Clinical trial results:
An Open Label, Multi-Center, 24 Week, Exploratory Study to Assess the Efficacy and Safety of Skilarence® (Dimethyl Fumarate) in Patients with Moderate Plaque Psoriasis

Summary

EudraCT number	2018-004010-18
Trial protocol	GB DK IE
Global end of trial date	24 June 2021

Results information

Result version number	v1 (current)
This version publication date	14 August 2022
First version publication date	14 August 2022

Trial information

Trial identification

Sponsor protocol code	M-41008-47

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	CRO: SMR-3612

Notes:

Sponsors

Sponsor organisation name	Almirall Ltd.
Sponsor organisation address	Harman House 1 George Street Uxbridge, Uxbridge, United Kingdom, UB8 1QQ
Public contact	Dr Amanda Knock, Smerud Medical Research UK Limited, +44 01618708129, regulatory.uk@smerud.com
Scientific contact	Dr Amanda Knock, Smerud Medical Research UK Limited, +44 01618708129, regulatory.uk@smerud.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 June 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to assess the efficacy of Skilarence® (Dimethyl Fumarate) at week 24 of treatment as measured by static Physician's Global Assessment score (sPGA) multiplied by percentage Body Surface Area (BSA).

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 July 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 10
Country: Number of subjects enrolled	United Kingdom: 66
Country: Number of subjects enrolled	Denmark: 18
Country: Number of subjects enrolled	Ireland: 6
Worldwide total number of subjects	100
EEA total number of subjects	34

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)	90

From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 23 sites in the United Kingdom, Ireland, Norway and Denmark from 29 July 2019 to 24 June 2021.

Pre-assignment

Screening details:

A total of 124 subjects were screened out of which 100 were enrolled in trial. The study was performed in 4 countries including the UK, Ireland, Norway and Denmark.

Period 1

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

Arms

Arm title	Skilarence®

Arm description:

Subjects received starting dose of 30 mg of Skilarence® tablet once a day (in the evening) for seven days (± 3 days). The dose of Skilarence® taken by the subject was then gradually increased and given up to 24 weeks. In the second week, Skilarence® 30 mg was taken twice daily (1 tablet in the morning and 1 in the evening). In the third week, Skilarence® 30 mg was taken three times daily (1 tablet in the morning, 1 at midday, and 1 in the evening). From the fourth week, treatment was switched to only 1 tablet of Skilarence® 120mg in the evening; although flexibility with dose adjustments and timing of dose adjustments was allowed. Skilarence® dose could then be increased by 1 Skilarence® 120mg tablet per week at different times of day for the subsequent 5 weeks. The maximum daily dose allowed was 720mg (3 x 2 tablets of Skilarence® 120mg).

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

Dosage and administration details:

Subjects received Skilarence® tablet once daily for first week then gradually increased in subsequent weeks up to 24 week of treatment period.

Number of subjects in period 1	Skilarence®
Started	100
Treated	97
Safety population	100
Intention-to-treat (ITT) population	97
Per-protocol (PP) population	54 [1]
Completed	58
Not completed	42

subject's decision	19
Not specified	4
Adverse event	12
Unexplained non-attendance	1
Investigator’s decision	5
Lack of treatment efficacy	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Here, number of subjects are listed based on analysis set.

Baseline characteristics

Reporting groups	
Reporting group title	Overall Subjects

Reporting group description: -

Reporting group values	Overall Subjects	Total	
Number of subjects	100	100	
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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
The safety population included all patients who received at least one dose of Skilarence®.			
Units: years			
arithmetic mean	44.2		
standard deviation	± 13.9	-	
Gender categorical			
The safety population included all patients who received at least one dose of Skilarence®.			
Units: Subjects			
Female	36	36	
Male	64	64	

End points

End points reporting groups

Reporting group title	Skilarence®

Reporting group description:

Subjects received starting dose of 30 mg of Skilarence® tablet once a day (in the evening) for seven days (± 3 days). The dose of Skilarence® taken by the subject was then gradually increased and given up to 24 weeks. In the second week, Skilarence® 30 mg was taken twice daily (1 tablet in the morning and 1 in the evening). In the third week, Skilarence® 30 mg was taken three times daily (1 tablet in the morning, 1 at midday, and 1 in the evening). From the fourth week, treatment was switched to only 1 tablet of Skilarence® 120mg in the evening; although flexibility with dose adjustments and timing of dose adjustments was allowed. Skilarence® dose could then be increased by 1 Skilarence® 120mg tablet per week at different times of day for the subsequent 5 weeks. The maximum daily dose allowed was 720mg (3 x 2 tablets of Skilarence® 120mg).

Primary: Mean Percentage Change From Baseline in Static Physician's Global Assessment Score (sPGA) Multiplied by Percentage Body Surface Area (BSA) at Week 24

End point title	Mean Percentage Change From Baseline in Static Physician's Global Assessment Score (sPGA) Multiplied by Percentage Body Surface Area (BSA) at Week 24[1]

End point description:

BSA is a measurement of involved skin. The overall BSA affected by psoriasis is estimated based on the palm area of the subject's hand (entire palmar surface or "handprint" including the fingers), which equates to approximately 1% of total body surface area. The sPGA is a 6-point scale ranging from 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), to 4 (moderate to severe), 5 (severe) incorporating a separate assessment of the severity of the three primary signs of the plaques of all involved areas: erythema, scaling and plaque elevation with an overall sPGA. Scores for each assessment are rounded to the nearest whole number to result in the final score. Higher scores represented worse outcomes. ITT population included all subjects who are enrolled into the study, received at least one administration of Skilarence® and had at least one post dosing evaluation. Last Observation Carried Forward (LOCF) methodology was used to impute missing efficacy measurements for this outcome.

End point type	Primary

End point timeframe:

At week 24

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: Only descriptive summary statistics was planned for this endpoint.

End point values	Skilarence®			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: Percent change				
arithmetic mean (standard deviation)	-27 (± 94)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Psoriasis Area and Severity Index (PASI 75) (≥75% Reduction from Baseline) at Weeks 12, 16 and 24

End point title	Percentage of Subjects with Psoriasis Area and Severity Index (PASI 75) (≥75% Reduction from Baseline) at Weeks 12, 16 and 24

End point description:

Psoriasis Area and Severity Index (PASI) 75 response: subjects who achieved >= 75% improvement (reduction) in PASI score compared to baseline were defined as PASI 75 responders. PASI scores can range from 0, corresponding to no signs of psoriasis up to theoretical maximum of 72.0, which means a higher PASI score reflects a higher psoriasis activity. ITT population included all subjects who are enrolled into the study, received at least one administration of Skilarence® and had at least one post dosing evaluation. Last Observation Carried Forward (LOCF) methodology was used to impute missing efficacy measurements for this outcome. Here, Number analyzed (n) signifies those subjects who were evaluable for this outcome at specified timepoint.

End point type	Secondary

End point timeframe:

At Weeks 12, 16 and 24

End point values	Skilarence®			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: Percentage				
number (not applicable)				
At week 12 (n=95)	7.4			
At week 16 (n=96)	9.4			
At week 24 (n=97)	20.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Psoriasis Area and Severity Index (PASI 50) (≥50% Reduction from Baseline) at Weeks 12, 16 and 24

End point title	Percentage of Subjects with Psoriasis Area and Severity Index (PASI 50) (≥50% Reduction from Baseline) at Weeks 12, 16 and 24

End point description:

Psoriasis Area and Severity Index (PASI) 50 response: subjects who achieved ≥ 50% improvement (reduction) in PASI score compared to baseline were defined as PASI 50 responders. PASI scores can range from 0, corresponding to no signs of psoriasis up to theoretical maximum of 72.0, which means a higher PASI score reflects a higher psoriasis activity. ITT population included all subjects who are enrolled into the study, received at least one administration of Skilarence® and had at least one post dosing evaluation. Last Observation Carried Forward (LOCF) methodology was used to impute missing efficacy measurements for this outcome. Here, Number analyzed (n) signifies those subjects who were evaluable for this outcome at specified timepoint.

End point type	Secondary

End point timeframe:

At Weeks 12, 16 and 24

End point values	Skilarence®			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: Percentage of Subjects				
number (not applicable)				
At week 12 (n=95)	28.4			
At week 16 (n=96)	38.5			
At week 24 (n=97)	45.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change From Baseline in Psoriasis Area and Severity Index (PASI) Score at Weeks 12, 16 and 24

End point title	Percentage Change From Baseline in Psoriasis Area and Severity Index (PASI) Score at Weeks 12, 16 and 24

End point description:

The Psoriasis Area and Severity Index (PASI) is a composite score based on the degree of effect on body surface area of psoriasis and the extension of erythema (reddening), infiltration, desquamation (scaling) of the lesions and area affected as observed on the day of examination. The severity of each sign is assessed using a 5-point scale, where 0=no symptoms, 1=slight, 2=moderate, 3=marked, 4=very marked. The PASI score ranges from 0 to 72, where 0 indicates no psoriasis and 72 indicates very severe psoriasis. Negative mean change is favorable; positive mean change is unfavorable. ITT population included all subjects who are enrolled into the study, received at least one administration of Skilarence® and had at least one post dosing evaluation. Last Observation Carried Forward (LOCF) methodology was used to impute missing efficacy measurements for this outcome. Here, n=Number Analyzed,
signifies those subject who were evaluable for specified timepoint.

End point type	Secondary

End point timeframe:

At Weeks 12, 16 and 24

End point values	Skilarence®			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: Percent change				
arithmetic mean (standard deviation)				
At week 12 (n=95)	-0.2771 (± 0.3873)			
At week 16 (n=96)	-0.2920 (± 0.4280)			
At week 24 (n=97)	-0.3518 (± 0.4798)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieved Psoriasis Area and Severity Index (PASI) Score of Less Than (<) 1, 3 and 5 at Week 24

End point title	Percentage of Subjects Achieved Psoriasis Area and Severity Index (PASI) Score of Less Than (<) 1, 3 and 5 at Week 24

End point description:

PASI is a combination of the intensity of psoriasis, assessed by the erythema (reddening), induration (plaque thickness) and scaling on a scale range from 0 (no symptoms) to 4 (very marked). PASI scoring is performed at four body areas, the head, arms, trunk, and legs. The total PASI score ranges from 0 (no psoriasis) to 72 (the most severe disease). Percentage of subjects who achieved an absolute PASI score <1, 3 and 5 at Week 24 reported. ITT population included all subjects who are enrolled into the study, received at least one administration of Skilarence® and had at least one post dosing evaluation. Last Observation Carried Forward (LOCF) methodology was used to impute missing efficacy measurements for both outcome.

End point type	Secondary

End point timeframe:

At Week 24

End point values	Skilarence®			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: Percentage of subjects				
number (not applicable)				
PASI < 1	11.3			
PASI < 3	33.0			
PASI < 5	60.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Psoriasis Area and Severity Index (PASI) Score at Weeks 12, 16 and 24

End point title	Absolute Psoriasis Area and Severity Index (PASI) Score at Weeks 12, 16 and 24

End point description:

The Psoriasis Area and Severity Index (PASI) is a composite score based on the degree of effect on body surface area of psoriasis and the extension of erythema (reddening), induration (thickness), desquamation (scaling) of the lesions and area affected as observed on the day of examination. The severity of each sign is assessed using a 5-point scale, where 0=no symptoms, 1=slight, 2=moderate,

3=marked, 4=very marked. The PASI score ranges from 0 to 72, where 0 indicates no psoriasis and 72 indicates very severe psoriasis. Negative mean change is favorable; positive mean change is unfavorable. ITT population included all subjects who are enrolled into the study, received at least one administration of Skilarence® and had at least one post dosing evaluation. Last Observation Carried Forward (LOCF) methodology was used to impute missing efficacy measurements for this outcome.

End point type	Secondary

End point timeframe:

At weeks 12, 16 and 24

End point values	Skilarence®			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: score on a scale				
arithmetic mean (standard deviation)				
At week 12	5.48 (± 2.87)			
At week 16	5.33 (± 3.12)			
At week 24	4.87 (± 3.54)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline in Body Surface Area (BSA) at Weeks 12, 16 and 24

End point title	Percentage Change from Baseline in Body Surface Area (BSA) at Weeks 12, 16 and 24

End point description:

Body Surface Area (BSA) was assessed as a percentage of the body surface area affected by psoriasis. BSA was assessed at week 12, 16 and 24 to conform the severity of psoriasis and to assess efficacy of Skilarence®. BSA was measured using the palm method (investigators whole hand print including palm and fingers reflects approximately 1% BSA).

- Palm (to proximal interphalangeal joint and thumb)= 1%
-Head and neck = 10 palms (10%)
-Upper extremities = 20 palms (20%)
-Trunk (chest, abdomen and back) = 30 palms (30%)
-Lower extremities = 40 palms (40%)
-Total BSA = 100% (100 palms)

ITT population included all subjects who are enrolled into the study, received at least one administration of Skilarence® and had at least one post dosing evaluation. Last Observation Carried Forward (LOCF) methodology was used to impute missing efficacy measurements for this outcome.

End point type	Secondary

End point timeframe:

At weeks 12, 16 and 24

End point values	Skilarence®			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: Percent change				
arithmetic mean (standard deviation)				
At week 12	-4 (± 65)			
At week 16	-9 (± 71)			
At week 24	-15 (± 82)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change From Baseline in Dermatology Quality of Life Index (DLQI) at Weeks 12, 16 and 24

End point title	Percentage Change From Baseline in Dermatology Quality of Life Index (DLQI) at Weeks 12, 16 and 24

End point description:

DLQI is a questionnaire which is to evaluate the impact on subject's quality of life due to psoriasis. It is composed of ten items related to symptoms, feelings, daily activities, leisure, working or studying activities, personal relationships and opinions about dermatological treatment. Each item is scored from 0 (not affected at all) to 3 (very much affected). The DLQI score is the sum of the 10 individual question scores and ranges from 0 to 30, with lower scores indicating better quality of life. The higher the score, the more quality of life is impaired. ITT population included all subjects who are enrolled into the study, received at least one administration of Skilarence® and had at least one post dosing evaluation. Last Observation Carried Forward (LOCF) methodology was used to impute missing efficacy measurements for this outcome. Here, n=Number Analyzed, signifies those subjects who were evaluable for specified timepoint.

End point type	Secondary

End point timeframe:

At weeks 12, 16 and 24

End point values	Skilarence®			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: score on scale				
arithmetic mean (standard deviation)				
At week 12 (n=95)	-0.3051 (± 0.4070)			
At week 16 (n=96)	-0.3650 (± 0.4686)			
At week 24 (n=97)	-0.4799 (± 0.4528)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change From Baseline in static Physician's Global Assessment Score (sPGA) Multiplied by Percent Body Surface Area (BSA) at Weeks 12 and 16

End point title	Percentage Change From Baseline in static Physician's Global Assessment Score (sPGA) Multiplied by Percent Body Surface Area (BSA) at Weeks 12 and 16

End point description:

BSA is a measurement of involved skin. The overall BSA affected by psoriasis is estimated based on the palm area of the subject's hand (entire palmar surface or "handprint" including the fingers), which equates to approximately 1% of total body surface area. The sPGA is a 6-point scale ranging from 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), to 4 (moderate to severe), 5 (severe) incorporating a separate assessment of the severity of the three primary signs of the plaques of all involved areas: erythema, scaling and plaque elevation with an overall sPGA. Scores for each assessment are rounded to the nearest whole number to result in the final score. Higher scores represented worse outcomes. ITT population included all subjects who are enrolled into the study, received at least one administration of Skilarence® and had at least one post dosing evaluation. Last Observation Carried Forward (LOCF) methodology was used to impute missing efficacy measurements for this outcome.

End point type	Secondary

End point timeframe:

At weeks 12 and 16

End point values	Skilarence®			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: Percent change				
arithmetic mean (standard deviation)				
At week 12	-13 (± 70)			
At week 16	-20 (± 89)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving a Score of "Clear" or "Almost Clear" in Static Physician Global Assessment (sPGA) at Weeks 12, 16 and 24

End point title	Percentage of Subjects Achieving a Score of "Clear" or "Almost Clear" in Static Physician Global Assessment (sPGA) at Weeks 12, 16 and 24

End point description:

sPGA is an average assessment of all psoriatic lesions, based on erythema, scale and induration; it does not quantify body surface area nor evaluate individual lesion locations. 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4=moderate to severe, 5 = severe. Here, n=Number Analyzed, signifies those subject who were evaluable for specified timepoint.

End point type	Secondary

End point timeframe:

At weeks 12, 16 and 24

End point values	Skilarence®			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: Percenatge of subjects				
number (not applicable)				
At week 12 (n=95)	13.7			
At week 16 (n=96)	19.8			
At week 24 (n=97)	29.9			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to 24 weeks	
Adverse event reporting additional description:	
The safety population included all subjects who received at least one dose of Skilarence®.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	Skilarence®

Reporting group description:

Subjects received starting dose of 30 mg of Skilarence® tablet once a day (in the evening) for seven days (± 3 days). The dose of Skilarence® taken by the patient was then gradually increased and given up to 24 weeks. In the second week, Skilarence® 30 mg was taken twice daily (1 tablet in the morning and 1 in the evening). In the third week, Skilarence® 30 mg was taken three times daily (1 tablet in the morning, 1 at midday, and 1 in the evening). From the fourth week, treatment was switched to only 1 tablet of Skilarence® 120mg in the evening; although flexibility with dose adjustments and timing of dose adjustments was allowed. Skilarence® dose could then be increased by 1 Skilarence® 120mg tablet per week at different times of day for the subsequent 5 weeks. The maximum daily dose allowed was 720mg (3 x 2 tablets of Skilarence® 120mg).

Serious adverse events	Skilarence®		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 100 (2.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Skin laceration			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Paronychia			

subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Skilarence®		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	96 / 100 (96.00%)		
Vascular disorders			
Flushing			
subjects affected / exposed	49 / 100 (49.00%)		
occurrences (all)	76		
Hot flush			
subjects affected / exposed	7 / 100 (7.00%)		
occurrences (all)	8		
Surgical and medical procedures			
Nasal polypectomy			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Polypectomy			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Chest discomfort			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	7 / 100 (7.00%)		
occurrences (all)	10		
Feeling hot			
subjects affected / exposed	3 / 100 (3.00%)		
occurrences (all)	6		

Influenza like illness subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1		
Malaise subjects affected / exposed occurrences (all)	2 / 100 (2.00%) 4		
Pain subjects affected / exposed occurrences (all)	2 / 100 (2.00%) 2		
Pyrexia subjects affected / exposed occurrences (all)	2 / 100 (2.00%) 2		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	5 / 100 (5.00%) 5		
Oropharyngeal pain subjects affected / exposed occurrences (all)	3 / 100 (3.00%) 3		
Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1		
Throat irritation subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1		
Wheezing subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 3		
Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	2 / 100 (2.00%) 3		
Depressed mood			

subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	4		
Depression			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Basophil count increased			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Blood bilirubin increased			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
Blood pressure increased			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Blood urine present			
subjects affected / exposed	3 / 100 (3.00%)		
occurrences (all)	4		
Colonoscopy			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Eosinophil count increased			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	3		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	2		
Glycosylated haemoglobin increased			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Granulocyte count increased			

subjects affected / exposed	1 / 100 (1.00%)			
occurrences (all)	1			
Hepatic enzyme increased				
subjects affected / exposed	2 / 100 (2.00%)			
occurrences (all)	2			
Lymphocyte count				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences (all)	1			
Lymphocyte count abnormal				
subjects affected / exposed	4 / 100 (4.00%)			
occurrences (all)	4			
Lymphocyte count decreased				
subjects affected / exposed	27 / 100 (27.00%)			
occurrences (all)	42			
Lymphocyte count increased				
subjects affected / exposed	3 / 100 (3.00%)			
occurrences (all)	3			
Lymphocyte morphology abnormal				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences (all)	1			
Monocyte count decreased				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences (all)	1			
Monocyte count increased				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences (all)	1			
Neutrophil count increased				
subjects affected / exposed	3 / 100 (3.00%)			
occurrences (all)	4			
Protein urine present				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences (all)	1			
Sputum abnormal				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences (all)	1			
Vitamin B12 decreased				

subjects affected / exposed occurrences (all) White blood cell count decreased subjects affected / exposed occurrences (all) White blood cell count increased subjects affected / exposed occurrences (all) White blood cells urine subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1 1 / 100 (1.00%) 1 3 / 100 (3.00%) 3 2 / 100 (2.00%) 2		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) Soft tissue injury subjects affected / exposed occurrences (all)	 2 / 100 (2.00%) 2 1 / 100 (1.00%) 1		
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	 2 / 100 (2.00%) 2		
Nervous system disorders Burning sensation subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Migraine subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all)	 2 / 100 (2.00%) 2 15 / 100 (15.00%) 15 2 / 100 (2.00%) 2 10 / 100 (10.00%) 12		
Blood and lymphatic system disorders			

Eosinophilia			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Lymphopenia			
subjects affected / exposed	8 / 100 (8.00%)		
occurrences (all)	10		
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Eye disorders			
Blepharitis			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Eye swelling			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	9 / 100 (9.00%)		
occurrences (all)	9		
Abdominal distension			
subjects affected / exposed	5 / 100 (5.00%)		
occurrences (all)	5		
Abdominal pain			
subjects affected / exposed	22 / 100 (22.00%)		
occurrences (all)	30		
Abdominal pain lower			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	26 / 100 (26.00%)		
occurrences (all)	32		
Bowel movement irregularity			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Coating in mouth			

subjects affected / exposed	1 / 100 (1.00%)			
occurrences (all)	1			
Constipation				
subjects affected / exposed	5 / 100 (5.00%)			
occurrences (all)	5			
Diarrhoea				
subjects affected / exposed	44 / 100 (44.00%)			
occurrences (all)	67			
Dry mouth				
subjects affected / exposed	3 / 100 (3.00%)			
occurrences (all)	3			
Dyspepsia				
subjects affected / exposed	3 / 100 (3.00%)			
occurrences (all)	3			
Faeces soft				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences (all)	1			
Flatulence				
subjects affected / exposed	9 / 100 (9.00%)			
occurrences (all)	10			
Food poisoning				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences (all)	1			
Frequent bowel movements				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences (all)	1			
Gastrointestinal disorder				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences (all)	1			
Gastrooesophageal reflux disease				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences (all)	1			
Lip swelling				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences (all)	1			
Nausea				

subjects affected / exposed	18 / 100 (18.00%)		
occurrences (all)	19		
Vomiting			
subjects affected / exposed	8 / 100 (8.00%)		
occurrences (all)	12		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	2		
Angioedema			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Blister			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	5 / 100 (5.00%)		
occurrences (all)	7		
Flushing			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	2		
Hyperhidrosis			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Pain of skin			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	3		
Pruritus			
subjects affected / exposed	15 / 100 (15.00%)		
occurrences (all)	18		
Psoriasis			
subjects affected / exposed	9 / 100 (9.00%)		
occurrences (all)	9		

Rash subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1		
Rash macular subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1		
Seborrhoeic dermatitis subjects affected / exposed occurrences (all)	2 / 100 (2.00%) 2		
Skin burning sensation subjects affected / exposed occurrences (all)	4 / 100 (4.00%) 16		
Urticaria subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1		
Renal and urinary disorders Chromaturia subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1		
Glycosuria subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1		
Pollakiuria subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 2		
Urine odour abnormal subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	4 / 100 (4.00%) 4		
Back pain subjects affected / exposed occurrences (all)	2 / 100 (2.00%) 2		
Bursitis			

subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	3 / 100 (3.00%)		
occurrences (all)	7		
Musculoskeletal discomfort			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	2		
Musculoskeletal pain			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Psoriatic arthropathy			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Infections and infestations			
Bacterial vaginosis			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Corona virus infection			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Cystitis			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Ear infection			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		

Gastroenteritis viral				
subjects affected / exposed	2 / 100 (2.00%)			
occurrences (all)	2			
Gastrointestinal infection				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences (all)	1			
Infection				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences (all)	1			
Influenza				
subjects affected / exposed	4 / 100 (4.00%)			
occurrences (all)	4			
Lower respiratory tract infection				
subjects affected / exposed	2 / 100 (2.00%)			
occurrences (all)	3			
Nasopharyngitis				
subjects affected / exposed	3 / 100 (3.00%)			
occurrences (all)	13			
Oral herpes				
subjects affected / exposed	3 / 100 (3.00%)			
occurrences (all)	3			
Penile infection				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences (all)	1			
Post procedural infection				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences (all)	1			
Respiratory tract infection				
subjects affected / exposed	2 / 100 (2.00%)			
occurrences (all)	2			
Rhinitis				
subjects affected / exposed	2 / 100 (2.00%)			
occurrences (all)	2			
Sinusitis				
subjects affected / exposed	2 / 100 (2.00%)			
occurrences (all)	2			

Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 3 / 100 (3.00%) 3 2 / 100 (2.00%) 2		
Metabolism and nutrition disorders Gout subjects affected / exposed occurrences (all) Type 2 diabetes mellitus subjects affected / exposed occurrences (all)	 1 / 100 (1.00%) 1 1 / 100 (1.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported