N = 0, 17)	99999 (± 99999)	4.29 (± 4.058)		
Week 32 (N = 56, 18)	2.34 (± 3.9)	3.72 (± 3.478)		
Week 36 (N = 0, 17)	99999 (± 99999)	3.29 (± 3.158)		
Week 40 (N = 51, 13)	2.86 (± 5.056)	3.92 (± 3.013)		
Week 46 (N = 40, 9)	2.18 (± 3.129)	5.22 (± 4.522)		
Week 52 (N = 37, 8)	2.57 (± 3.678)	3.88 (± 3.758)		
Week 60 (N = 35, 7)	3.31 (± 5.661)	4.57 (± 3.309)		

Notes:

[1] - Participants age 10 to 16 years at screening

[2] - Participants age 10 to 16 years at screening

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Dermatology Life Quality Index Scores Over Time

End point title	Mean Dermatology Life Quality Index Scores Over Time

End point description:

The Dermatology Life Quality Index (DLQI) was completed by participants who were 17 years or older at screening. The DLQI consists of 10 questions addressing disease-related quality of life during the last 7 days. Each question is answered on a scale from 0 (not at all) to 3 (very much). The total score is calculated by summing the scores from each question and ranges from 0 to 30; the higher the score, the more quality of life is impaired.
The analysis was conducted using the full analysis set aged 17 with non-missing data at each time point. Participants in the Fumaderm/Fumaderm treatment group did not have study visits at weeks 26, 28, 30 and 36; "99999" indicates not applicable.

End point type	Secondary

End point timeframe:

Baseline and weeks 2, 4, 6, 8, 10, 12, 16, 20, 22, 24, 26, 28, 30, 32, 36, 40, 46, 52, and 60

End point values	Fumaderm/Fumaderm	Placebo/Fumaderm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14[3]	9[4]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (N = 14, 9)	9.21 (± 3.806)	10.44 (± 6.425)		
Week 2 (N = 13, 7)	7.92 (± 3.861)	10.14 (± 8.03)		
Week 4 (N = 12, 8)	7.5 (± 3.802)	9.5 (± 8.071)		
Week 6 (N = 12, 7)	5.83 (± 3.157)	6.43 (± 5.682)		
Week 8 (N = 11, 6)	6.36 (± 4.589)	6.17 (± 6.178)		
Week 10 (N = 12, 5)	5.5 (± 4.815)	6 (± 6.205)		
Week 12 (N = 12, 5)	4.33 (± 4.716)	6.8 (± 6.686)		
Week 16 (N = 11, 5)	2.82 (± 3.401)	6.4 (± 7.021)		
Week 20 (N = 10, 5)	1.3 (± 2.263)	7.4 (± 6.841)		
Week 22 (N = 11, 4)	2 (± 3.194)	7.5 (± 7.55)		
Week 24 (N = 10, 4)	2 (± 3.333)	7.25 (± 8.139)		
Week 26 (N = 0, 4)	99999 (± 99999)	7.25 (± 8.261)		
Week 28 (N = 0, 3)	99999 (± 99999)	8 (± 6.557)		
Week 30 (N = 0, 3)	99999 (± 99999)	8 (± 6)		
Week 32 (N = 9, 3)	0.89 (± 1.691)	8.67 (± 6.658)		
Week 36 (N = 0, 2)	99999 (± 9999)	14 (± 7.071)		
Week 40 (N = 8, 2)	1.38 (± 1.598)	14 (± 7.071)		
Week 46 (N = 6, 1)	0.67 (± 0.816)	5 (± 99999)		
Week 52 (N = 4, 1)	0.5 (± 0.577)	3 (± 99999)		
Week 60 (N = 5, 1)	0.6 (± 0.548)	9 (± 99999)		

Notes:

[3] - Participants age 17 years at screening

[4] - Participants age 17 years at screening

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Phase 1 (double-blind treatment phase): 20 weeks
Phase 2 (open-label treatment phase plus follow-up phase): 40 weeks

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Phase 1: Fumaderm

Reporting group description:

Participants first received Fumaderm Initial for three weeks, titrating up from one tablet/day in the first week of the study (week 0) to three tablets/day in week 2. Participants were then switched to Fumaderm, and were up-titrated from one tablet/day in the fourth week of the study (week 3) to three tablets/day in week 5. Participants continued to receive 3 tablets/day until week 19, unless they met protocol-specified criteria allowing further up-titration to 4 tablets/day from week 12 onwards.

Reporting group title	Phase 1: Placebo

Reporting group description:

Participants received matching placebo tablets for 20 weeks.

Reporting group title	Phase 2: Fumaderm/Fumaderm

Reporting group description:

Participants continued to receive Fumaderm at the same dose received at the end of the first 20 weeks for another 20 weeks.

Reporting group title	Phase 2: Placebo/Fumaderm

Reporting group description:

At week 20 participants switched from placebo to receive Fumaderm Initial for three weeks, starting at one tablet/day in week 20 and titrating up to three tablets/day in week 22. Participants were then switched to receive Fumaderm, starting at one tablet/day in week 23 and titrating up to three tablets/day in week 25. Participants continued to received 3 tablets/day until week 40, unless they met protocol-specified criteria allowing up-titration to 4 tablets/day from week 32 onwards.

Serious adverse events	Phase 1: Fumaderm	Phase 1: Placebo	Phase 2: Fumaderm/Fumaderm
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 91 (9.89%)	3 / 43 (6.98%)	7 / 91 (7.69%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Urobilinogen urine increased			
subjects affected / exposed	1 / 91 (1.10%)	0 / 43 (0.00%)	0 / 91 (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
Injury, poisoning and procedural complications			

Concussion			
subjects affected / exposed	0 / 91 (0.00%)	0 / 43 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral injury			
subjects affected / exposed	0 / 91 (0.00%)	0 / 43 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			
subjects affected / exposed	0 / 91 (0.00%)	0 / 43 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament rupture			
subjects affected / exposed	1 / 91 (1.10%)	0 / 43 (0.00%)	0 / 91 (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
Meniscus lesion			
subjects affected / exposed	1 / 91 (1.10%)	0 / 43 (0.00%)	0 / 91 (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
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 91 (0.00%)	0 / 43 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 91 (0.00%)	0 / 43 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 91 (1.10%)	0 / 43 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 91 (0.00%)	0 / 43 (0.00%)	0 / 91 (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
Constipation			
subjects affected / exposed	0 / 91 (0.00%)	1 / 43 (2.33%)	0 / 91 (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
Vomiting			
subjects affected / exposed	1 / 91 (1.10%)	0 / 43 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	1 / 91 (1.10%)	0 / 43 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Nasal septum deviation			
subjects affected / exposed	1 / 91 (1.10%)	0 / 43 (0.00%)	0 / 91 (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
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	3 / 91 (3.30%)	3 / 43 (6.98%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 3	0 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 91 (1.10%)	0 / 43 (0.00%)	0 / 91 (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			

Muscular weakness			
subjects affected / exposed	0 / 91 (0.00%)	0 / 43 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 91 (0.00%)	0 / 43 (0.00%)	1 / 91 (1.10%)
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			
Abscess jaw			
subjects affected / exposed	0 / 91 (0.00%)	0 / 43 (0.00%)	0 / 91 (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
Nasopharyngitis			
subjects affected / exposed	0 / 91 (0.00%)	0 / 43 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase 2: Placebo/Fumaderm		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 43 (4.65%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Investigations			
Urobilinogen urine increased			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Craniocerebral injury			

subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Forearm fracture			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ligament rupture			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Meniscus lesion			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Constipation			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Nasal septum deviation			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			

subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess jaw			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nasopharyngitis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Phase 1: Fumaderm	Phase 1: Placebo	Phase 2: Fumaderm/Fumaderm
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 91 (90.11%)	36 / 43 (83.72%)	59 / 91 (64.84%)
Vascular disorders			
Flushing			
subjects affected / exposed	33 / 91 (36.26%)	5 / 43 (11.63%)	15 / 91 (16.48%)
occurrences (all)	69	5	41
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	1 / 91 (1.10%)	0 / 43 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 91 (5.49%)	1 / 43 (2.33%)	1 / 91 (1.10%)
occurrences (all)	6	1	1
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 91 (1.10%)	2 / 43 (4.65%)	1 / 91 (1.10%)
occurrences (all)	1	2	1
Respiratory, thoracic and mediastinal			

disorders			
Cough			
subjects affected / exposed	6 / 91 (6.59%)	7 / 43 (16.28%)	4 / 91 (4.40%)
occurrences (all)	6	10	4
Oropharyngeal pain			
subjects affected / exposed	5 / 91 (5.49%)	4 / 43 (9.30%)	3 / 91 (3.30%)
occurrences (all)	6	4	3
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 91 (0.00%)	2 / 43 (4.65%)	0 / 91 (0.00%)
occurrences (all)	0	2	0
Joint injury			
subjects affected / exposed	0 / 91 (0.00%)	2 / 43 (4.65%)	0 / 91 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 91 (18.68%)	10 / 43 (23.26%)	7 / 91 (7.69%)
occurrences (all)	22	15	10
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	6 / 91 (6.59%)	2 / 43 (4.65%)	0 / 91 (0.00%)
occurrences (all)	6	2	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 91 (1.10%)	2 / 43 (4.65%)	0 / 91 (0.00%)
occurrences (all)	1	2	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	27 / 91 (29.67%)	6 / 43 (13.95%)	8 / 91 (8.79%)
occurrences (all)	42	10	12
Diarrhoea			
subjects affected / exposed	26 / 91 (28.57%)	3 / 43 (6.98%)	6 / 91 (6.59%)
occurrences (all)	34	3	7
Abdominal pain			
subjects affected / exposed	21 / 91 (23.08%)	4 / 43 (9.30%)	5 / 91 (5.49%)
occurrences (all)	35	6	5
Nausea			

subjects affected / exposed	18 / 91 (19.78%)	5 / 43 (11.63%)	0 / 91 (0.00%)
occurrences (all)	22	7	0
Vomiting			
subjects affected / exposed	9 / 91 (9.89%)	2 / 43 (4.65%)	1 / 91 (1.10%)
occurrences (all)	10	2	1
Abdominal discomfort			
subjects affected / exposed	4 / 91 (4.40%)	0 / 43 (0.00%)	0 / 91 (0.00%)
occurrences (all)	5	0	0
Toothache			
subjects affected / exposed	0 / 91 (0.00%)	3 / 43 (6.98%)	0 / 91 (0.00%)
occurrences (all)	0	3	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	6 / 91 (6.59%)	3 / 43 (6.98%)	2 / 91 (2.20%)
occurrences (all)	6	5	3
Acne			
subjects affected / exposed	0 / 91 (0.00%)	3 / 43 (6.98%)	2 / 91 (2.20%)
occurrences (all)	0	3	2
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	6 / 91 (6.59%)	1 / 43 (2.33%)	3 / 91 (3.30%)
occurrences (all)	6	1	4
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	6 / 91 (6.59%)	1 / 43 (2.33%)	1 / 91 (1.10%)
occurrences (all)	9	1	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	36 / 91 (39.56%)	13 / 43 (30.23%)	29 / 91 (31.87%)
occurrences (all)	51	20	49
Gastrointestinal infection			
subjects affected / exposed	1 / 91 (1.10%)	2 / 43 (4.65%)	2 / 91 (2.20%)
occurrences (all)	1	2	2
Cystitis			
subjects affected / exposed	2 / 91 (2.20%)	2 / 43 (4.65%)	2 / 91 (2.20%)
occurrences (all)	2	2	2

Gastroenteritis			
subjects affected / exposed	1 / 91 (1.10%)	0 / 43 (0.00%)	0 / 91 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 91 (0.00%)	2 / 43 (4.65%)	0 / 91 (0.00%)
occurrences (all)	0	2	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 91 (1.10%)	3 / 43 (6.98%)	0 / 91 (0.00%)
occurrences (all)	1	3	0

Non-serious adverse events	Phase 2: Placebo/Fumaderm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 43 (53.49%)		
Vascular disorders			
Flushing			
subjects affected / exposed	9 / 43 (20.93%)		
occurrences (all)	21		
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			

subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Joint injury			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	5		
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	4		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	15		
Diarrhoea			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	9		
Abdominal pain			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	8		
Nausea			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Vomiting			

subjects affected / exposed occurrences (all) Abdominal discomfort subjects affected / exposed occurrences (all) Toothache subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1 2 / 43 (4.65%) 2 0 / 43 (0.00%) 0		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) Acne subjects affected / exposed occurrences (all)	 0 / 43 (0.00%) 0 1 / 43 (2.33%) 1		
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	 2 / 43 (4.65%) 3		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	 1 / 43 (2.33%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Gastrointestinal infection subjects affected / exposed occurrences (all) Cystitis subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all)	 9 / 43 (20.93%) 10 1 / 43 (2.33%) 1 0 / 43 (0.00%) 0 2 / 43 (4.65%) 2		

Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 February 2013	The amendment included the following changes: • Change of 2 exclusion criteria: 1. Exclusion of topical therapy with Vitamin D3 analogues, dithranol, corticosteroids or any other topical treatment of psoriasis was changed from 1 month to within 2 weeks prior to study start or during the study. 2. The wording of the exclusion for patient or patient's parents relationship to site personnel was updated. • The procedure for SAE follow-up reporting in the eCRF was changed: Follow-up information has to be sent to Sponsor's Drug Safety department by updating the SAE report form for this specific SAE in eCRF and checking a tickbox that this is a follow-up to the previously reported SAE.
04 April 2014	The amendment included the following changes: • The approximate Duration of Study was increased from 30 months to 46 months. Synopsis: "The study is estimated to have duration of approximately 46 months from FPI to LPO. Competitive enrolment is planned. Enrolment will cease if the target number of patients is reached." • In the inclusion criteria "a history of psoriasis vulgaris" was added to the definition of moderate to severe psoriasis vulgaris. • A new exclusion criteria "Values of lymphocytes and leukocytes below the normal range" was added. • Exclusion criteria "Differential blood count outside the normal range" was changed to "Remaining differential blood counts outside the normal range if judged as clinically significant." • Exclusion criteria "Platelet count outside the normal range" was changed to "Platelet count outside the normal range if judged as clinically significant." • Serum creatinine exclusion criteria were changed to "serum creatinine > upper limit of normal (ULN), reduced creatinine-clearance (calculated) (if the calculated creatinine clearance is reduced with a normal serum creatinine, undertake a 12 h urine collection and re-test the creatinine clearance in this sample)." • Abnormal values of lymphocytes or leukocytes was removed from Gamma-GT exclusion criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported