Clinical trial results:
Open clinical study to assess long-term efficacy and safety of dimethyl fumarate in adults with moderate to severe chronic plaque psoriasis in real practice (DIMESKIN 1 Trial)

Summary

EudraCT number	2017-001368-40
Trial protocol	ES
Global end of trial date	02 April 2020

Results information

Result version number	v1 (current)
This version publication date	09 April 2022
First version publication date	09 April 2022

Trial information

Trial identification

Sponsor protocol code	M-41008-41

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Almirall S.A.
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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	07 September 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of dimethylfumarate (DMF) at treatment week 24 by reducing at least 75% in the Psoriasis Area and Severity Index (PASI75) compared to baseline in adults with moderate to severe chronic plaque psoriasis.

Protection of trial subjects:

The present clinical trial was conducted in accordance with the protocol, the principles established in the revised version of the Declaration of Helsinki concerning medical research involving human subjects (64th General Assembly, Fortaleza, Brazil, 2013), and the International Conference on Harmonization (ICH) Tripartite Harmonized Standards for Good Clinical Practice 1996. It was also conducted in accordance with applicable regulatory requirements, in particular Royal Decree 1090/2015 and Regulation (EU) 536/2014, regulating clinical trials with medicinal products in Spain and the European Union, respectively, and Law 14/2007, concerning biomedical research. By signing the protocol, the investigators agreed to follow the instructions and procedures described therein and therefore to comply with the GCP principles on which it is based. The study began once CEIm and AEMPS approval was obtained. The informed consent of each subject was freely given prior to participation in the clinical trial, either in writing or orally in front of witnesses. The study personnel involved in the conduct of this trial were sufficiently qualified by education, training, and experience to perform their assigned tasks. This trial did not use the services of personnel who had been sanctioned/suspended for scientific fraud or clinical malpractice.

Background therapy:

No other therapies, (other than the subject's usual treatments which do not fall in the non-inclusion criteria defined in the protocol), were administered in the framework of the study.

Evidence for comparator:

This is a single arm, a non-comparative study carried out in real clinical situation.

Actual start date of recruitment	12 September 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 282
Worldwide total number of subjects	282
EEA total number of subjects	282

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)	258
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patient recruitment for the study was conducted between October 2017 and March 2019. A total of 300 patients were recruited in 36 Spanish centers, of which 18 were considered a selection failure.

Pre-assignment

Screening details:

Patients recruited in the study had a moderate to severe psoriasis (defined as PASI ≥ 10 or BSA ≥ 10 and PASI ≥ 5 or DLQI ≥ 10 and PASI ≥ 5), a diagnosis of chronic plaque psoriasis at least 6 months before, a good and stable medical condition for the clinical trial conduction, and were suitable subjects for systemic treatment of psoriasis.

Period 1

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

Arms

Arm title	DMF (Skilarence)

Arm description:

The patients included in the clinical trial received Dimethyl fumarate (DMF) as stated in the datasheet, with gradual dose increments during the first 9 weeks.

Arm type	Experimental
Investigational medicinal product name	Dimethyl fumarate (DMF)
Investigational medicinal product code	624-49-7
Other name	Skilarance
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Each gastro-resistant tablet contains 30 mg or 120g of DMF, and 34.2 and 136.8 mg of lactose as excipient, respectively. In the first week patients took one 30 mg DMF tablet once a day; in the second week one 30 mg DMF tablet twice a day; and in the third week of treatment one 30 mg DMF tablet three times a day. They switched to one 120 mg DMF tablet once a day in the fourth week of treatment. After that, the dose was increased by one 120 mg DMF tablet per week for the next 5 weeks, reaching a maximum dose of 720 mg per day.

Number of subjects in period 1	DMF (Skilarence)
Started	282
Week 24	169
Completed	77
Not completed	205
Adverse event, serious fatal	1
Consent withdrawn by subject	48
Physician decision	7
Adverse event, non-fatal	104
More than 7 days without follow-up	1

Patient's decision	4
Lost to follow-up	11
Protocol deviation	17
Lack of efficacy	12

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial
Reporting group description:	
Patients who took at least one dose of study medication. It is also the safety population.	

Reporting group values	Overall trial	Total	
Number of subjects	282	282	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	258	258	
From 65-84 years	24	24	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	46.5		
standard deviation	± 13.0	-	
Gender categorical Units: Subjects			
Female	97	97	
Male	185	185	
Race Units: Subjects			
Caucasian	271	271	
Asian	3	3	
Arab	4	4	
Hispanic	4	4	
Type of psoriasis at diagnosis Units: Subjects			
Plaque psoriasis	274	274	
Guttate psoriasis	6	6	
Pustular psoriasis	2	2	
Last previous treatment received Units: Subjects			
Topical + systemic + phototherapy	75	75	
Topical + systemic	69	69	
Topical + phototherapy	36	36	
Systemic + phototherapy	5	5	
Topical	73	73	
Systemic	9	9	

Phototherapy	2	2	
None	13	13	
Last previous topical and systemic treatment Units: Subjects			
Acitretin	6	6	
Acitretin + Corticosteroids + D vitamin analogues	1	1	
D vitamin analogues	4	4	
Cyclosporine	15	15	
Cyclosporine +Corticosteroids +D vitamin analogues	2	2	
Corticosteroids	33	33	
Corticosteroids + A vitamin analogues	1	1	
Corticosteroids+A vitamin analogues+salicylic acid	1	1	
Corticosteroids + D vitamin analogues	124	124	
Corticosteroids + D vitamin analogues + Ebastina	1	1	
Corticosteroids+D vitamin analogues+Other topicals	7	7	
Corticosteroids+D vitamin analogues+Salicylic acid	13	13	
CS+D vitamin anologues+Salicylic acid+Gentamicin	1	1	
Corticosteroids + Pimecrolimus	2	2	
Corticosteroids + Salicylic acid	4	4	
Difur	1	1	
Emollients	1	1	
Methotrexate	27	27	
Methotrexate + Corticosteroids	2	2	
Methotrexate +Corticosteroids +D vitamin analogues	8	8	
Methotrexate+CS+D vitamin anologues+Other topicals	2	2	
Methotrexate+CS+D vitamin anologues+Salicylic acid	1	1	
Methotrexate + Salicylic acid	1	1	
Other unknown topical treatment	1	1	
Prednisone	2	2	
Salicylic acid formulations	3	3	
None	15	15	
Not available	3	3	
Last previous phototherapy received Units: Subjects			
PUVA + UVB	16	16	
PUVA	22	22	
UVB	80	80	
None	161	161	
Not available	3	3	
Baseline PGA			
There is one patient with no information on PGA at screening, baseline, or subsequent visits.			
Units: Subjects			
Mild	12	12	

Moderate	193	193	
Moderate-severe	72	72	
Severe	4	4	
Not available	1	1	
Body mass index (BMI)			
Units: Kg/m2			
arithmetic mean	27.9		
standard deviation	± 4.9	-	
Time since diagnosis			
Units: Years			
arithmetic mean	18.1		
standard deviation	± 13.5	-	
Number of relapses in the previous year			
Units: number			
arithmetic mean	2.1		
standard deviation	± 2.5	-	
No. of visits to dermatologist in the last 6 months			
Units: number			
arithmetic mean	2.4		
standard deviation	± 1.4	-	
Weight			
Units: Kg			
arithmetic mean	80.2		
standard deviation	± 16.0	-	
Height			
Units: meters			
arithmetic mean	1.7		
standard deviation	± 0.1	-	
Number of systemic treatments per patient			
Units: number			
arithmetic mean	1.4		
standard deviation	± 2.0	-	
No. of different systemic treatments per patient			
The "other" category has been counted as a single different treatment.			
Units: number			
arithmetic mean	0.9		
standard deviation	± 1.0	-	
Baseline PASI			
In 2 patients, without baseline PASI, the information was completed with the screening visit.			
Units: Score			
arithmetic mean	13.3		
standard deviation	± 5.7	-	
Baseline BSA			
One patient has not indicated a BSA value at either the baseline or screening visit, but has information available at subsequent visits.			
Units: Score			
arithmetic mean	17.4		
standard deviation	± 11.8	-	
Baseline DLQI			
Units: Score			

arithmetic mean	12.2		
standard deviation	± 7.3	-	
Baseline pruritus EVA			
Units: Score			
arithmetic mean	6.9		
standard deviation	± 2.4	-	

Subject analysis sets	
Subject analysis set title	DMF (ITTm)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Those patients who took the medication and had at least one PASI measurement after the baseline visit.	
Subject analysis set title	DMF (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Those patients who met the selection criteria, took the medication and had at least one PASI measurement after the baseline visit.	
Subject analysis set title	DMF (PP)
Subject analysis set type	Per protocol
Subject analysis set description:	
Those patients who took the corresponding medication and for whom all the requested information was available without significant deviations from the protocol.	
Subject analysis set title	Statistical analysis
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
This is a single-arm study. Unfortunately, this EudraCT form cannot accommodate for this type of study. Hence, this subgroup has been artificially created for statistical analysis in some endpoints.	

Reporting group values	DMF (ITTm)	DMF (ITT)	DMF (PP)
Number of subjects	274	264	156
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	250		
From 65-84 years	24		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	46.6		
standard deviation	± 13.0	±	±
Gender categorical			
Units: Subjects			
Female	93		
Male	181		

Race Units: Subjects			
Caucasian	263		
Asian	3		
Arab	4		
Hispanic	4		
Type of psoriasis at diagnosis Units: Subjects			
Plaque psoriasis	266		
Guttate psoriasis	6		
Pustular psoriasis	2		
Last previous treatment received Units: Subjects			
Topical + systemic + phototherapy	73		
Topical + systemic	69		
Topical + phototherapy	34		
Systemic + phototherapy	4		
Topical	70		
Systemic	9		
Phototherapy	2		
None	13		
Last previous topical and systemic treatment Units: Subjects			
Acitretin	6		
Acitretin + Corticosteroids + D vitamin analogues	1		
D vitamin analogues	4		
Cyclosporine	14		
Cyclosporine +Corticosteroids +D vitamin analogues	2		
Corticosteroids	30		
Corticosteroids + A vitamin analogues	1		
Corticosteroids+A vitamin analogues+salicylic acid	1		
Corticosteroids + D vitamin analogues	121		
Corticosteroids + D vitamin analogues + Ebastina	1		
Corticosteroids+D vitamin analogues+Other topicals	7		
Corticosteroids+D vitamin analogues+Salicylic acid	13		
CS+D vitamin anologues+Salicylic acid+Gentamicin	1		
Corticosteroids + Pimecrolimus	2		
Corticosteroids + Salicylic acid	4		
Difur	1		
Emollients	1		
Methotrexate	27		
Methotrexate + Corticosteroids	2		
Methotrexate +Corticosteroids +D vitamin analogues	8		

Methotrexate+CS+D vitamin anologues+Other topicals	2		
Methotrexate+CS+D vitamin anologues+Salicylic acid	1		
Methotrexate + Salicylic acid	1		
Other unknown topical treatment	1		
Prednisone	2		
Salicylic acid formulations	2		
None	15		
Not available	3		
Last previous phototherapy received			
Units: Subjects			
PUVA + UVB	14		
PUVA	21		
UVB	78		
None	158		
Not available	3		
Baseline PGA			
There is one patient with no information on PGA at screening, baseline, or subsequent visits.			
Units: Subjects			
Mild	11		
Moderate	188		
Moderate-severe	70		
Severe	4		
Not available	1		
Body mass index (BMI)			
Units: Kg/m2			
arithmetic mean	27.9		
standard deviation	± 4.8	±	±
Time since diagnosis			
Units: Years			
arithmetic mean	18.2		
standard deviation	± 13.6	±	±
Number of relapses in the previous year			
Units: number			
arithmetic mean	2.1		
standard deviation	± 2.5	±	±
No. of visits to dermatologist in the last 6 months			
Units: number			
arithmetic mean	2.4		
standard deviation	± 1.5	±	±
Weight			
Units: Kg			
arithmetic mean	80.3		
standard deviation	± 16.0	±	±
Height			
Units: meters			
arithmetic mean	1.7		
standard deviation	± 0.1	±	±
Number of systemic treatments per patient			
Units: number			

arithmetic mean	2.6		
standard deviation	± 2.1	±	±
No. of different systemic treatments per patient			
The "other" category has been counted as a single different treatment.			
Units: number			
arithmetic mean	1.6		
standard deviation	± 0.7	±	±
Baseline PASI			
In 2 patients, without baseline PASI, the information was completed with the screening visit.			
Units: Score			
arithmetic mean	13.3		
standard deviation	± 5.8	±	±
Baseline BSA			
One patient has not indicated a BSA value at either the baseline or screening visit, but has information available at subsequent visits.			
Units: Score			
arithmetic mean	17.4		
standard deviation	± 11.9	±	±
Baseline DLQI			
Units: Score			
arithmetic mean	12.3		
standard deviation	± 7.3	±	±
Baseline pruritus EVA			
Units: Score			
arithmetic mean	6.9		
standard deviation	± 2.4	±	±

Reporting group values	Statistical analysis		
Number of subjects	1		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	±		
Gender categorical			
Units: Subjects			
Female			
Male			

Race Units: Subjects			
Caucasian Asian Arab Hispanic			
Type of psoriasis at diagnosis Units: Subjects			
Plaque psoriasis Guttate psoriasis Pustular psoriasis			
Last previous treatment received Units: Subjects			
Topical + systemic + phototherapy Topical + systemic Topical + phototherapy Systemic + phototherapy Topical Systemic Phototherapy None			
Last previous topical and systemic treatment Units: Subjects			
Acitretin Acitretin + Corticosteroids + D vitamin analogues D vitamin analogues Cyclosporine Cyclosporine +Corticosteroids +D vitamin analogues Corticosteroids Corticosteroids + A vitamin analogues Corticosteroids+A vitamin analogues+salicylic acid Corticosteroids + D vitamin analogues Corticosteroids + D vitamin analogues + Ebastina Corticosteroids+D vitamin analogues+Other topicals Corticosteroids+D vitamin analogues+Salicylic acid CS+D vitamin anologues+Salicylic acid+Gentamicin Corticosteroids + Pimecrolimus Corticosteroids + Salicylic acid Difur Emollients Methotrexate Methotrexate + Corticosteroids Methotrexate +Corticosteroids +D vitamin analogues			

Methotrexate+CS+D vitamin anologues+Other topicals Methotrexate+CS+D vitamin anologues+Salicylic acid Methotrexate + Salicylic acid Other unknown topical treatment Prednisone Salicylic acid formulations None Not available			
Last previous phototherapy received Units: Subjects			
PUVA + UVB PUVA UVB None Not available			
Baseline PGA			
There is one patient with no information on PGA at screening, baseline, or subsequent visits.			
Units: Subjects			
Mild Moderate Moderate-severe Severe Not available			
Body mass index (BMI) Units: Kg/m2 arithmetic mean standard deviation	 ±		
Time since diagnosis Units: Years arithmetic mean standard deviation	 ±		
Number of relapses in the previous year Units: number arithmetic mean standard deviation	 ±		
No. of visits to dermatologist in the last 6 months Units: number arithmetic mean standard deviation	 ±		
Weight Units: Kg arithmetic mean standard deviation	 ±		
Height Units: meters arithmetic mean standard deviation	 ±		
Number of systemic treatments per patient Units: number			

arithmetic mean standard deviation	±		
No. of different systemic treatments per patient			
The "other" category has been counted as a single different treatment.			
Units: number arithmetic mean standard deviation	±		
Baseline PASI			
In 2 patients, without baseline PASI, the information was completed with the screening visit.			
Units: Score arithmetic mean standard deviation	±		
Baseline BSA			
One patient has not indicated a BSA value at either the baseline or screening visit, but has information available at subsequent visits.			
Units: Score arithmetic mean standard deviation	±		
Baseline DLQI Units: Score arithmetic mean standard deviation	±		
Baseline pruritus EVA Units: Score arithmetic mean standard deviation	±		

End points

End points reporting groups

Reporting group title	DMF (Skilarence)

Reporting group description:

The patients included in the clinical trial received Dimethyl fumarate (DMF) as stated in the datasheet, with gradual dose increments during the first 9 weeks.

Subject analysis set title	DMF (ITTm)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Those patients who took the medication and had at least one PASI measurement after the baseline visit.

Subject analysis set title	DMF (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Those patients who met the selection criteria, took the medication and had at least one PASI measurement after the baseline visit.

Subject analysis set title	DMF (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

Those patients who took the corresponding medication and for whom all the requested information was available without significant deviations from the protocol.

Subject analysis set title	Statistical analysis
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This is a single-arm study. Unfortunately, this EudraCT form cannot accommodate for this type of study. Hence, this subgroup has been artificially created for statistical analysis in some endpoints.

Primary: Number of subjects who achieved PASI75 response at Week 24 (ADO)

End point title	Number of subjects who achieved PASI75 response at Week 24 (ADO)[1]

End point description:

The primary endpoint of the study was the number of patients achieving a reduction ≥ 75% in PASI compared to baseline (PASI75) at week 24 of DMF treatment. PASI is a scoring method for the assessment and classification of patient psoriasis severity. PASI combines the assessment of each psoriasis lesion from 0 to 4 (0=none, 1=mild, 2=moderate, 3=marked, 4=very marked) based on three parameters: erythema, infiltration and desquamation, as well as a weighted assessment of the area affected divided into body parts (head, trunk, upper extremities and lower extremities). The PASI ranges between 0 and 72. Analysis carried out with available data only (ADO). The "number of subjects analyzed" means subjects analyzed for this endpoint.

End point type	Primary

End point timeframe:

From baseline up to Week 24 of treatment.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a single-arm study. No comparative analyses were planned for this endpoint (only descriptive statistics).

End point values	DMF (ITTm)	DMF (ITT)	DMF (PP)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	162	156	156	
Units: subjects	96	93	93	

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects who achieved PASI75 response at Week 24 (LOCF)

End point title	Number of subjects who achieved PASI75 response at Week 24 (LOCF)[2]

End point description:

The primary endpoint of the study was the number of patients achieving a reduction ≥ 75% in PASI compared to baseline (PASI75) at week 24 of DMF treatment. PASI is a scoring method for the assessment and classification of patient psoriasis severity. PASI combines the assessment of each psoriasis lesion from 0 to 4 (0=none, 1=mild, 2=moderate, 3=marked, 4=very marked) based on three parameters: erythema, infiltration and desquamation, as well as a weighted assessment of the area affected divided into body parts (head, trunk, upper extremities and lower extremities). The PASI ranges between 0 and 72. Data analyzed with Last Observation Carried Forward (LOCF) method. The "number of subjects analyzed" means subjects analyzed for this endpoint.

End point type	Primary

End point timeframe:

From baseline up to Week 24 of treatment.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a single-arm study. No comparative analyses were planned for this endpoint (only descriptive statistics).

End point values	DMF (ITTm)	DMF (ITT)	DMF (PP)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	274	264	156	
Units: subjects	108	104	93	

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects who achieved PASI75 response at Week 24 (MI)

End point title	Number of subjects who achieved PASI75 response at Week 24 (MI)[3]

End point description:

The primary endpoint of the study was the number of patients achieving a reduction ≥ 75% in PASI compared to baseline (PASI75) at week 24 of DMF treatment. PASI is a scoring method for the assessment and classification of patient psoriasis severity. PASI combines the assessment of each psoriasis lesion from 0 to 4 (0=none, 1=mild, 2=moderate, 3=marked, 4=very marked) based on three parameters: erythema, infiltration and desquamation, as well as a weighted assessment of the area affected divided into body parts (head, trunk, upper extremities and lower extremities). The PASI ranges between 0 and 72. Data analyzed with Multiple Imputation (MI) method. The "number of subjects analyzed" means subjects analyzed for this endpoint.

End point type	Primary

End point timeframe:

From baseline up to Week 24 of treatment.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a single-arm study. No comparative analyses were planned for this endpoint (only descriptive statistics).

End point values	DMF (ITTm)	DMF (ITT)	DMF (PP)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	274	264	156	
Units: subjects	126	121	93	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects who achieved PASI75 response over 52 weeks

End point title	Number of subjects who achieved PASI75 response over 52 weeks

End point description:

This secondary endpoint of the study was the number of patients achieving a reduction ≥ 75% in PASI compared to baseline (PASI75) at weeks 4, 8, 12, 24, 36, 48, and 52 of DMF treatment. Analysis carried out with available data only (ADO). Here, 'n'= subjects analyzed for this endpoint for specified rows (time points).

No comparative statistical analysis was performed, only descriptive statistics.

End point type	Secondary

End point timeframe:

From baseline up to Weeks 4, 8, 12, 24, 36, 48, and 52 of treatment.

End point values	DMF (ITTm)			
Subject group type	Subject analysis set			
Number of subjects analysed	274[4]			
Units: subjects				
Week 4 (n=270)	3			
Week 8 (n=244)	27			
Week 12 (n=203)	72			
Week 24 (n=162)	96			
Week 36 (n=121)	94			
Week 48 (n=95)	73			
Week 52 (n=77)	61			

Notes:

[4] - Number of subjects at baseline. The number of subjects analyzed at each time point is shown below.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects who achieved PASI50 response over 52 weeks

End point title	Number of subjects who achieved PASI50 response over 52 weeks

End point description:

This secondary endpoint of the study was the number of patients achieving a reduction ≥ 50% in PASI compared to baseline (PASI50) at weeks 4, 8, 12, 24, 36, 48, and 52 of DMF treatment. Analysis carried out with available data only (ADO). Here, 'n'= subjects analyzed for this endpoint for specified rows (time points).

No comparative statistical analysis was performed, only descriptive statistics.

End point type	Secondary

End point timeframe:

From baseline up to Weeks 4, 8, 12, 24, 36, 48, and 52 of treatment.

End point values	DMF (ITTm)			
Subject group type	Subject analysis set			
Number of subjects analysed	274[5]			
Units: subjects				
Week 4 (n=270)	39			
Week 8 (n=244)	96			
Week 12 (n=203)	128			
Week 24 (n=162)	133			
Week 36 (n=121)	109			
Week 48 (n=95)	84			
Week 52 (n=77)	71			

Notes:

[5] - Number of subjects at baseline. The number of subjects analyzed at each time point is shown below.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects who achieved PASI90 response over 52 weeks

End point title	Number of subjects who achieved PASI90 response over 52 weeks

End point description:

This secondary endpoint of the study was the number of patients achieving a reduction ≥ 90% in PASI compared to baseline (PASI90) at weeks 4, 8, 12, 24, 36, 48, and 52 of DMF treatment. Analysis carried out with available data only (ADO). Here, 'n'= subjects analyzed for this endpoint for specified rows (time points).

No comparative statistical analysis was performed, only descriptive statistics.

End point type	Secondary

End point timeframe:

From baseline up to Weeks 4, 8, 12, 24, 36, 48, and 52 of treatment.

End point values	DMF (ITTm)			
Subject group type	Subject analysis set			
Number of subjects analysed	274[6]			
Units: subjects				
Week 4 (n=270)	0			
Week 8 (n=244)	8			
Week 12 (n=203)	27			
Week 24 (n=162)	59			
Week 36 (n=121)	61			
Week 48 (n=95)	42			
Week 52 (n=77)	36			

Notes:

[6] - Number of subjects at baseline. The number of subjects analyzed at each time point is shown below.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects who achieved PASI100 response over 52 weeks

End point title	Number of subjects who achieved PASI100 response over 52 weeks

End point description:

This secondary endpoint of the study was the number of patients achieving a reduction ≥ 100% in PASI compared to baseline (PASI100) at weeks 4, 8, 12, 24, 36, 48, and 52 of DMF treatment. Analysis carried out with available data only (ADO). Here, 'n'= subjects analyzed for this endpoint for specified rows (time points).

No comparative statistical analysis was performed, only descriptive statistics.

End point type	Secondary

End point timeframe:

From baseline up to Weeks 4, 8, 12, 24, 36, 48, and 52 of treatment.

End point values	DMF (ITTm)			
Subject group type	Subject analysis set			
Number of subjects analysed	274[7]			
Units: subjects				
Week 4 (n=270)	0			
Week 8 (n=244)	1			
Week 12 (n=203)	11			
Week 24 (n=162)	30			
Week 36 (n=121)	34			
Week 48 (n=95)	24			
Week 52 (n=77)	27			

Notes:

[7] - Number of subjects at baseline. The number of subjects analyzed at each time point is shown below.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in PASI score over 52 weeks

End point title	Change in PASI score over 52 weeks

End point description:

Change in the mean ± SD of the PASI score (score change) during 52 weeks. PASI is a scoring method for the assessment and classification of patient psoriasis severity. PASI combines the assessment of each psoriasis lesion from 0 to 4 (0=none, 1=mild, 2=moderate, 3=marked, 4=very marked) based on three parameters: erythema, infiltration and desquamation, as well as a weighted assessment of the area affected divided into body parts (head, trunk, upper extremities and lower extremities). The PASI ranges between 0 and 72. Analysis carried out with available data only (ADO). Here, 'n'= subjects analyzed for this endpoint for specified rows (time points).

End point type	Secondary

End point timeframe:

From baseline up to Weeks 4, 8, 12, 24, 36, 48, and 52 of treatment.

End point values	DMF (ITTm)	Statistical analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	76[8]	1[9]		
Units: Score				
arithmetic mean (standard deviation)				
Baseline (n=274)	13.3 (± 5.8)	0 (± 0)		
Week 4 (n=270)	10.3 (± 5.2)	0 (± 0)		
Week 8 (n=244)	8.4 (± 5.3)	0 (± 0)		
Week 12 (n=203)	5.7 (± 4.6)	0 (± 0)		
Week 24 (n=162)	3.5 (± 4.2)	0 (± 0)		
Week 36 (n=121)	2.5 (± 3.6)	0 (± 0)		
Week 48 (n=95)	2.4 (± 3.4)	0 (± 0)		
Week 52 (n=77)	2.2 (± 3.1)	0 (± 0)		

Notes:

[8] - Number of patients used for Wilcoxon signed-rank test with data from baseline to week 52 (N=77).

[9] - This form cannot cater for single-arm study. So, this subgroup was artificially set up for analysis.

Statistical analyses

Statistical analysis title	Change in PASI score over 52 weeks

Statistical analysis description:

Change in the mean ± SD of the PASI score from baseline up to Week 52.

Comparison groups	DMF (ITTm) v Statistical analysis
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	< 0.001 [11]
Method	Wilcoxon signed-rank test

Notes:

[10] - This form is not suitable for single-arm clinical trials and does not allow statistical analysis of paired data from two observations at different time points for the same population. Therefore, the "statistical analysis" subgroup had to be artificially created to analyze the statistical significance of change score from baseline up to Week 52 by Wilcoxon signed-rank test.

[11] - There was a significant improvement in PASI score at Week 52 from Baseline.

Secondary: Number of subjects who achieved a PGA 0 response over 52 weeks

End point title	Number of subjects who achieved a PGA 0 response over 52 weeks

End point description:

Number of patients achieving a PGA = 0 at baseline and Weeks 4, 8, 12, 24, 36, 48, and 52 of treatment. The PGA score provides a subjective assessment of the severity of the disease and evaluates the intensity, but not the extent or symptomatology of the lesions. PGA uses a score between 0 and 5 (0=blank [no signs of psoriasis, post-inflammatory hyperpigmentation may be present]; 1=almost mild [intermediate between slight and mild]; 2=mild [mild elevation of plaque, scaling and/or erythema]; 3=moderate [moderate elevation of plaque, scaling and/or erythema]; 4=moderate-severe [marked elevation of plaque, scaling and/or erythema]; 5=severe [very marked elevation of plaque, scaling and/or erythema]). Analysis carried out with available data only (ADO). Here, 'n'= subjects analyzed for this endpoint for specified rows (time points).

End point type	Secondary

End point timeframe:

From baseline up to Weeks 4, 8, 12, 24, 36, 48, and 52 of treatment.

End point values	DMF (ITTm)	Statistical analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	74[12]	1[13]		
Units: subjects				
Baseline (n=273)	0	0		
Week 4 (n=269)	0	0		
Week 8 (n=241)	2	0		
Week 12 (n=201)	13	0		
Week 24 (n=162)	31	0		
Week 36 (n=121)	36	0		
Week 48 (n=93)	31	0		
Week 52 (n=75)	31	0		

Notes:

[12] - Number of patients used for Chi-Square test with data from baseline to week 52 (N=75).

[13] - This form cannot cater for single-arm study. So, this subgroup was artificially set up for analysis.

Statistical analyses

Statistical analysis title	Change in subjects' percentage achieving a PGA = 0

Statistical analysis description:

Change in the percentage of subjects achieving a PGA score of 0 (blank) from baseline up to Week 52 of treatment.

Comparison groups	DMF (ITTm) v Statistical analysis
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	< 0.001 [15]
Method	Chi-squared

Notes:

[14] - This form is not suitable for single-arm clinical trials and does not allow statistical analysis of paired data from two observations at different time points for the same population. Therefore, the "statistical analysis" subgroup had to be artificially created to analyze the statistical significance of change score from baseline up to Week 52 by Chi-Square test.

[15] - There was a significant increase in subjects' percentage achieving a PGA score of 0 at Week 52

from Baseline.

Secondary: Number of subjects who achieved a PGA 1 response over 52 weeks

End point title	Number of subjects who achieved a PGA 1 response over 52 weeks

End point description:

Number of subjects achieving a PGA = 1 at baseline and Weeks 4, 8, 12, 24, 36, 48, and 52 of treatment. The PGA score provides a subjective assessment of the severity of the disease and evaluates the intensity, but not the extent or symptomatology of the lesions. PGA uses a score between 0 and 5 (0=blank [no signs of psoriasis, post-inflammatory hyperpigmentation may be present]; 1=almost mild [intermediate between slight and mild]; 2=mild [mild elevation of plaque, scaling and/or erythema]; 3=moderate [moderate elevation of plaque, scaling and/or erythema]; 4=moderate-severe [marked elevation of plaque, scaling and/or erythema]; 5=severe [very marked elevation of plaque, scaling and/or erythema]). Analysis carried out with available data only (ADO). Here, 'n'= subjects analyzed for this endpoint for specified rows (time points).

End point type	Secondary

End point timeframe:

From baseline up to Weeks 4, 8, 12, 24, 36, 48, and 52 of treatment.

End point values	DMF (ITTm)	Statistical analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	74[16]	1[17]		
Units: subjects				
Baseline (n=273)	0	0		
Week 4 (n=269)	8	0		
Week 8 (n=241)	23	0		
Week 12 (n=201)	52	0		
Week 24 (n=162)	62	0		
Week 36 (n=121)	51	0		
Week 48 (n=93)	40	0		
Week 52 (n=75)	29	0		

Notes:

[16] - Number of patients used for Chi-Square test with data from baseline to week 52 (N=75).

[17] - This form cannot cater for single-arm study. So, this subgroup was artificially set up for analysis.

Statistical analyses

Statistical analysis title	Change in subjects' percentage achieving a PGA = 1

Statistical analysis description:

Change in the percentage of subjects achieving a PGA score of 1 (almost blank) from baseline up to Week 52 of treatment.

Comparison groups	DMF (ITTm) v Statistical analysis
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	< 0.001 [19]
Method	Chi-squared

Notes:

[18] - This form is not suitable for single-arm clinical trials and does not allow statistical analysis of paired data from two observations at different time points for the same population. Therefore, the "statistical analysis" subgroup had to be artificially created to analyze the statistical significance of change score from baseline up to Week 52 by Chi-Square test.

[19] - There was a significant increase in subjects' percentage achieving a PGA score of 1 at Week 52 from baseline.

Secondary: Change in BSA score over 52 weeks

End point title	Change in BSA score over 52 weeks

End point description:

Change in the mean ± SD of the BSA score (score change) during 52 weeks. The BSA measures the surface area affected by psoriasis lesions using the palm of the patient's hand (including fingers), as equivalent to 1% of the patient's total body surface area. Psoriasis is considered mild when it affects less than 3% of the skin surface, moderate when it affects between 3 and 8%, and severe when it affects more than 10%. Analysis carried out with available data only (ADO). Here, 'n'= subjects analyzed for this endpoint for specified rows (time points).

End point type	Secondary

End point timeframe:

From baseline up to Weeks 4, 8, 12, 24, 36, 48, and 52 of treatment.

End point values	DMF (ITTm)	Statistical analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	76[20]	1[21]		
Units: Score				
arithmetic mean (standard deviation)				
Baseline (n=273)	17.4 (± 11.9)	0 (± 0)		
Week 4 (n=268)	15.0 (± 10.2)	0 (± 0)		
Week 8 (n=243)	12.7 (± 9.9)	0 (± 0)		
Week 12 (n=202)	9.7 (± 9.9)	0 (± 0)		
Week 24 (n=161)	5.1 (± 8.0)	0 (± 0)		
Week 36 (n=121)	3.2 (± 4.6)	0 (± 0)		
Week 48 (n=95)	2.6 (± 4.2)	0 (± 0)		
Week 52 (n=77)	2.8 (± 5.5)	0 (± 0)		

Notes:

[20] - Number of patients used for Wilcoxon signed-rank test with data from baseline to week 52 (N=77).

[21] - This form cannot cater for single-arm study. So, this subgroup was artificially set up for analysis.

Statistical analyses

Statistical analysis title	Change in BSA score over 52 weeks

Statistical analysis description:

Change in the mean ± SD of the BSA score from baseline up to Week 52.

Comparison groups	DMF (ITTm) v Statistical analysis
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other[22]
P-value	< 0.001 [23]
Method	Wilcoxon signed-rank test

Notes:

[22] - This form is not suitable for single-arm clinical trials and does not allow statistical analysis of paired data from two observations at different time points for the same population. Therefore, the "statistical analysis" subgroup had to be artificially created to analyze the statistical significance of change score from baseline up to Week 52 by Wilcoxon signed-rank test.

[23] - There was a significant improvement in BSA score at Week 52 from Baseline.

Secondary: Change in EVA score of pruritus over 52 weeks

End point title	Change in EVA score of pruritus over 52 weeks

End point description:

Change in the mean ± SD of the EVA score of pruritus (score change) during 52 weeks. It is a single-item scale for the evaluation of the degree of itching, delimited by the terms "no itching" at point 0 and the term "unbearable itching" at the end of the scale. Analysis carried out with available data only (ADO). Here, 'n'= subjects analyzed for this endpoint for specified rows (time points).

End point type	Secondary

End point timeframe:

From baseline up to Weeks 4, 8, 12, 24, 36, 48, and 52 of treatment.

End point values	DMF (ITTm)	Statistical analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	76[24]	1[25]		
Units: Score				
arithmetic mean (standard deviation)				
Baseline (n=274)	6.9 (± 2.4)	0 (± 0)		
Week 4 (n=270)	5.9 (± 2.5)	0 (± 0)		
Week 8 (n=242)	5.2 (± 2.8)	0 (± 0)		
Week 12 (n=203)	3.7 (± 2.6)	0 (± 0)		
Week 24 (n=161)	2.8 (± 2.9)	0 (± 0)		
Week 36 (n=118)	2.5 (± 2.9)	0 (± 0)		
Week 48 (n=93)	2.2 (± 2.8)	0 (± 0)		
Week 52 (n=77)	2.1 (± 2.6)	0 (± 0)		

Notes:

[24] - Number of patients used for Wilcoxon signed-rank test with data from baseline to week 52 (N=77).

[25] - This form cannot cater for single-arm study. So, this subgroup was artificially set up for analysis

Statistical analyses

Statistical analysis title	Change in EVA score of pruritus over 52 weeks

Statistical analysis description:

Change in the mean ± SD of the EVA score of pruritus from baseline up to Week 52.

Comparison groups	Statistical analysis v DMF (ITTm)
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other[26]
P-value	< 0.001 [27]
Method	Wilcoxon signed-rank test

Notes:

[26] - This form is not suitable for single-arm clinical trials and does not allow statistical analysis of paired data from two observations at different time points for the same population. Therefore, the "statistical analysis" subgroup had to be artificially created to analyze the statistical significance of change score from baseline up to Week 52 by Wilcoxon signed-rank test.

[27] - There was a significant improvement in EVA score of pruritus at Week 52 from Baseline.

Secondary: Change in DLQI score over 52 weeks

End point title	Change in DLQI score over 52 weeks

End point description:

Change in the mean ± SD of the DLQI score (score change) during 52 weeks. It is a dermatology-specific health-related quality of life (HRQoL) assessment tool developed to evaluate the impact of a dermatological disease on the patient's daily life. Analysis carried out with available data only (ADO). Here, 'n'= subjects analyzed for this endpoint for specified rows (time points).

End point type	Secondary

End point timeframe:

From baseline up to Weeks 4, 8, 12, 24, 36, 48, and 52 of treatment.

End point values	DMF (ITTm)	Statistical analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	76[28]	1[29]		
Units: score				
arithmetic mean (standard deviation)				
Baseline (n=274)	12.3 (± 7.3)	0 (± 0)		
Week 4 (n=271)	9.5 (± 7.0)	0 (± 0)		
Week 8 (n=243)	8.0 (± 7.0)	0 (± 0)		
Week 12 (n=203)	5.8 (± 5.9)	0 (± 0)		
Week 24 (n=161)	3.5 (± 5.0)	0 (± 0)		
Week 36 (n=119)	2.5 (± 3.8)	0 (± 0)		
Week 48 (n=94)	2.3 (± 4.2)	0 (± 0)		
Week 52 (n=77)	1.9 (± 3.0)	0 (± 0)		

Notes:

[28] - Number of patients used for Wilcoxon signed-rank test with data from baseline to week 52 (N=77).
[29] - This form cannot cater for single-arm study. So, this subgroup was artificially set up for analysis.

Statistical analyses

Statistical analysis title	Change in DLQI score over 52 weeks

Statistical analysis description:

Change in the mean ± SD of the EVA score of pruritus from baseline up to Week 52.

Comparison groups	Statistical analysis v DMF (ITTm)
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other[30]
P-value	< 0.001 [31]
Method	Wilcoxon signed-rank test

Notes:

[30] - This form is not suitable for single-arm clinical trials and does not allow statistical analysis of paired data from two observations at different time points for the same population. Therefore, the "statistical analysis" subgroup had to be artificially created to analyze the statistical significance of change score from baseline up to Week 52 by Wilcoxon signed-rank test.
[31] - There was a significant improvement in DLQI score of pruritus at Week 52 from Baseline.

Secondary: Change in the satisfaction EVA score from Week 24 up to 52 or the discontinuation week

End point title	Change in the satisfaction EVA score from Week 24 up to 52 or the discontinuation week

End point description:

Change in the mean ± SD of the satisfaction EVA score (score change) during 52 weeks. It is a single-item scale for the evaluation of the degree of satisfaction with the treatment, delimited by the terms "completely unsatisfactory" for the score 0 and "completely satisfactory" for the score 10 of the scale. Analysis carried out with available data only (ADO). Here, 'n'= subjects analyzed for this endpoint for specified rows (time points).

End point type	Secondary

End point timeframe:

From Week 24 up to Week 52 or discontinuation week.

End point values	DMF (ITTm)	Statistical analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	73[32]	1[33]		
Units: score				
arithmetic mean (standard deviation)				
Week 24	7.6 (± 2.7)	0 (± 0)		
Week of discontinuation	3.4 (± 3.4)	0 (± 0)		
Week 52	8.4 (± 2.1)	0 (± 0)		

Notes:

[32] - Number of patients used for Wilcoxon signed-rank test with data from baseline to week 52 (N=74).

[33] - This form cannot cater for single-arm study. So, this subgroup was artificially set up for analysis

Statistical analyses

Statistical analysis title	Change in the satisfaction EVA score

Statistical analysis description:

Change in the mean ± SD of the satisfaction EVA score from Week 24 to Week 52 of treatment.

Comparison groups	DMF (ITTm) v Statistical analysis
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	other[34]
P-value	= 0.191 [35]
Method	Wilcoxon signed-rank test

Notes:

[34] - This form is not suitable for single-arm clinical trials and does not allow statistical analysis of paired data from two observations at different time points for the same population. Therefore, the "statistical analysis" subgroup had to be artificially created to analyze the statistical significance of change score from Week 24 to Week 52 by Wilcoxon signed-rank test.

[35] - Not statistically significant.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline to Week 52.

Adverse event reporting additional description:

AEs were obtained by asking patients neutral questions during visits and/or by collecting AEs spontaneously reported by the patient to the investigator. All AEs obtained by the investigator throughout the study were appropriately noted in the eCRF. SAEs were reported to the sponsor by e-mail or fax within 24 hours of their occurrence.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	DMF (Skilarence)

Reporting group description:

The patients included in the clinical trial received Dimethyl fumarate (DMF) as stated in the datasheet, with gradual dose increments during the first 9 weeks.

Serious adverse events	DMF (Skilarence)		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 282 (1.77%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal cell carcinoma	Additional description: Hospitalization of the patient. Not related to treatment.		
subjects affected / exposed	1 / 282 (0.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral infarction	Additional description: Posible relation to Skilarence. Permanent withdrawal of study treatment. Recovery with sequelae.		
subjects affected / exposed	1 / 282 (0.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Eosinofilia	Additional description: Related to Skilarence. Permanent withdrawal of study treatment. Complete recovery.		

subjects affected / exposed	1 / 282 (0.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatitis acute	Additional description: Posible relation to Skilarence. Permanent withdrawal of study treatment. Complete recovery.		
subjects affected / exposed	1 / 282 (0.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis	Additional description: Not related to Skilarence. Temporary discontinuation of medication. Complete recovery.		
subjects affected / exposed	1 / 282 (0.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	DMF (Skilarence)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	272 / 282 (96.45%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 282 (2.48%)		
occurrences (all)	7		
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	5 / 282 (1.77%)		
occurrences (all)	6		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	7 / 282 (2.48%)		
occurrences (all)	8		
Burning sensation			
subjects affected / exposed	6 / 282 (2.13%)		
occurrences (all)	6		
Fatigue			

subjects affected / exposed	8 / 282 (2.84%)		
occurrences (all)	10		
Feeling hot			
subjects affected / exposed	9 / 282 (3.19%)		
occurrences (all)	10		
Flushing			
subjects affected / exposed	79 / 282 (28.01%)		
occurrences (all)	171		
Hot flush			
subjects affected / exposed	7 / 282 (2.48%)		
occurrences (all)	9		
Inflammation			
subjects affected / exposed	4 / 282 (1.42%)		
occurrences (all)	4		
Malaise			
subjects affected / exposed	8 / 282 (2.84%)		
occurrences (all)	9		
Oedema peripheral			
subjects affected / exposed	4 / 282 (1.42%)		
occurrences (all)	4		
Pain			
subjects affected / exposed	4 / 282 (1.42%)		
occurrences (all)	6		
Pyrexia			
subjects affected / exposed	5 / 282 (1.77%)		
occurrences (all)	5		
Respiratory, thoracic and mediastinal disorders			
Bronchitis			
subjects affected / exposed	3 / 282 (1.06%)		
occurrences (all)	3		
Catarrh			
subjects affected / exposed	22 / 282 (7.80%)		
occurrences (all)	23		
Cough			

subjects affected / exposed occurrences (all)	4 / 282 (1.42%) 5		
Nasal congestion subjects affected / exposed occurrences (all)	3 / 282 (1.06%) 3		
Oropharyngeal pain subjects affected / exposed occurrences (all)	3 / 282 (1.06%) 3		
Pharyngitis subjects affected / exposed occurrences (all)	4 / 282 (1.42%) 4		
Rhinitis subjects affected / exposed occurrences (all)	3 / 282 (1.06%) 3		
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	5 / 282 (1.77%) 6		
Weight decreased subjects affected / exposed occurrences (all)	3 / 282 (1.06%) 3		
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	14 / 282 (4.96%) 15		
Formication subjects affected / exposed occurrences (all)	3 / 282 (1.06%) 3		
Headache subjects affected / exposed occurrences (all)	35 / 282 (12.41%) 59		
Insomnia subjects affected / exposed occurrences (all)	5 / 282 (1.77%) 5		
Paraesthesia			

subjects affected / exposed occurrences (all)	5 / 282 (1.77%) 5		
Syncope subjects affected / exposed occurrences (all)	3 / 282 (1.06%) 3		
Blood and lymphatic system disorders Eosinofilia subjects affected / exposed occurrences (all)	3 / 282 (1.06%) 3		
Leukopenia subjects affected / exposed occurrences (all)	4 / 282 (1.42%) 4		
Lymphopenia subjects affected / exposed occurrences (all)	88 / 282 (31.21%) 110		
Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all)	31 / 282 (10.99%) 44		
Abdominal distension subjects affected / exposed occurrences (all)	7 / 282 (2.48%) 10		
Abdominal pain subjects affected / exposed occurrences (all)	99 / 282 (35.11%) 139		
Abdominal pain upper subjects affected / exposed occurrences (all)	42 / 282 (14.89%) 56		
Constipation subjects affected / exposed occurrences (all)	10 / 282 (3.55%) 13		
Diarrhoea subjects affected / exposed occurrences (all)	141 / 282 (50.00%) 253		
Dyspepsia			

subjects affected / exposed	12 / 282 (4.26%)		
occurrences (all)	12		
Flatulence			
subjects affected / exposed	10 / 282 (3.55%)		
occurrences (all)	13		
Gastroenteritis			
subjects affected / exposed	5 / 282 (1.77%)		
occurrences (all)	5		
Gastrointestinal pain			
subjects affected / exposed	8 / 282 (2.84%)		
occurrences (all)	10		
Nausea			
subjects affected / exposed	38 / 282 (13.48%)		
occurrences (all)	40		
Toothache			
subjects affected / exposed	3 / 282 (1.06%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	37 / 282 (13.12%)		
occurrences (all)	42		
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	32 / 282 (11.35%)		
occurrences (all)	53		
Pruritus			
subjects affected / exposed	37 / 282 (13.12%)		
occurrences (all)	57		
Psoriasis			
subjects affected / exposed	4 / 282 (1.42%)		
occurrences (all)	4		
Rash			
subjects affected / exposed	4 / 282 (1.42%)		
occurrences (all)	4		
Skin burning sensation			
subjects affected / exposed	3 / 282 (1.06%)		
occurrences (all)	3		

Urticaria subjects affected / exposed occurrences (all)	4 / 282 (1.42%) 4		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	3 / 282 (1.06%) 3		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Neck pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 5 / 282 (1.77%) 5 13 / 282 (4.61%) 16 6 / 282 (2.13%) 8 6 / 282 (2.13%) 8		
Infections and infestations Influenza subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Pneumonia subjects affected / exposed occurrences (all) Respiratory tract infection subjects affected / exposed occurrences (all) Tooth abscess subjects affected / exposed occurrences (all)	 10 / 282 (3.55%) 11 15 / 282 (5.32%) 18 3 / 282 (1.06%) 3 3 / 282 (1.06%) 3 3 / 282 (1.06%) 3		

Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	9 / 282 (3.19%) 10 6 / 282 (2.13%) 6		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Feeding intolerance subjects affected / exposed occurrences (all) Hypertriglyceridaemia subjects affected / exposed occurrences (all)	3 / 282 (1.06%) 5 8 / 282 (2.84%) 12 3 / 282 (1.06%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This is a single-arm study; comparative analyses could not be performed.

Notes: