Clinical trial results:
A Randomized, Controlled, Multicenter, Open-label Study With Blinded Assessment of the Efficacy of Subcutaneous Secukinumab Compared to Fumaderm® in Adults With Moderate to Severe Plaque Psoriasis.

Summary

EudraCT number	2014-005258-20
Trial protocol	DE
Global end of trial date	13 June 2016

Results information

Result version number	v1 (current)
This version publication date	27 June 2017
First version publication date	27 June 2017

Trial information

Trial identification

Sponsor protocol code	CAIN457ADE06

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02474082
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,

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	13 June 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary study objective was to demonstrate the superiority of secukinumab compared to Fumaric Acid in subjects with moderate to severe plaque psoriasis based on the proportion of Psoriasis Area Severity Index (PASI) 75 responders at week 24.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 April 2015
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	Germany: 202
Worldwide total number of subjects	202
EEA total number of subjects	202

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)	188
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 202 (secukinumab: 105 and fumaric acid derivatives: 97) subjects were randomized in the study out of which 200 (secukinumab: 105 and fumaric acid derivatives: 95) received treatment. 2 subjects were discontinued from the study due to non-compliance with study treatment (1) and withdrawal of informed consent (1).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Blinding implementation details:

This was an open label study. However, a blinded assessor performed all non-subject-reported efficacy assessments to minimize bias.

Arms

Are arms mutually exclusive?	Yes
Arm title	Secukinumab

Arm description:

Subjects were self-administered subcutaneously (s.c.) with a dose of 300 milligrams (mg) of secukinumab at weeks 0, 1, 2, 3, 4, 8, 12, 16 and 20. Secukinumab was injected in non-affected areas of the skin at front of thighs or lower abdomen (but not the area 5 centimeters (cm) around the navel).

Arm type	Experimental
Investigational medicinal product name	Secukinumab
Investigational medicinal product code	AIN457
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Secukinumab 150 mg [1 ml liquid formulation in a pre-filled pen for s.c. injection]

Arm title	Fumaric acid (initial and maintenance therapy)

Arm description:

Subjects were daily self-administered with fumaric acid derivatives initial and maintenance therapy in dose-titrated scheme as per protocol. Dose was up-titrated weekly (1 tablet/day) until objective was achieved or until tapering was required or until the maximum dose of 2 tablets each at morning, noon and evening was reached, whichever occurred earlier.

Arm type	Active comparator
Investigational medicinal product name	Fumaric acid,
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Fumaric acid initial therapy (tablet contains 30 mg dimethylfumarate, 67 mg ethylhydrogenfumarate calcium salt, 5 mg ethylhydrogenfumarate magnesium salt, 3 mg ethylhydrogenfumarate zinc salt) and Fumaric acid maintenance therapy (tablet contains 120 mg dimethylfumarate, 87 mg ethylhydrogenfumarate calcium salt, 5 mg ethylhydrogenfumarate magnesium salt, 3 mg ethylhydrogenfumarate zinc salt)

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: A blinded assessor performed all non-subject-reported efficacy assessments to minimize bias.

Number of subjects in period 1	Secukinumab	Fumaric acid (initial and maintenance therapy)
Started	105	97
Full analysis set (FAS)	105	95
Completed	99	43
Not completed	6	54
Dose tapering not achieved	-	4
Adverse event, non-fatal	2	32
Non-compliance with study treatment	-	2
Protocol deviation	-	1
Withdrawal of informed consent	1	11
Lost to follow-up	2	2
Participant/guardian decision	-	2
Subject/guardian decision	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Secukinumab
Reporting group description:	
Subjects were self-administered subcutaneously (s.c.) with a dose of 300 milligrams (mg) of secukinumab at weeks 0, 1, 2, 3, 4, 8, 12, 16 and 20. Secukinumab was injected in non-affected areas of the skin at front of thighs or lower abdomen (but not the area 5 centimeters (cm) around the navel).	
Reporting group title	Fumaric acid (initial and maintenance therapy)
Reporting group description:	
Subjects were daily self-administered with fumaric acid derivatives initial and maintenance therapy in dose-titrated scheme as per protocol. Dose was up-titrated weekly (1 tablet/day) until objective was achieved or until tapering was required or until the maximum dose of 2 tablets each at morning, noon and evening was reached, whichever occurred earlier.	

Reporting group values	Secukinumab	Fumaric acid (initial and maintenance therapy)	Total
Number of subjects	105	97	202
Age categorical Units: Subjects			
Adults (18-64 years)	98	90	188
From 65-84 years	7	7	14
Age Continuous Units: years			
arithmetic mean	43.2	42.4	
standard deviation	± 14.2	± 13.2	-
Gender, Male/Female Units: Subjects			
Female	40	37	77
Male	65	60	125

End points

End points reporting groups

Reporting group title	Secukinumab

Reporting group description:

Subjects were self-administered subcutaneously (s.c.) with a dose of 300 milligrams (mg) of secukinumab at weeks 0, 1, 2, 3, 4, 8, 12, 16 and 20. Secukinumab was injected in non-affected areas of the skin at front of thighs or lower abdomen (but not the area 5 centimeters (cm) around the navel).

Reporting group title	Fumaric acid (initial and maintenance therapy)

Reporting group description:

Subjects were daily self-administered with fumaric acid derivatives initial and maintenance therapy in dose-titrated scheme as per protocol. Dose was up-titrated weekly (1 tablet/day) until objective was achieved or until tapering was required or until the maximum dose of 2 tablets each at morning, noon and evening was reached, whichever occurred earlier.

Primary: Percentage of subjects achieving Psoriasis Area and Severity Index (PASI) 75 Response at week 24

End point title	Percentage of subjects achieving Psoriasis Area and Severity Index (PASI) 75 Response at week 24

End point description:

PASI score is average degree of severity of signs in head[H],trunk[T],upper limbs[U] and lower limbs[L],assessed separately for erythema[E],thickening (plaque elevation, induration)[I], and scaling (desquamation)[D]. Area[A] covered by lesions on each body region was estimated as percentage (%) of total area of that particular body region and was assigned score of 0=0%; 1=1-9%; 2=10-29%; 3=30-49%; 4=50-69%; 5=70-89%; 6=90-100%. Head and neck, upper limbs, trunk and lower limbs correspond to approximately 10%, 20%, 30% and 40% of the body surface area, respectively. PASI score was calculated as: PASI = 0.1(EH+IH+DH) AH + 0.2(EU+IU+DU) AU + 0.3(ET+IT+DT) AT + 0.4(EL+IL+DL) AL. PASI scores can range from 0 (no signs) to maximum of 72. PASI 75 responders were subjects who achieved >=75% improvement (reduction) in PASI score compared to baseline. The analysis was performed in Full analysis set (FAS) population defined as all randomized subjects who received at least one dose of study drug.

End point type	Primary

End point timeframe:

Baseline, Week 24

End point values	Secukinumab	Fumaric acid (initial and maintenance therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	95		
Units: Percentage of subjects				
number (not applicable)	89.52	33.68		

Statistical analyses

Statistical analysis title	PASI 75 response at week 24
Comparison groups	Secukinumab v Fumaric acid (initial and maintenance therapy)

Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	16.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.79
upper limit	35.4

Secondary: Percentage of subjects achieving Psoriasis Area and Severity Index (PASI) 50 Response at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point title	Percentage of subjects achieving Psoriasis Area and Severity Index (PASI) 50 Response at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point description:

PASI score is average degree of severity of signs in head[H],trunk[T],upper limbs[U] and lower limbs[L], assessed separately for erythema[E],thickening (plaque elevation, induration)[I], and scaling (desquamation)[D]. Area[A] covered by lesions on each body region was estimated as percentage(%) of total area of that particular body region and was assigned score of 0=0%; 1=1-9%; 2=10-29%; 3=30-49%; 4=50-69%; 5=70-89%; 6=90-100%. Head and neck, upper limbs, trunk and lower limbs correspond to approximately 10%, 20%, 30% and 40% of the body surface area, respectively. PASI score was calculated as: PASI = 0.1(EH+IH+DH) AH + 0.2(EU+IU+DU) AU + 0.3(ET+IT+DT) AT + 0.4(EL+IL+DL) AL. PASI scores can range from 0(no signs) to a maximum of 72. PASI 50 responders were subjects who achieved >=50% improvement (reduction) in PASI score compared to baseline. The analysis was performed in FAS population. Here 'n' signifies subjects evaluable for PASI 50 at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24.

End point type	Secondary

End point timeframe:

Baseline, Week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point values	Secukinumab	Fumaric acid (initial and maintenance therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	95		
Units: Percentage of subjects				
number (not applicable)				
Week 1 (n = 105, 91)	9.5	1.1		
Week 2 (n = 105, 95)	37.1	6.3		
Week 3 (n= 105, 95)	63.8	10.5		
Week 4 (n = 105, 95)	81.9	14.7		
Week 6 (n = 105, 95)	93.3	28.4		
Week 8 (n = 105, 95)	96.2	41.1		
Week 12 (n = 105, 95)	97.1	56.8		
Week 16 (n = 105, 95)	98.1	60		
Week 20 (n = 105, 95)	98.1	61.1		

Week 24 (n = 105, 95)	98.1	61.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects achieving Psoriasis Area and Severity Index (PASI) 75 Response at week 1, 2, 3, 4, 6, 8, 12, 16 and 20

End point title	Percentage of subjects achieving Psoriasis Area and Severity Index (PASI) 75 Response at week 1, 2, 3, 4, 6, 8, 12, 16 and 20

End point description:

PASI score is average degree of severity of signs in head[H],trunk[T],upper limbs[U] and lower limbs[L], assessed separately for erythema[E], thickening (plaque elevation, induration)[I], and scaling (desquamation)[D]. Area[A] covered by lesions on each body region was estimated as percentage(%) of total area of that particular body region and was assigned a score of 0=0%; 1=1-9%; 2=10-29%; 3=30-49%; 4=50-69%; 5=70-89%; 6=90-100%. Head and neck, upper limbs, trunk and lower limbs correspond to approximately 10%, 20%, 30% and 40% of the body surface area, respectively. PASI score was calculated as: PASI = 0.1(EH+IH+DH) AH + 0.2(EU+IU+DU) AU + 0.3(ET+IT+DT) AT + 0.4(EL+IL+DL) AL. PASI scores can range from 0 (no signs) to a maximum of 72. PASI 75 responders were subjects who achieved >=75% improvement (reduction) in PASI score compared to baseline. The analysis was performed in FAS population. Here 'n' signifies participants evaluable for PASI 75 at week 1, 2, 3, 4, 6, 8, 12, 16 and 20.

End point type	Secondary

End point timeframe:

Baseline, Week 1, 2, 3, 4, 6, 8, 12, 16 and 20

End point values	Secukinumab	Fumaric acid (initial and maintenance therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	95		
Units: Percentage of subjects				
number (not applicable)				
Week 1 (n = 105, 91)	0	0		
Week 2 (n = 105, 95)	5.7	0		
Week 3 (n = 105, 95)	24.8	0		
Week 4 (n = 105, 95)	47.6	1.1		
Week 6 (n = 105, 95)	69.5	2.1		
Week 8 (n = 105, 95)	80	8.4		
Week 12 (n = 105, 95)	87.6	21.1		
Week 16 (n = 105, 95)	88.6	27.4		
Week 20 (n = 105, 95)	88.6	36.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects achieving Psoriasis Area and Severity Index (PASI) 90 Response at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point title	Percentage of subjects achieving Psoriasis Area and Severity Index (PASI) 90 Response at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point description:

PASI score is average degree of severity of signs in head[H],trunk[T], upper limbs[U] and lower limbs[L], assessed separately for erythema[E], thickening(plaque elevation, induration)[I], and scaling (desquamation) [D]. Area[A] covered by lesions on each body region was estimated as percentage(%) of total area of that particular body region and was assigned a score of 0=0%; 1=19%; 2=10-29%; 3=30-49%; 4=50-69%; 5=70-89%; 6=90-100%. Head and neck, upper limbs, trunk and lower limbs correspond to approximately 10%,20%,30% and 40% of the body surface area, respectively. PASI score was calculated as: PASI = 0.1(EH+IH+DH) AH + 0.2(EU+IU+DU) AU + 0.3(ET+IT+DT) AT + 0.4(EL+IL+DL) AL. PASI scores can range from 0 (no signs) to maximum of 72. PASI 90 responders were subjects who achieved >=90% improvement (reduction) in PASI score compared to baseline. The analysis was performed in FAS population. Here 'n' signifies subjects evaluable for PASI 90 at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24.

End point type	Secondary

End point timeframe:

Baseline, Week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point values	Secukinumab	Fumaric acid (initial and maintenance therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	95		
Units: Percentage of subjects				
number (not applicable)				
Week 1 (n = 105, 91)	0	0		
Week 2 (n = 105, 95)	1.9	0		
Week 3 (n = 105, 95)	2.9	0		
Week 4 (n = 105, 95)	17.1	0		
Week 6 (n = 105, 95)	32.4	0		
Week 8 (n = 105, 95)	46.7	1.1		
Week 12 (n = 105, 95)	63.8	2.1		
Week 16 (n = 105, 95)	68.6	8.4		
Week 20 (n = 105, 95)	75.2	14.7		
Week 24 (n = 105, 95)	75.2	18.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects achieving Psoriasis Area and Severity Index (PASI) 100 Response at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point title	Percentage of subjects achieving Psoriasis Area and Severity Index (PASI) 100 Response at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point description:

PASI score is average degree of severity of signs in head[H],trunk[T], upper limbs[U] and lower limbs[L], assessed separately for erythema [E], thickening (plaque elevation, induration) [I], and scaling (desquamation)[D]. Area[A] covered by lesions on each body region was estimated as a percentage (%) of total area of that particular body region and was assigned a score of 0=0%; 1=1-9%; 2=10-29%; 3=30-49%; 4=50-69%; 5=70-89%; 6=90-100%. The head and neck, upper limbs, trunk and lower limbs correspond to approximately 10%, 20%, 30% and 40% of the body surface area, respectively. PASI score was calculated as: PASI = 0.1(EH+IH+DH) AH + 0.2(EU+IU+DU) AU + 0.3(ET+IT+DT) AT + 0.4(EL+IL+DL) AL. PASI scores can range from 0 (no signs) to maximum of 72. PASI 100 responders were subjects who achieved complete clearance of psoriasis (PASI=0). The analysis was performed in FAS population. Here 'n' signifies subjects evaluable for PASI 100 at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point type	Secondary

End point timeframe:

Baseline, Week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point values	Secukinumab	Fumaric acid (initial and maintenance therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	95		
Units: Percentage of subjects				
number (not applicable)				
Week 1 (n = 105, 91)	0	0		
Week 2 (n = 105, 95)	0	0		
Week 3 (n = 105, 95)	0	0		
Week 4 (n = 105, 95)	3.8	0		
Week 6 (n = 105, 95)	7.6	0		
Week 8 (n = 105, 95)	15.2	0		
Week 12 (n = 105, 95)	28.6	0		
Week 16 (n = 105, 95)	37.1	0		
Week 20 (n = 105, 95)	41	0		
Week 24 (n = 105, 95)	43.8	3.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Body surface area (BSA) at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point title	Body surface area (BSA) at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point description:

The Body surface area (BSA) affected by plaque-type psoriasis was the total of percentages of areas affected, including head, trunk, upper limbs and lower limbs. Each reported percentage was multiplied by its respective body region corresponding factor (head = 0.1, trunk = 0.3, upper limbs = 0.2, lower limbs = 0.4). The resulting four percentages were added to estimate the total BSA affected by plaque-type psoriasis. The analysis was performed in FAS population. Here 'n' signifies subjects evaluable for BSA at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24.

End point type	Secondary

End point timeframe:

Week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point values	Secukinumab	Fumaric acid (initial and maintenance therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	95		
Units: Percentage of area				
arithmetic mean (standard deviation)				
Week 1 (n = 105, 94)	23.8 (± 12.82)	23.2 (± 14.11)		
Week 2 (n = 105, 91)	20.1 (± 12.25)	22.5 (± 14.37)		
Week 3 (n = 105, 89)	17 (± 11.95)	22.1 (± 14.33)		
Week 4 (n = 103, 84)	13 (± 11.93)	21.6 (± 14.12)		
Week 6 (n = 98, 82)	9.8 (± 11.12)	19.7 (± 13.52)		
Week 8 (n = 102, 75)	7.6 (± 10.19)	17.8 (± 12.65)		
Week 12 (n = 103, 67)	5.2 (± 9.12)	13.7 (± 11.6)		
Week 16 (n = 99, 59)	3.7 (± 6.72)	11.4 (± 11.52)		
Week 20 (n = 99, 50)	2.6 (± 5.77)	9.2 (± 11.87)		
Week 24 (n = 99, 48)	2.9 (± 6.43)	7.9 (± 9.92)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects achieving Nail Psoriasis Severity Index (NAPSI) 50 response at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point title	Percentage of subjects achieving Nail Psoriasis Severity Index (NAPSI) 50 response at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point description:

NAPSI was used to assess psoriatic nail involvement in subjects with nail psoriasis. NAPSI = total of nail matrix and nail bed score, ranging from 0-8 per nail. Total NAPSI score ranges from 0-80 for all fingernails. Each nail was divided with imaginary horizontal and longitudinal lines into quadrants and given score 0-4 for nail matrix and nail bed psoriasis 0–4 (0: none, 1: 1 quadrant, 2: 2 quadrants, 3: 3 quadrants, 4: all 4 quadrants), based on presence of any feature of nail psoriasis in that quadrant. Nail matrix psoriasis feature includes: pitting, leukonychia red spots in lunula, crumbling. Nail bed psoriasis feature includes: onycholysis, splinter hemorrhages, subungual hyperkeratosis, "oil drop" (salmon patch dyschroma). NPASI 50 responders were subjects who achieved >=50% improvement (reduction) in NPASI score compared to baseline. The analysis was performed on FAS population. Here 'n' signifies subjects evaluable for NAPSI 50 at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point values	Secukinumab	Fumaric acid (initial and maintenance therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	95		
Units: Percentage of subjects				
number (not applicable)				
Week 1 (n = 56, 49)	1.8	4.1		
Week 2 (n = 56, 49)	3.6	8.2		
Week 3 (n = 56, 49)	5.4	10.2		
Week 4 (n = 56, 49)	7.1	12.2		
Week 6 (n = 56, 49)	19.6	10.2		
Week 8 (n = 56, 49)	23.2	8.2		
Week 12 (n = 56, 49)	41.1	12.2		
Week 16 (n = 56, 49)	51.8	10.2		
Week 20 (n = 56, 49)	62.5	18.4		
Week 24 (n = 56, 49)	67.9	18.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects achieving Nail Psoriasis Severity Index (NAPSI) 75 response at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point title	Percentage of subjects achieving Nail Psoriasis Severity Index (NAPSI) 75 response at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point description:

NAPSI was used to assess psoriatic nail involvement in subjects with nail psoriasis. NAPSI=total of nail matrix and nail bed score, ranging from 0-8 per nail. Total NAPSI score ranges from 0-80 for all fingernails. Each nail was divided with imaginary horizontal and longitudinal lines into quadrants. Each nail was given a score of 0-4 for nail matrix and nail bed psoriasis 0–4(0: none, 1: 1 quadrant, 2: 2 quadrants, 3: 3 quadrants, 4: all 4 quadrants), based on presence of any feature of nail psoriasis in that quadrant. Nail matrix psoriasis feature includes: pitting, leukonychia red spots in lunula, crumbling. Nail bed psoriasis feature includes: onycholysis, splinter hemorrhages, subungual hyperkeratosis, “oil drop” (salmon patch dyschroma). NPASI 75 responders were subjects who achieved >=75% improvement (reduction) in NPASI score compared to baseline. The analysis was performed on FAS population. Here 'n' signifies subjects evaluable for NAPSI 75 at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point values	Secukinumab	Fumaric acid (initial and maintenance therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	95		
Units: Percentage of subjects				
number (not applicable)				

Week 1 (n = 56, 49)	1.8	0		
Week 2 (n = 56, 49)	1.8	2		
Week 3 (n = 56, 49)	5.4	2		
Week 4 (n = 56, 49)	7.1	2		
Week 6 (n = 56, 49)	8.9	2		
Week 8 (n = 56, 49)	17.9	2		
Week 12 (n = 56, 49)	28.6	2		
Week 16 (n = 56, 49)	30.4	2		
Week 20 (n = 56, 49)	44.6	6.1		
Week 24 (n = 56, 49)	53.6	4.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects achieving Nail Psoriasis Severity Index (NAPSI) 90 response at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point title	Percentage of subjects achieving Nail Psoriasis Severity Index (NAPSI) 90 response at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point description:

NAPSI was used to assess psoriatic nail involvement in subjects with nail psoriasis. NAPSI = total of nail matrix and nail bed score, ranging from 0-8 per nail. Total NAPSI score ranges from 0-80 for all fingernails. Each nail was divided with imaginary horizontal and longitudinal lines into quadrants and given a score of 0-4 nail matrix and nail bed psoriasis 0–4 (0: none, 1: 1 quadrant, 2: 2 quadrants, 3: 3 quadrants, 4: all 4 quadrants), based on presence of any feature of nail psoriasis in that quadrant. Nail matrix psoriasis feature includes: pitting, leukonychia red spots in lunula, crumbling. Nail bed psoriasis feature includes: onycholysis, splinter hemorrhages, subungual hyperkeratosis, "oil drop" (salmon patch dyschroma). NPASI 90 responders were subjects who achieved >=90% improvement (reduction) in NPASI score compared to baseline. The analysis was performed on FAS population. Here 'n' signifies the subjects evaluable for NAPSI 90 response at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point values	Secukinumab	Fumaric acid (initial and maintenance therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	95		
Units: Percentage of subjects				
number (not applicable)				
Week 1 (n = 56, 49)	1.8	0		
Week 2 (n = 56, 49)	1.8	0		
Week 3 (n = 56, 49)	0	0		
Week 4 (n = 56, 49)	3.6	0		
Week 6 (n = 56, 49)	3.6	0		
Week 8 (n = 56, 49)	7.1	2		
Week 12 (n = 56, 49)	14.3	2		

Week 16 (n = 56, 49)	21.4	2		
Week 20 (n = 56, 49)	26.8	4.1		
Week 24 (n = 56, 49)	35.7	4.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects achieving Nail Psoriasis Severity Index (NAPSI) 100 response at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point title	Percentage of subjects achieving Nail Psoriasis Severity Index (NAPSI) 100 response at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point description:

NAPSI was used to assess psoriatic nail involvement in subjects with nail psoriasis. NAPSI = total of nail matrix and nail bed score,ranging from 0-8 per nail. Total NAPSI score ranges from 0-80 for all fingernails. Each nail was divided with imaginary horizontal and longitudinal lines into quadrants and given score of 0-4 for nail matrix and nail bed psoriasis 0–4 (0: none, 1: 1 quadrant, 2: 2 quadrants, 3: 3 quadrants, 4: all 4 quadrants), based on presence of any feature of nail psoriasis in that quadrant. Nail matrix psoriasis feature includes: pitting, leukonychia red spots in lunula, crumbling. Nail bed psoriasis feature includes: onycholysis,splinter hemorrhages,subungual hyperkeratosis, "oil drop" (salmon patch dyschroma). NPASI 100 responders were subjects who PASI 100 responders were subjects who achieved complete clearance of psoriasis. Analysis was performed on FAS population. Here 'n' signifies the subjects evaluable for NAPSI 100 response at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point values	Secukinumab	Fumaric acid (initial and maintenance therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	95		
Units: Percentage of subjects				
number (not applicable)				
Week 1 (n = 56, 49)	1.8	0		
Week 2 (n = 56, 49)	0	0		
Week 3 (n = 56, 49)	0	0		
Week 4 (n =56, 49)	3.6	0		
Week 6 (n = 56, 49)	3.6	0		
Week 8 (n = 56, 49)	5.4	2		
Week 12 (n = 56, 49)	10.7	2		
Week 16 (n = 56, 49)	19.6	2		
Week 20 (n = 56, 49)	19.6	2		
Week 24 (n = 56, 49)	23.2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Investigator's global assessment (IGA mod 2011) at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point title	Number of subjects with Investigator's global assessment (IGA mod 2011) at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point description:

IGA mod 2011 is a global static severity rating scale referring exclusively to the subject's disease state at the time of the assessments and don't attempt comparison with subject's any previous disease states at baseline or visit. IGA mod 2011 has a scale of 0-4 with the lower scores correlating to better performance. Scores used were: 0/Clear: no signs of psoriasis, Post-inflammatory hyperpigmentation may be present; 1/almost clear: Normal to pink coloration of lesions/no thickening/no to minimal focal scaling; 2/Mild: Pink to light red coloration/just detectable to mild thickening/predominantly fine scaling; 3/Moderate: Dull bright red, clearly distinguishable erythema/clearly distinguishable to moderate thickening/moderate scaling; 4/Severe: Bright to deep dark red coloration/severe thickening with hard edges/severe or coarse scaling covering almost all or all lesions. The analysis was performed in FAS population. Here 'n' signifies the subjects evaluable for IGA mod 2011 at week

End point type	Secondary

End point timeframe:

Week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point values	Secukinumab	Fumaric acid (initial and maintenance therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	95		
Units: subjects				
Week 1 (n = 105, 94) : Clear	0	0		
Week 1 (n = 105, 94) : Almost Clear	0	0		
Week 1 (n = 105, 94) : Mild	18	8		
Week 1 (n = 105, 94) : Moderate	65	58		
Week 1 (n = 105, 94) : Severe	22	28		
Week 2 (n = 105, 91) : Clear	0	0		
Week 2 (n = 105, 91) : Almost Clear	6	0		
Week 2 (n = 105, 91) : Mild	38	15		
Week 2 (n = 105, 91) : Moderate	49	56		
Week 2 (n = 105, 91) : Severe	12	20		
Week 3 (n = 105, 89) : Clear	0	0		
Week 3 (n = 105, 89) : Almost Clear	14	1		
Week 3 (n = 105, 89) : Mild	51	18		
Week 3 (n = 105, 89) : Moderate	35	51		
Week 3 (n = 105, 89) : Severe	5	19		
Week 4 (n = 103, 84) : Clear	4	0		
Week 4 (n = 103, 84) : Almost Clear	31	1		
Week 4 (n = 103, 84) : Mild	46	21		
Week 4 (n = 103, 84) : Moderate	19	46		
Week 4 (n = 103, 84) : Severe	3	16		
Week 6 (n = 98, 82) : Clear	9	0		
Week 6 (n = 98, 82) : Almost Clear	42	2		
Week 6 (n = 98, 82) : Mild	39	26		

Week 6 (n = 98, 82) : Moderate	7	44		
Week 6 (n = 98, 82) : Severe	1	10		
Week 8 (n = 102, 75) : Clear	17	0		
Week 8 (n = 102, 75) : Almost Clear	52	4		
Week 8 (n = 102, 75) : Mild	29	32		
Week 8 (n = 102, 75) : Moderate	2	34		
Week 8 (n = 102, 75) : Severe	2	5		
Week 12 (n = 103, 67) : Clear	31	0		
Week 12 (n = 103, 67) : Almost Clear	49	11		
Week 12 (n = 103, 67) : Mild	19	35		
Week 12 (n = 103, 67) : Moderate	4	19		
Week 12 (n = 103, 67) : Severe	0	2		
Week 16 (n = 99, 59) : Clear	38	0		
Week 16 (n = 99, 59) : Almost Clear	42	12		
Week 16 (n = 99, 59) : Mild	15	35		
Week 16 (n = 99, 59) : Moderate	4	11		
Week 16 (n = 99, 59) : Severe	0	1		
Week 20 (n = 99, 50) : Clear	43	0		
Week 20 (n = 99, 50) : Almost Clear	36	17		
Week 20 (n = 99, 50) : Mild	18	24		
Week 20 (n = 99, 50) : Moderate	2	8		
Week 20 (n = 99, 50) : Severe	0	1		
Week 24 (n = 99, 48) : Clear	45	4		
Week 24 (n = 99, 48) : Almost Clear	36	21		
Week 24 (n = 99, 48) : Mild	13	15		
Week 24 (n = 99, 48) : Moderate	5	7		
Week 24 (n = 99, 48) : Severe	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with IGA mod. 2011 0/1-response at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point title	Percentage of subjects with IGA mod. 2011 0/1-response at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point description:

The IGA mod 2011 scale has been developed based on a previous version of the scale used in secukinumab phase II studies in collaboration with health authorities, in particular the FDA. The explanations/descriptions of the points on the scale have been improved to ensure appropriate differentiation between the points. The IGA mod 2011 used in this study is static, i.e. it refers exclusively to the subject's disease state at the time of the assessments, and does not attempt a comparison with any of the subject's previous disease states, whether at baseline or at a previous visit.IGA mod 2011 has a scale of 0-4 with the lower scores correlating to better performance. A score of 0= clear skin, 1= almost clear skin, 2=mild, 3=moderate,4=severe. The analysis was performed on FAS population. IGA 0/1 responders: who achieved score of 0/1 and improved by at least 2 points on the IGA scale compared to baseline.

End point type	Secondary

End point timeframe:

Week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point values	Secukinumab	Fumaric acid (initial and maintenance therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	95		
Units: Percentage of subjects				
number (not applicable)				
Week 1	0	0		
Week 2	5.7	0		
Week 3	13.3	1.1		
Week 4	34.3	1.1		
Week 6	50.5	2.1		
Week 8	66.7	4.2		
Week 12	77.1	12.6		
Week 16	80	14.7		
Week 20	79	20		
Week 24	81	28.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Dermatology Life Quality Index (DLQI) at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point title	Dermatology Life Quality Index (DLQI) at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point description:

DLQI is a 10-item general dermatology disability index designed to assess health-related quality of life in adult subjects with skin diseases such as eczema, psoriasis, acne, and viral. The measure was self-administered and included domains of daily activities, leisure, personal relationships, symptoms and feelings, treatment, and work/school. Each item had four response categories ranging from 0 (not at all) to 3 (very much). “Not relevant” was also a valid response and was scored as 0. The DLQI total score was a sum of the 10 questions. Scores ranged from 0 to 30, with higher scores indicating greater impairment in health related quality of life. The analysis was performed on FAS population. Here 'n' signifies the subjects evaluable for DLQI at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24.

End point type	Secondary

End point timeframe:

Week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point values	Secukinumab	Fumaric acid (initial and maintenance therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	95		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 1 (n = 105, 94)	13.9 (± 5.86)	16.3 (± 6.44)		
Week 2 (n = 105, 91)	10.5 (± 6.22)	15.3 (± 6.99)		
Week 3 (n = 105, 89)	8.4 (± 5.96)	14.6 (± 7.01)		
Week 4 (n = 102, 84)	6.6 (± 5.13)	13.8 (± 7.23)		
Week 6 (n = 98, 82)	5.3 (± 5.79)	12.4 (± 7.24)		
Week 8 (n = 102, 77)	4.2 (± 4.75)	11 (± 7.16)		
Week 12 (n = 103, 67)	3.1 (± 4.41)	8.8 (± 7.1)		
Week 16 (n = 99, 59)	2.7 (± 3.95)	6.8 (± 6.05)		
Week 20 (n = 98, 50)	2.5 (± 3.84)	5.9 (± 5.67)		
Week 24 (n = 99, 48)	2 (± 3.58)	5.4 (± 5.56)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with DLQI 0/1 response at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point title	Percentage of subjects with DLQI 0/1 response at week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point description:

DLQI is a 10-item general dermatology disability index designed to assess health-related quality of life in adult subjects with skin diseases such as eczema, psoriasis, acne, and viral. The measure was self-administered and included domains of daily activities, leisure, personal relationships, symptoms and feelings, treatment, and work/school. Each item had four response categories ranging from 0 (not at all) to 3 (very much). "Not relevant" was also a valid response and was scored as 0. The DLQI total score was a sum of the 10 questions. Scores ranged from 0 to 30, with higher scores indicating greater impairment in health related quality of life. DLQI 0/1 response was the achievement of a DLQI score of 0 or 1. The analysis was performed on FAS population.

End point type	Secondary

End point timeframe:

Week 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24

End point values	Secukinumab	Fumaric acid (initial and maintenance therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	95		
Units: Percentage of subjects				
number (not applicable)				
Week 1	0	0		
Week 2	3.8	1.1		

Week 3	7.6	0		
Week 4	19	2.1		
Week 6	30.5	4.2		
Week 8	40	6.3		
Week 12	57.1	10.5		
Week 16	59	14.7		
Week 20	64.8	15.8		
Week 24	71.4	25.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with Short Form 36 (SF-36) response at week 4, 16 and 24

End point title	Percentage of subjects with Short Form 36 (SF-36) response at week 4, 16 and 24

End point description:

SF-36 is a generic indicator of health status for use in population surveys and evaluative studies of health policy. The SF-36 included 36 items in a Likert-type or forced-choice format measured on eight dimensions. The scores for each domain range from 0 to 100, with high scores indicating a better status. SF-36 responder is defined as subject reaching at least an improvement of minimum important difference (MID).
The SF-36 measure dimensions and their MID includes:
• Physical Functioning:4.3
• Role-Physical: 3.4
• Bodily Pain: 6.2
• General Health: 7.2
• Vitality: 6.2
• Social Functioning: 6.9
• Role-Emotional: 4.5
• Mental Health: 6.2

Two component scores and their MID which were derived from the above mentioned 8 domains includes:
• Physical component summary: 3.4
• Mental component summary: 4.6.

The analysis was performed on FAS population. Here 'n' signifies the subjects evaluable for SF-36 response at week 4, 16 and 24.

End point type	Secondary

End point timeframe:

Week 4, 16 and 24

End point values	Secukinumab	Fumaric acid (initial and maintenance therapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	95		
Units: Percentage of subjects				
number (not applicable)				
Physical Component Summary Week 4 (n= 97, 88)	38.1	26.1		

Mental component summary Week 4 (n= 97, 88)	41.2	36.4		
Physical functioning scale Week 4 (n= 102, 92)	24.5	19.6		
Role physical scale Week 4 (n= 104, 93)	44.2	23.7		
Bodily pain scale Week 4 (n= 105, 95)	53.3	31.6		
General health scale Week 4 (n= 102, 95)	32.4	21.1		
Vitality scale Week 4 (n= 104, 93)	31.7	20.4		
Social functioning scale Week 4 (n= 102, 94)	39.2	27.7		
Role emotional scale Week 4 (n= 104, 95)	41.3	34.7		
Mental health scale Week 4 (n = 105, 95)	33.3	32.6		
Physical Component Summary Week 16 (n= 97, 88)	52.6	39.8		
Mental component summary Week 16 (n= 97, 88)	63.9	46.6		
Physical functioning scale Week 16 (n= 102, 92)	36.3	31.5		
Role physical scale Week 16 (n= 104, 93)	52.9	36.6		
Bodily pain scale Week 16 (n= 105, 95)	63.8	45.3		
General health scale Week 16 (n= 102, 95)	38.2	22.1		
Vitality scale Week 16 (n= 104, 93)	45.2	23.7		
Social functioning scale Week 16 (n= 102, 94)	57.8	41.5		
Role emotional scale Week 16 (n= 104, 95)	56.7	43.2		
Mental health scale Week 16 (n = 105, 95)	54.3	42.1		
Physical Component Summary Week 24 (n= 97, 88)	57.7	43.2		
Mental component summary Week 24 (n= 97, 88)	63.9	50		
Physical functioning scale Week 24 (n= 102, 92)	38.2	31.5		
Role physical scale Week 24 (n= 104, 93)	52.9	37.6		
Bodily pain scale Week 24 (n= 105, 95)	64.8	49.5		
General health scale Week 24 (n= 102, 95)	41.2	21.1		
Vitality scale Week 24 (n= 104, 93)	48.1	29		
Social functioning scale Week 24 (n= 102, 94)	63.7	45.7		
Role emotional scale Week 24 (n= 104, 95)	54.8	41.1		
Mental health scale Week 24 (n = 105, 95)	53.3	38.9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit (up to 29 weeks).

Adverse event reporting additional description:

The safety analysis set consisted of all patients who took at least one dose of study treatment during the treatment period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Fumaric acid (initial and maintenance therapy)

Reporting group description:

Participants were daily self-administered with fumaric acid derivatives initial and maintenance therapy in dose-titrated scheme as per protocol. Dose was up-titrated weekly (1 tablet/day) until objective was achieved or until tapering was required or until the maximum dose of 2 tablets each at morning, noon and evening was reached, whichever occurred earlier.

Reporting group title	Secukinumab

Reporting group description:

Participants were self-administered subcutaneously (s.c.) with a dose of 300 milligrams (mg) of secukinumab at weeks 0, 1, 2, 3, 4, 8, 12, 16 and 20. Secukinumab was injected in non-affected areas of the skin at front of thighs or lower abdomen (but not the area 5 centimeters (cm) around the navel).

Serious adverse events	Fumaric acid (initial and maintenance therapy)	Secukinumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 95 (4.21%)	4 / 105 (3.81%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
METASTASES TO CENTRAL NERVOUS SYSTEM			
subjects affected / exposed	0 / 95 (0.00%)	1 / 105 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL CELL LUNG CANCER			
subjects affected / exposed	0 / 95 (0.00%)	1 / 105 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural			

complications			
CLAVICLE FRACTURE			
subjects affected / exposed	0 / 95 (0.00%)	1 / 105 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
THROMBOSIS			
subjects affected / exposed	0 / 95 (0.00%)	1 / 105 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
BRAIN OEDEMA			
subjects affected / exposed	0 / 95 (0.00%)	1 / 105 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	0 / 95 (0.00%)	1 / 105 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ANAL HAEMORRHAGE			
subjects affected / exposed	1 / 95 (1.05%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	1 / 95 (1.05%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
PSORIASIS			
subjects affected / exposed	2 / 95 (2.11%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

PILONIDAL CYST			
subjects affected / exposed	1 / 95 (1.05%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	0 / 95 (0.00%)	1 / 105 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Fumaric acid (initial and maintenance therapy)	Secukinumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	85 / 95 (89.47%)	75 / 105 (71.43%)	
Investigations			
BLOOD CREATININE INCREASED			
subjects affected / exposed	6 / 95 (6.32%)	1 / 105 (0.95%)	
occurrences (all)	6	3	
Vascular disorders			
FLUSHING			
subjects affected / exposed	34 / 95 (35.79%)	1 / 105 (0.95%)	
occurrences (all)	90	1	
HOT FLUSH			
subjects affected / exposed	7 / 95 (7.37%)	1 / 105 (0.95%)	
occurrences (all)	8	1	
HYPERTENSION			
subjects affected / exposed	1 / 95 (1.05%)	6 / 105 (5.71%)	
occurrences (all)	1	7	
Nervous system disorders			
HEADACHE			
subjects affected / exposed	15 / 95 (15.79%)	15 / 105 (14.29%)	
occurrences (all)	19	26	
Blood and lymphatic system disorders			
EOSINOPHILIA			

subjects affected / exposed	17 / 95 (17.89%)	1 / 105 (0.95%)	
occurrences (all)	20	2	
LEUKOCYTOSIS			
subjects affected / exposed	5 / 95 (5.26%)	2 / 105 (1.90%)	
occurrences (all)	8	3	
LEUKOPENIA			
subjects affected / exposed	5 / 95 (5.26%)	1 / 105 (0.95%)	
occurrences (all)	5	3	
LYMPHOPENIA			
subjects affected / exposed	23 / 95 (24.21%)	2 / 105 (1.90%)	
occurrences (all)	32	2	
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	6 / 95 (6.32%)	4 / 105 (3.81%)	
occurrences (all)	6	9	
Gastrointestinal disorders			
ABDOMINAL DISTENSION			
subjects affected / exposed	6 / 95 (6.32%)	1 / 105 (0.95%)	
occurrences (all)	6	1	
ABDOMINAL PAIN			
subjects affected / exposed	11 / 95 (11.58%)	2 / 105 (1.90%)	
occurrences (all)	13	2	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	37 / 95 (38.95%)	3 / 105 (2.86%)	
occurrences (all)	67	5	
DIARRHOEA			
subjects affected / exposed	48 / 95 (50.53%)	7 / 105 (6.67%)	
occurrences (all)	87	7	
FLATULENCE			
subjects affected / exposed	5 / 95 (5.26%)	0 / 105 (0.00%)	
occurrences (all)	6	0	
NAUSEA			
subjects affected / exposed	20 / 95 (21.05%)	3 / 105 (2.86%)	
occurrences (all)	24	3	
VOMITING			

subjects affected / exposed	7 / 95 (7.37%)	2 / 105 (1.90%)	
occurrences (all)	8	2	
Skin and subcutaneous tissue disorders			
PRURITUS			
subjects affected / exposed	8 / 95 (8.42%)	7 / 105 (6.67%)	
occurrences (all)	9	8	
Renal and urinary disorders			
HAEMATURIA			
subjects affected / exposed	3 / 95 (3.16%)	6 / 105 (5.71%)	
occurrences (all)	3	6	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	4 / 95 (4.21%)	6 / 105 (5.71%)	
occurrences (all)	4	6	
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	40 / 95 (42.11%)	54 / 105 (51.43%)	
occurrences (all)	55	86	
URINARY TRACT INFECTION			
subjects affected / exposed	3 / 95 (3.16%)	6 / 105 (5.71%)	
occurrences (all)	3	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 May 2015	This amendment came into effect when randomization was 6% completed in order to align study treatment with the German guidelines, to clarify handling of laboratory abnormalities and discontinuation criteria, and to introduce photography as an optional procedure in the study. Following changes were introduced: • It was clarified that subject with hematology lab results >1 x upper limit to normal (ULN) or <1 x lower limit to normal can be included, if the laboratory abnormality is deemed clinically irrelevant by the investigator • Based on a recommendation in the German guidelines, affected renal function (including but not limited to subject who experience proteinuria), was added a reason for dose tapering. • It was clarified that pathological changes of blood counts are marked positive on the laboratory results of the central laboratory and that the decision, whether a change is deemed pathological and thus constitutes a reason for discontinuation, is at the discretion of the investigator. • Based on a recommendation in the German guidelines, it was clarified that eosinophilia during fumaric acid treatment is usually transient and occurs between weeks 4 and 10 of treatment. Subject with eosinophilia, even if marked positive by the central laboratory, may continue the study, if eosinophilia is deemed transient and the overall benefit of continuing outweighs the risk at the discretion of the investigator. • Signs and symptoms of progressive multifocal leukoencephalopathy (PML) were added as examples of AEs that, in the judgment of the investigator/qualified site staff, taking into account the patient's overall status, might prevent the patient from continuing study treatment. • Dispensing fumaric acid was added to the visit schedule.
08 October 2015	Amendment No. 2 introduced the following changes: • For interaction with health technology assessment (HTA) bodies and payers, as interim analysis of the data available during the first quarter of 2016, or as required was introduced. The results were to be analyzed by an independent statistician and released to a pre-defined and limited group of Novartis personnel only for interactions with HTA bodies and payers. The clinical study team, the investigators, site personnel, and the subjects remained blinded to the result of the interim analysis until the full study data base was locked and the blinded data review meeting was completed. • It was clarified that subjects with serum creatinine above 1 x ULN may be included, if the laboratory abnormality was deemed clinically irrelevant by the investigator. • It was clarified that subjects treated with fumaric acid, who develop a serum creatinine above 1 x ULN, may continue in the study, if the laboratory abnormality was deemed clinically irrelevant by the investigator. • A new inclusion criterion was added: "Subjects for whom fumaric acid is expected to be the patient individually optimized standard therapy under consideration of fumaric acid, ciclosporin, methotrexate or phototherapy as per investigator's discretion." • The confirmation that fumaric acid was expected to be the patient-individually optimized standard therapy as per investigator's discretion was to be documented as part of the baseline characteristics. If needed, the confirmation was allowed to be collected retrospectively. • Discontinuation criteria were updated to reflect precautions with respect to PML. • Examinations for signs and symptoms of PML were added to the visit schedule and assessments. • Errors in the assessment schedule and assessments were corrected.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported