Clinical trial results:
Long term clear skin maintenance treatment optimization in patients with moderate to severe chronic plaque psoriasis: A randomized, multicenter, open-label with blinded-assessment, comparative, 52 week study to evaluate the efficacy, safety and tolerability of secukinumab 300 mg s.c.

Summary

EudraCT number	2014-005339-15
Trial protocol	PT ES IE NL CZ SK AT BE HU SE DE BG DK FI LV LT FR GR GB PL HR IT
Global end of trial date	08 May 2017
Results information	
Result version number	v1 (current)
This version publication date	20 May 2018
First version publication date	20 May 2018

Trial information

Trial identification	
Sponsor protocol code	CAIN457A3302
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02409667
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, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.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	08 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to demonstrate in the patient pool of PASI 90 responders at Week 24 that secukinumab 300 mg subcutaneous (s.c.) every 6 weeks treatment is non-inferior to secukinumab 300 mg s.c. every 4 weeks treatment with respect to maintaining a PASI 90 response rate at Week 52.

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	07 May 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	Austria: 22
Country: Number of subjects enrolled	Belgium: 29
Country: Number of subjects enrolled	Bulgaria: 50
Country: Number of subjects enrolled	Croatia: 20
Country: Number of subjects enrolled	Czech Republic: 73
Country: Number of subjects enrolled	Denmark: 16
Country: Number of subjects enrolled	Finland: 13
Country: Number of subjects enrolled	France: 131
Country: Number of subjects enrolled	Germany: 307
Country: Number of subjects enrolled	United Kingdom: 50
Country: Number of subjects enrolled	Greece: 23
Country: Number of subjects enrolled	Hungary: 56
Country: Number of subjects enrolled	Israel: 46
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Latvia: 49
Country: Number of subjects enrolled	Lithuania: 32
Country: Number of subjects enrolled	Netherlands: 43
Country: Number of subjects enrolled	Poland: 122

Country: Number of subjects enrolled	Portugal: 37
Country: Number of subjects enrolled	Russian Federation: 85
Country: Number of subjects enrolled	Slovakia: 29
Country: Number of subjects enrolled	Spain: 351
Country: Number of subjects enrolled	Sweden: 20
Country: Number of subjects enrolled	Switzerland: 22
Worldwide total number of subjects	1647
EEA total number of subjects	1494

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)	1553
From 65 to 84 years	91
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The screening period was up to 4 weeks and rescreening was allowed for an unlimited number of times. At the Screening Visit, every patient was registered in an Interactive Response Technology and the Investigator ensured that the patient fulfilled all the inclusion/exclusion criteria.

Period 1

Period 1 title	Treatment Period 1 ->Treatment Period 2 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	No
Arm title	Treatment Period 1: All participants

Arm description:

Participants received secukinumab 300 mg subcutaneous (s.c.) every 4 weeks for 24 weeks.

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

Dosage and administration details:

Secukinumab 300 mg subcutaneous (s.c.) every 4 weeks for 24 weeks.

Arm title	Treatment Period 2: Group 1

Arm description:

Participants with moderate to severe plaque psoriasis who had reached PASI 90 response after 24 weeks of treatment with secukinumab 300 mg s.c. every 4 weeks were treated with Secukinumab 300 mg s.c. from week 24 until Week 52 every 4 weeks.

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

Dosage and administration details:

Secukinumab 300 mg subcutanous (s.c.) from week 24 until Week 52 every 4 weeks

Arm title	Treatment Period 2: Group 2

Arm description:

Participants with moderate to severe plaque psoriasis who had reached PASI 90 response after 24 weeks of treatment with secukinumab 300 mg s.c. every 4 weeks were treated with Secukinumab 300 mg s.c. from week 24 until Week 52 every 6 weeks.

Arm type	Experimental

Investigational medicinal product name	Secukinumab
Investigational medicinal product code	AIN457
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Secukinumab 300 mg subcutanous (s.c.) from week 24 until Week 52 every 6 weeks

Arm title	Treatment period 2: Group 3

Arm description:

Participants with moderate to severe plaque psoriasis who had reached PASI 75 to <90 response after 24 weeks of treatment with secukinumab 300 mg s.c. every 4 weeks will be treated with Secukinumab 300 mg s.c. from week 24 until Week 52 every 4 weeks.

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

Dosage and administration details:

Secukinumab 300 mg subcutanous (s.c.) from week 24 until Week 52 every 4 weeks.

Arm title	Treatment period 2: Group 4

Arm description:

Participants with moderate to severe plaque psoriasis, who had reached PASI 75 to <90 response after 24 weeks of treatment with secukinumab 300 mg s.c. every 4 weeks, were treated with Secukinumab 300 mg s.c. from week 24 until Week 52 every 2 weeks.

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

Dosage and administration details:

Secukinumab 300 mg subcutanous (s.c.) from week 24 until Week 52 every 2 weeks

Number of subjects in period 1	Treatment Period 1: All participants	Treatment Period 2: Group 1	Treatment Period 2: Group 2
Started	1647	644	662
Completed	1526	621	641
Not completed	121	23	21
Consent withdrawn by subject	6	5	4
Physician decision	4	-	-
Adverse event, non-fatal	25	7	4
Protocol deviation	20	-	-
Non-compliance with study treatment	5	-	-
Pregnancy	1	-	1
Withdrawal of informed consent	6	-	-

Lost to follow-up	6	7	4
Lack of efficacy	48	-	-
Withdrawal by subject	-	4	5
Protocol deviation	-	-	3

Number of subjects in period 1	Treatment period 2: Group 3	Treatment period 2: Group 4
Started	114	93
Completed	106	90
Not completed	8	3
Consent withdrawn by subject	-	-
Physician decision	-	-
Adverse event, non-fatal	1	2
Protocol deviation	-	-
Non-compliance with study treatment	-	-
Pregnancy	-	1
Withdrawal of informed consent	-	-
Lost to follow-up	3	-
Lack of efficacy	2	-
Withdrawal by subject	2	-
Protocol deviation	-	-

Baseline characteristics

Reporting groups

Reporting group title	Treatment Period 1 ->Treatment Period 2

Reporting group description: -

Reporting group values	Treatment Period 1 ->Treatment Period 2	Total	
Number of subjects	1647	1647	
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)	1553	1553	
From 65-84 years	91	91	
85 years and over	3	3	
Age Continuous Units: Years			
arithmetic mean	43.1		
standard deviation	± 13.38	-	
Sex: Female, Male Units: Subjects			
Female	476	476	
Male	1171	1171	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	16	16	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	4	4	
White	1597	1597	
More than one race	0	0	
Unknown or Not Reported	30	30	

End points

End points reporting groups

Reporting group title	Treatment Period 1: All participants
Reporting group description:	
Participants received secukinumab 300 mg subcutaneous (s.c.) every 4 weeks for 24 weeks.	
Reporting group title	Treatment Period 2: Group 1
Reporting group description:	
Participants with moderate to severe plaque psoriasis who had reached PASI 90 response after 24 weeks of treatment with secukinumab 300 mg s.c. every 4 weeks were treated with Secukinumab 300 mg s.c. from week 24 until Week 52 every 4 weeks.	
Reporting group title	Treatment Period 2: Group 2
Reporting group description:	
Participants with moderate to severe plaque psoriasis who had reached PASI 90 response after 24 weeks of treatment with secukinumab 300 mg s.c. every 4 weeks were treated with Secukinumab 300 mg s.c. from week 24 until Week 52 every 6 weeks.	
Reporting group title	Treatment period 2: Group 3
Reporting group description:	
Participants with moderate to severe plaque psoriasis who had reached PASI 75 to <90 response after 24 weeks of treatment with secukinumab 300 mg s.c. every 4 weeks will be treated with Secukinumab 300 mg s.c. from week 24 until Week 52 every 4 weeks.	
Reporting group title	Treatment period 2: Group 4
Reporting group description:	
Participants with moderate to severe plaque psoriasis, who had reached PASI 75 to <90 response after 24 weeks of treatment with secukinumab 300 mg s.c. every 4 weeks, were treated with Secukinumab 300 mg s.c. from week 24 until Week 52 every 2 weeks.	

Primary: Maintenance of PASI 90 response at Week 52 in participants with a PASI 90 response at Week 24

End point title	Maintenance of PASI 90 response at Week 52 in participants with a PASI 90 response at Week 24[1]
End point description:	
PASI is a combined assessment of lesion severity and affected area into a single score: 0 (no disease) to 72(maximal disease). Body is divided into 4 areas for scoring (head, arms, trunk, legs; each area is scored by itself and scores are combined for final PASI. For each area, percent of skin involved is estimated: 0 (0%) to 6 (90-100%), and severity is estimated by clinical signs, erythema, induration and desquamation; scale 0 (none) to 4 (maximum). Final PASI = sum of severity parameters for each area* area score weight of section (head: 0.1, arms: 0.2 body: 0.3 legs: 0.4).	
End point type	Primary
End point timeframe:	
Week 52	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint applies to Group 1 and Group 2 at the time of observation.

End point values	Treatment Period 2: Group 1	Treatment Period 2: Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	644	662		
Units: Participants	552	496		

Statistical analyses

Statistical analysis title	Maintenance of PASI 90
Comparison groups	Treatment Period 2: Group 1 v Treatment Period 2: Group 2
Number of subjects included in analysis	1306
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1499
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.44
upper limit	2.55

Secondary: Key secondary: PASI 90 response rate at Week 52 in participants with a PASI response of ≥75 to <90 at week 24

End point title	Key secondary: PASI 90 response rate at Week 52 in participants with a PASI response of ≥75 to <90 at week 24[2]

End point description:

PASI is a combined assessment of lesion severity and affected area into a single score: 0 (no disease) to 72(maximal disease). Body is divided into 4 areas for scoring (head, arms, trunk, legs; each area is scored by itself and scores are combined for final PASI. For each area, percent of skin involved is estimated: 0 (0%) to 6 (90-100%), and severity is estimated by clinical signs, erythema, induration and desquamation; scale 0 (none) to 4 (maximum). Final PASI = sum of severity parameters for each area* area score weight of section (head: 0.1, arms: 0.2 body: 0.3 legs: 0.4).

End point type	Secondary

End point timeframe:

Week 52

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint applies to Group 3 and Group 4 at the time of observation.

End point values	Treatment period 2: Group 3	Treatment period 2: Group 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	92		
Units: Participants	53	52		

Statistical analyses

Statistical analysis title	PASI 90 rate
Comparison groups	Treatment period 2: Group 3 v Treatment period 2: Group 4
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1013
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	1.1

Secondary: PASI 50, PASI 75, PASI 100 and IGA mod 2011 0 or 1 responders at Week 52 in participants with a PASI 90 response at Week 24

End point title	PASI 50, PASI 75, PASI 100 and IGA mod 2011 0 or 1 responders at Week 52 in participants with a PASI 90 response at Week 24[3]

End point description:

PASI is a combined assessment of lesion severity and affected area into a single score: 0 (no disease) to 72 (maximal disease). Body is divided into 4 areas for scoring (head, arms, trunk, legs; each area is scored by itself and scores are combined for final PASI. For each area, percent of skin involved is estimated: 0 (0%) to 6 (90-100%), and severity is estimated by clinical signs, erythema, induration and desquamation; scale 0 (none) to 4 (maximum). Final PASI = sum of severity parameters for each area* area score weight of section (head: 0.1, arms: 0.2 body: 0.3 legs: 0.4). PASI 50, 75, 90 and 100 were defined as participants achieving ≥ 50%, 75%, 90% or 100% improvement from baseline. The IGA mod 2011 scale is static, i.e. it referred exclusively to the participant's disease at the time of the assessment, and did not compare with any of the participant's previous disease states at previous visits. The scores are: 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate and 4 = severe.

End point type	Secondary

End point timeframe:

week 52

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint applies to Group 1 and Group 2 at the time of observation.

End point values	Treatment Period 2: Group 1	Treatment Period 2: Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	644	662		
Units: Participants				
PASI 50 (n=610,629)|	608	624		
PASI 75 (n=610,629)|	597	588		
PASI 90 (n=610,629)|	553	496		
PASI 100 (n=610,629)|	378	305		
IGA mod 2011 (n=609,628)|	564	529		

Statistical analyses

No statistical analyses for this end point

Secondary: PASI 50, PASI 75, PASI 100 and IGA mod 2011 0 or 1 responders at Week 52 in participants with a PASI response of ≥75 to <90 at week 24

End point title	PASI 50, PASI 75, PASI 100 and IGA mod 2011 0 or 1 responders at Week 52 in participants with a PASI response of ≥75 to <90 at week 24[4]

End point description:

PASI is a combined assessment of lesion severity and affected area into a single score: 0 (no disease) to 72 (maximal disease). Body is divided into 4 areas for scoring (head, arms, trunk, legs; each area is scored by itself and scores are combined for final PASI. For each area, percent of skin involved is estimated: 0 (0%) to 6 (90-100%), and severity is estimated by clinical signs, erythema, induration and desquamation; scale 0 (none) to 4 (maximum). Final PASI = sum of severity parameters for each area* area score weight of section (head: 0.1, arms: 0.2 body: 0.3 legs: 0.4). PASI 50, 75, 90 and 100 were defined as participants achieving ≥ 50%, 75%, 90% or 100% improvement from baseline. The IGA mod 2011 scale is static, i.e. it referred exclusively to the participant's disease at the time of the assessment, and did not compare with any of the participant's previous disease states at previous visits. The scores are: 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate and 4 = severe.

End point type	Secondary

End point timeframe:

Week 52

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint applies to Group 3 and Group 4 at the time of observation.

End point values	Treatment period 2: Group 3	Treatment period 2: Group 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	90		
Units: Participants				
PASI 50|	98	88		
PASI 75|	74	80		
PASI 90|	53	52		
PASI 100|	12	13		
IGA mod 2011 0 or 1|	64	72		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in PASI in participants with a PASI 90 response at Week 24

End point title	Change from baseline in PASI in participants with a PASI 90

	response at Week 24[5]

End point description:

PASI is a combined assessment of lesion severity and affected area into a single score: 0 (no disease) to 72(maximal disease). Body is divided into 4 areas for scoring (head, arms, trunk, legs; each area is scored by itself and scores are combined for final PASI. For each area, percent of skin involved is estimated: 0 (0%) to 6 (90-100%), and severity is estimated by clinical signs, erythema, induration and desquamation; scale 0 (none) to 4 (maximum). Final PASI = sum of severity parameters for each area* area score weight of section (head: 0.1, arms: 0.2 body: 0.3 legs: 0.4). A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

Weeks 28, 32, 36, 40, 44, 48 and 52

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint applies to Group 1 and Group 2 at the time of observation.

End point values	Treatment Period 2: Group 1	Treatment Period 2: Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	644	662		
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 28 (n=642,656)|	-20.7 (± 8.471)	-19.9 (± 8.511)		
Week 32 (n=638,655)|	-20.7 (± 8.581)	-19.8 (± 8.474)		
Week 36 (n=638,650)|	-20.6 (± 8.439)	-19.7 (± 8.563)		
Week 40 (n=632,649)|	-20.5 (± 8.392)	-19.6 (± 8.393)		
Week 44 (n=623,639)|	-20.5 (± 8.384)	-19.6 (± 8.484)		
Week 48 (n=625,638)|	-20.5 (± 8.472)	-19.2 (± 8.509)		
Week 52 (n=610,629)|	-20.4 (± 8.301)	-19.2 (± 8.513)		

Statistical analyses

Statistical analysis title	Change from baseline in PASI, week 28

Statistical analysis description:

Week 28

Comparison groups	Treatment Period 2: Group 1 v Treatment Period 2: Group 2
Number of subjects included in analysis	1306
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0489
Method	ANCOVA
Parameter estimate	Least square mean (LSM) estimate
Point estimate	-0.09

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0

Statistical analysis title	Change from baseline in PASI, week 32
Statistical analysis description: Week 32	
Comparison groups	Treatment Period 2: Group 1 v Treatment Period 2: Group 2
Number of subjects included in analysis	1306
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1073
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	0.02

Statistical analysis title	Change from baseline in PASI, week 36
Statistical analysis description: Week 36	
Comparison groups	Treatment Period 2: Group 1 v Treatment Period 2: Group 2
Number of subjects included in analysis	1306
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0001
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	-0.12

Statistical analysis title	Change from baseline in PASI, week 40
Statistical analysis description: Week 40	
Comparison groups	Treatment Period 2: Group 1 v Treatment Period 2: Group 2

Number of subjects included in analysis	1306
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0005
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	-0.11

Statistical analysis title	Change from baseline in PASI, week 44
Statistical analysis description:	
Week 44	
Comparison groups	Treatment Period 2: Group 1 v Treatment Period 2: Group 2
Number of subjects included in analysis	1306
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0001
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	-0.15

Statistical analysis title	Change from baseline in PASI, week 48
Statistical analysis description:	
Week 48	
Comparison groups	Treatment Period 2: Group 1 v Treatment Period 2: Group 2
Number of subjects included in analysis	1306
Analysis specification	Pre-specified
Analysis type	
P-value	= 0
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	-0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	-0.27

Statistical analysis title	Change from baseline in PASI, week 52
Comparison groups	Treatment Period 2: Group 1 v Treatment Period 2: Group 2
Number of subjects included in analysis	1306
Analysis specification	Pre-specified
Analysis type	
P-value	= 0
Method	ANCOVA
Parameter estimate	LSM mean
Point estimate	-0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.81
upper limit	-0.36

Secondary: Change from baseline in PASI in participants with a PASI response of ≥75 to <90 at week 24

End point title	Change from baseline in PASI in participants with a PASI response of ≥75 to <90 at week 24[6]

End point description:

PASI is a combined assessment of lesion severity and affected area into a single score: 0 (no disease) to 72(maximal disease). Body is divided into 4 areas for scoring (head, arms, trunk, legs; each area is scored by itself and scores are combined for final PASI. For each area, percent of skin involved is estimated: 0 (0%) to 6 (90-100%), and severity is estimated by clinical signs, erythema, induration and desquamation; scale 0 (none) to 4 (maximum). Final PASI = sum of severity parameters for each area* area score weight of section (head: 0.1, arms: 0.2 body: 0.3 legs: 0.4). A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

Weeks 28, 32, 36, 40, 44, 48 and 52

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint applies to Group 3 and Group 4 at the time of observation.

End point values	Treatment period 2: Group 3	Treatment period 2: Group 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	92		
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 28 (n=114,92)|	-16.1 (± 6.160)	-16.3 (± 8.029)		
Week 32 (n=112,91)|	-15.9 (± 6.002)	-16.6 (± 7.941)		
Week 36 (n=111,92)|	-16.1 (± 6.356)	-16.6 (± 7.996)		
Week 40 (n=111,90)|	-16.1 (± 6.908)	-16.8 (± 8.170)		

Week 44 (n=108,89)| Week 48 (n=109,90)| Week 52 (n=104,90)|	-16.1 (± 6.553) -15.6 (± 6.246) -15.5 (± 6.371)	-16.6 (± 8.259) -16.8 (± 8.307) -16.6 (± 8.011)		

Statistical analyses

Statistical analysis title	Change from baseline in PASI, week 28
Statistical analysis description: Week 28	
Comparison groups	Treatment period 2: Group 3 v Treatment period 2: Group 4
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.174
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.99

Statistical analysis title	Change from baseline in PASI, week 32
Statistical analysis description: Week 32	
Comparison groups	Treatment period 2: Group 3 v Treatment period 2: Group 4
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0287
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	1.5

Statistical analysis title	Change from baseline in PASI, week 36

Statistical analysis description: Week 36	
Comparison groups	Treatment period 2: Group 3 v Treatment period 2: Group 4
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1202
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	1.41

Statistical analysis title	Change from baseline in PASI, week 40
Statistical analysis description: Week 40	
Comparison groups	Treatment period 2: Group 3 v Treatment period 2: Group 4
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1157
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	1.68

Statistical analysis title	Change from baseline in PASI, week 44
Statistical analysis description: Week 44	
Comparison groups	Treatment period 2: Group 3 v Treatment period 2: Group 4
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3189
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	0.54

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.52
upper limit	1.59

Statistical analysis title	Change from baseline in PASI, week 48
Statistical analysis description: Week 48	
Comparison groups	Treatment period 2: Group 3 v Treatment period 2: Group 4
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.024
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	2.18

Statistical analysis title	Change from baseline in PASI, week 52
Statistical analysis description: Week 52	
Comparison groups	Treatment period 2: Group 3 v Treatment period 2: Group 4
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.009
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	1.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	2.57

Secondary: Change from baseline in DLQI in participants with a PASI 90 response at Week 24

End point title	Change from baseline in DLQI in participants with a PASI 90 response at Week 24[7]

End point description:

The DLQI is a ten item general dermatology disability index designed to assess health-related quality of life in adult participants with skin diseases such as eczema, psoriasis, acne and viral worts. It is a self-administered questionnaire which includes domains of daily activity, leisure, personal relationships, symptoms and feelings, treatment and school/work activities. Each domain has 4 response categories ranging from 0 (not at all) to 3 (very much). "Not relevant" is a valid score also and is scored as 0. The DLQI total score is a sum of all 10 responses. Scores range from 0 to 30 with higher scores indicating greater health-related quality of life impairment. A negative mean percentage change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

Week 52

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint applies to Group 1 and Group 2 at the time of observation.

End point values	Treatment Period 2: Group 1	Treatment Period 2: Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	605	624		
Units: score on a scale				
arithmetic mean (standard deviation)	-12.7 (± 7.325)	-11.4 (± 7.480)		

Statistical analyses

Statistical analysis title	Change from baseline in DLQI
Comparison groups	Treatment Period 2: Group 1 v Treatment Period 2: Group 2
Number of subjects included in analysis	1229
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0001
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	-0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.93
upper limit	-0.31

Secondary: Change from baseline in DLQI in participants with a PASI response of ≥75 to <90 at week 24

End point title	Change from baseline in DLQI in participants with a PASI response of ≥75 to <90 at week 24[8]

End point description:

The DLQI is a ten item general dermatology disability index designed to assess health-related quality of life in adult participants with skin diseases such as eczema, psoriasis, acne and viral worts. It is a self-administered questionnaire which includes domains of daily activity, leisure, personal relationships,

symptoms and feelings, treatment and school/work activities. Each domain has 4 response categories ranging from 0 (not at all) to 3 (very much). "Not relevant" is a valid score also and is scored as 0. The DLQI total score is a sum of all 10 responses. Scores range from 0 to 30 with higher scores indicating greater health-related quality of life impairment. A negative mean percentage change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

Week 52

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint applies to Group 3 and Group 4 at the time of observation.

End point values	Treatment period 2: Group 3	Treatment period 2: Group 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	89		
Units: score on a scale				
arithmetic mean (standard deviation)	-10.0 (± 6.605)	-9.72 (± 6.880)		

Statistical analyses

Statistical analysis title	Change from baseline in DLQI
Comparison groups	Treatment period 2: Group 3 v Treatment period 2: Group 4
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0675
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	2.42

Secondary: Change from baseline in Work Productivity and Activity Impairment Questionnaire - Psoriasis (WPAI-PSO) score in participants with a PASI 90 response at Week 24

End point title	Change from baseline in Work Productivity and Activity Impairment Questionnaire - Psoriasis (WPAI-PSO) score in participants with a PASI 90 response at Week 24[9]

End point description:

The WPAI-PSO is a self-administered questionnaire comprised of 6 questions about effects of psoriasis on the patient’s ability to work and perform regular activities based on the previous 7 days. The questionnaire quantifies the number of hours the respondent was unable to work and evaluates how much the respondent’s psoriasis affected productivity while working. For respondents who were not in paid employment, the questionnaire evaluated how much the respondent’s psoriasis affects their ability

to perform regular daily activities. Four outcomes were generated from the WPAI-PSO: % Absenteeism: percent work time missed due to health; % Presenteism: percent impairment while working due to health; % Total work productivity impairment: percent overall work impairment due to health; % Total activity impairment: percent activity impairment due to health for all respondents. First 3 outcomes applied to employed participants only. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

Week 52

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint applies to Group 1 and Group 2 at the time of observation.

End point values	Treatment Period 2: Group 1	Treatment Period 2: Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	644	662		
Units: score on a scale				
arithmetic mean (standard deviation)				
Absenteeism (n=360,356)|	-4.70 (± 19.590)	-1.99 (± 19.759)		
Presenteeism (n=351,348)|	-23.1 (± 25.968)	-23.0 (± 26.522)		
Total activity impairment (n=320,312)|	-24.3 (± 27.850)	-23.2 (± 29.861)		
Work productivity loss (n=546,550)|	-31.9 (± 29.392)	-28.6 (± 27.996)		

Statistical analyses

Statistical analysis title	Change in WPAI

Statistical analysis description:

Absenteeism

Comparison groups	Treatment Period 2: Group 1 v Treatment Period 2: Group 2
Number of subjects included in analysis	1306
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2101
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	-0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.48
upper limit	0.55

Statistical analysis title	Change in WPAI

Statistical analysis description: Presenteeism	
Comparison groups	Treatment Period 2: Group 1 v Treatment Period 2: Group 2
Number of subjects included in analysis	1306
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2971
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	-0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.93
upper limit	0.59

Statistical analysis title	Change in WPAI
Statistical analysis description: Total activity impairment	
Comparison groups	Treatment Period 2: Group 1 v Treatment Period 2: Group 2
Number of subjects included in analysis	1306
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5499
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	-0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.59
upper limit	1.38

Statistical analysis title	Change in WPAI
Comparison groups	Treatment Period 2: Group 1 v Treatment Period 2: Group 2
Number of subjects included in analysis	1306
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0758
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	-1.08

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.28
upper limit	0.11

Secondary: Change from baseline in WPAI-PSO score in participants with a PASI response of ≥75 to <90 at week 24

End point title	Change from baseline in WPAI-PSO score in participants with a PASI response of ≥75 to <90 at week 24[10]

End point description:

The WPAI-PSO is a self-administered questionnaire comprised of 6 questions about effects of psoriasis on the patient's ability to work and perform regular activities based on the previous 7 days. The questionnaire quantifies the number of hours the respondent was unable to work and evaluates how much the respondent's psoriasis affected productivity while working. For respondents who were not in paid employment, the questionnaire evaluated how much the respondent's psoriasis affects their ability to perform regular daily activities. Four outcomes were generated from the WPAI-PSO: % Absenteeism: percent work time missed due to health; % Presenteism: percent impairment while working due to health; % Total work productivity impairment: percent overall work impairment due to health; % Total activity impairment: percent activity impairment due to health for all respondents. First 3 outcomes applied to employed participants only. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

Week 52

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint applies to Group 3 and Group 4 at the time of observation.

End point values	Treatment period 2: Group 3	Treatment period 2: Group 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	92		
Units: score on a scale				
arithmetic mean (standard deviation)				
Absenteeism (n=54,49)|	-2.36 (± 12.990)	-3.45 (± 18.698)		
Presenteeism (n=52,48)|	-22.9 (± 28.377)	-22.1 (± 26.333)		
Total activity impairment (n=46,43)|	-23.1 (± 28.657)	-21.7 (± 29.905)		
Work productivity loss (n=89,77)|	-18.2 (± 28.824)	-22.5 (± 25.192)		

Statistical analyses

Statistical analysis title	Change in WPAI-PSO

Statistical analysis description:

Absenteeism

Comparison groups	Treatment period 2: Group 3 v Treatment period 2: Group 4

Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4156
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.71
upper limit	4.11

Statistical analysis title	Change in WPAI-PSO
Statistical analysis description: Presenteeism	
Comparison groups	Treatment period 2: Group 3 v Treatment period 2: Group 4
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8619
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.59
upper limit	7.85

Statistical analysis title	Change in WPAI-PSO
Statistical analysis description: Total activity impairment	
Comparison groups	Treatment period 2: Group 3 v Treatment period 2: Group 4
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6139
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	-0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.31
upper limit	10.61

Statistical analysis title	Change in WPAI-PSO
Statistical analysis description: Work productivity loss	
Comparison groups	Treatment period 2: Group 3 v Treatment period 2: Group 4
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5674
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.16
upper limit	7.56

Secondary: Change from baseline in pain, itching and scaling score in participants with a PASI 90 response at Week 24

End point title	Change from baseline in pain, itching and scaling score in participants with a PASI 90 response at Week 24[11]

End point description:

Self-administered, 11-point numeric rating scales (NRS, 0-10) were used to evaluate the patients' assessment of their current pain, itching and scaling. Respondents answered the following questions for the assessment: Pain: Overall, how severe was your psoriasis-related pain over the past 24 hours?; Itching: Overall, how severe was your psoriasis-related itch over the past 24 hours?; and Scaling: Overall, how severe was your psoriasis-related scaling over the past 24 hours? Patients had to rate their pain, itching, and scaling from 0 to 10 (11-point scale), with the understanding that the 0 represents the absence or null end of the pain, itching, or scale intensity (i.e. no pain, itching or scaling) and the 10 represents the other extreme of pain, itching, or scaling intensity (i.e. pain, itching or scaling as bad as it could be). The number that the patient selected represents his or her intensity score in the respective category. A negative change from baseline indicates improvement

End point type	Secondary

End point timeframe:

Week 52

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint applies to Group 1 and Group 2 at the time of observation.

End point values	Treatment Period 2: Group 1	Treatment Period 2: Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	644	662		
Units: score on a scale				
arithmetic mean (standard deviation)				
Pain (n=495,478)|	-4.56 (± 2.771)	-4.17 (± 2.2727)		

Itching (n=590,608)| Scaling (n=598,610)|	-5.59 (± 2.885) -6.05 (± 2.659)	-5.20 (± 2.985) -5.73 (± 2.757)		

Statistical analyses

Statistical analysis title	Change in pain score
Statistical analysis description: Pain	
Comparison groups	Treatment Period 2: Group 1 v Treatment Period 2: Group 2
Number of subjects included in analysis	1306
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1219
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.04

Statistical analysis title	Change in itching score
Statistical analysis description: Itching	
Comparison groups	Treatment Period 2: Group 1 v Treatment Period 2: Group 2
Number of subjects included in analysis	1306
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0001
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	-0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.57
upper limit	-0.18

Statistical analysis title	Change in scaling score
Statistical analysis description: Scaling	
Comparison groups	Treatment Period 2: Group 1 v Treatment Period 2: Group 2

Number of subjects included in analysis	1306
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0003
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	-0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	-0.14

Secondary: Change from baseline in pain, itching and scaling score in participants with a PASI response of ≥75 to <90 at week 24

End point title	Change from baseline in pain, itching and scaling score in participants with a PASI response of ≥75 to <90 at week 24[12]

End point description:

Self-administered, 11-point numeric rating scales (NRS, 0-10) were used to evaluate the patients' assessment of their current pain, itching and scaling. Respondents answered the following questions for the assessment: Pain: Overall, how severe was your psoriasis-related pain over the past 24 hours?; Itching: Overall, how severe was your psoriasis-related itch over the past 24 hours?; and Scaling: Overall, how severe was your psoriasis-related scaling over the past 24 hours? Patients had to rate their pain, itching, and scaling from 0 to 10 (11-point scale), with the understanding that the 0 represents the absence or null end of the pain, itching, or scale intensity (i.e. no pain, itching or scaling) and the 10 represents the other extreme of pain, itching, or scaling intensity (i.e. pain, itching or scaling as bad as it could be). The number that the patient selected represents his or her intensity score in the respective category. A negative change from baseline indicates improvement

End point type	Secondary

End point timeframe:

Week 52

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint applies to Group 3 and Group 4 at the time of observation.

End point values	Treatment period 2: Group 3	Treatment period 2: Group 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	92		
Units: score on a scale				
arithmetic mean (standard deviation)				
Pain (n=80,68)|	-3.59 (± 2.754)	-3.68 (± 3.049)		
Itching (n=101,83)|	-4.13 (± 2.883)	-4.49 (± 3.129)		
Scaling (n=102,89)|	-4.66 (± 2.960)	-5.40 (± 2.899)		

Statistical analyses

Statistical analysis title	Change in pain score
Statistical analysis description: Pain	
Comparison groups	Treatment period 2: Group 3 v Treatment period 2: Group 4
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6457
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.57
upper limit	0.92

Statistical analysis title	Change in itching score
Statistical analysis description: Itching	
Comparison groups	Treatment period 2: Group 3 v Treatment period 2: Group 4
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6136
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	0.94

Statistical analysis title	Change in scaling score
Statistical analysis description: Scaling	
Comparison groups	Treatment period 2: Group 3 v Treatment period 2: Group 4
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0203
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	0.75

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	1.39

Secondary: Change from baseline in the European Quality of Life - 5 Dimensions (EQ-5D) visual analogue scale (VAS) in participants with a PASI 90 response at Week 24

End point title	Change from baseline in the European Quality of Life - 5 Dimensions (EQ-5D) visual analogue scale (VAS) in participants with a PASI 90 response at Week 24[13]

End point description:

A visual analogue scale (VAS) was used within the EQ-5D. This scale recorded the respondent's self-rated health on a vertical 20-cm VAS where the endpoints were labeled "best imaginable health state" and "worst imaginable health state." This resulted in a numeric value set ranging from 0 (="worst imaginable health state") up to 100 (="best imaginable health state"). A positive change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

Week 52

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint applies to Group 1 and Group 2 at the time of observation.

End point values	Treatment Period 2: Group 1	Treatment Period 2: Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	603	620		
Units: score on a scale				
arithmetic mean (standard deviation)	24.34 (± 23.296)	21.24 (± 22.074)		

Statistical analyses

Statistical analysis title	Change in EQ-5D VAS
Comparison groups	Treatment Period 2: Group 1 v Treatment Period 2: Group 2
Number of subjects included in analysis	1223
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0027
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	2.22

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	3.68

Secondary: Change from baseline in the EQ-5D VAS in participants with a PASI response of ≥75 to <90 at week 24

End point title	Change from baseline in the EQ-5D VAS in participants with a PASI response of ≥75 to <90 at week 24[14]

End point description:

A visual analogue scale (VAS) was used within the EQ-5D. This scale recorded the respondent's self-rated health on a vertical 20-cm VAS where the endpoints were labeled "best imaginable health state" and "worst imaginable health state." This resulted in a numeric value set ranging from 0 (="worst imaginable health state") up to 100 (="best imaginable health state").

End point type	Secondary

End point timeframe:

Week 52

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint applies to Group 3 and Group 4 at the time of observation.

End point values	Treatment period 2: Group 3	Treatment period 2: Group 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	88		
Units: score on a scale				
arithmetic mean (standard deviation)	15.86 (± 20.099)	18.92 (± 19.855)		

Statistical analyses

Statistical analysis title	Change in EQ-5D VAS
Comparison groups	Treatment period 2: Group 3 v Treatment period 2: Group 4
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2823
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	-2.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.55
upper limit	1.92

Secondary: Change from baseline in the EQ-5D utility index (Germany, United Kingdom (UK)) in participants with a PASI 90 response at Week 24

End point title	Change from baseline in the EQ-5D utility index (Germany, United Kingdom (UK)) in participants with a PASI 90 response at Week 24[15]

End point description:

The EQ-5D quantifies the health state of a patient for the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. In the current study the EQ-5D-5L version has been used which evaluates each of these dimensions using the following five labels: "no problems", "slight problems", "moderate problems", "severe problems" and "unable to/extreme problems". Based on the five dimensions, a summary score (utility index) was derived using country specific value sets evaluating the patient condition described by the outcome in the single dimensions. For this trial, the EQ-5D-5L utility index based on the crosswalk value sets available from the EuroQol for Germany and for UK (https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/) was calculated. A positive change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

Week 52

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint applies to Group 1 and Group 2 at the time of observation.

End point values	Treatment Period 2: Group 1	Treatment Period 2: Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	605	623		
Units: score on a scale				
arithmetic mean (standard deviation)				
Germany|	0.17 (± 0.200)	0.13 (± 0.182)		
UK|	0.28 (± 0.250)	0.22 (± 0.230)		

Statistical analyses

Statistical analysis title	Change in EQ-5D utility index

Statistical analysis description:

Germany

Comparison groups	Treatment Period 2: Group 1 v Treatment Period 2: Group 2
Number of subjects included in analysis	1228
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0861
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	0.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.02

Statistical analysis title	Change in EQ-5D utitlity index
Statistical analysis description:	
UK	
Comparison groups	Treatment Period 2: Group 1 v Treatment Period 2: Group 2
Number of subjects included in analysis	1228
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0117
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.04

Secondary: Change from baseline in the EQ-5D utility index (Germany, UK) in participants with a PASI response of ≥75 to <90 at week 24

End point title	Change from baseline in the EQ-5D utility index (Germany, UK) in participants with a PASI response of ≥75 to <90 at week 24[16]

End point description:

The EQ-5D quantifies the health state of a patient for the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. In the current study the EQ-5D-5L version has been used which evaluates each of these dimensions using the following five labels: "no problems", "slight problems", "moderate problems", "severe problems" and "unable to/extreme problems". Based on the five dimensions, a summary score (utility index) was derived using country specific value sets evaluating the patient condition described by the outcome in the single dimensions. For this trial, the EQ-5D-5L utility index based on the crosswalk value sets available from the EuroQol for Germany and for UK (https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/) was calculated.

End point type	Secondary

End point timeframe:

Week 52

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint applies to Group 3 and Group 4 at the time of observation.

End point values	Treatment period 2: Group 3	Treatment period 2: Group 4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	89		
Units: score on a scale				
arithmetic mean (standard deviation)				
Germany|	0.11 (± 0.164)	0.13 (± 0.164)		
UK|	0.18 (± 0.206)	0.21 (± 0.204)		

Statistical analyses

Statistical analysis title	Change in EQ-5D utitlity index
Statistical analysis description: Germany	
Comparison groups	Treatment period 2: Group 3 v Treatment period 2: Group 4
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1852
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.01

Statistical analysis title	Change in EQ-5D utitlity index
Statistical analysis description: UK	
Comparison groups	Treatment period 2: Group 3 v Treatment period 2: Group 4
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2203
Method	ANCOVA
Parameter estimate	LSM estimate
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.02

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events are monitored from date of First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All other adverse events are monitored from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

The Adverse Events (AE) dataset has MedDRA version 19.1 (5345 records) and 20.0 (1272 records). Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally relat

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	SAF-TP2: Group 1
Reporting group description:	
SAF-TP2: Group 1	
Reporting group title	SAF-TP1: Total
Reporting group description:	
SAF-TP1: Total	
Reporting group title	SAF-TP2: Group 3
Reporting group description:	
SAF-TP2: Group 3	
Reporting group title	SAF-TP2: Group 4
Reporting group description:	
SAF-TP2: Group 4	
Reporting group title	SAF-TP2: Group 2
Reporting group description:	
SAF-TP2: Group 2	

Serious adverse events	SAF-TP2: Group 1	SAF-TP1: Total	SAF-TP2: Group 3
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 644 (3.88%)	73 / 1647 (4.43%)	4 / 114 (3.51%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anogenital warts			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			

subjects affected / exposed	1 / 644 (0.16%)	2 / 1647 (0.12%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bowen's disease			
subjects affected / exposed	0 / 644 (0.00%)	2 / 1647 (0.12%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholesteatoma			
subjects affected / exposed	1 / 644 (0.16%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric cancer stage II			
subjects affected / exposed	1 / 644 (0.16%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	1 / 644 (0.16%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma in situ			
subjects affected / exposed	0 / 644 (0.00%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral fibroma			
subjects affected / exposed	1 / 644 (0.16%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plasma cell myeloma			

subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin cancer			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid adenoma			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 644 (0.00%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iliac artery occlusion			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Ectopic pregnancy			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			

subjects affected / exposed	0 / 644 (0.00%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Alcohol use			
subjects affected / exposed	0 / 644 (0.00%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Breast enlargement			
subjects affected / exposed	1 / 644 (0.16%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peyronie's disease			
subjects affected / exposed	0 / 644 (0.00%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatitis			
subjects affected / exposed	0 / 644 (0.00%)	0 / 1647 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal polyps			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed	0 / 644 (0.00%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Alcohol abuse			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety disorder			
subjects affected / exposed	1 / 644 (0.16%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 644 (0.00%)	2 / 1647 (0.12%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	1 / 644 (0.16%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 644 (0.16%)	9 / 1647 (0.55%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 1	2 / 9	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 644 (0.31%)	10 / 1647 (0.61%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	1 / 2	2 / 10	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood bilirubin increased			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 644 (0.00%)	3 / 1647 (0.18%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test increased			
subjects affected / exposed	1 / 644 (0.16%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 644 (0.00%)	2 / 1647 (0.12%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone contusion			
subjects affected / exposed	0 / 644 (0.00%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture			
subjects affected / exposed	1 / 644 (0.16%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Joint dislocation			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint injury			
subjects affected / exposed	0 / 644 (0.00%)	2 / 1647 (0.12%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament rupture			
subjects affected / exposed	0 / 644 (0.00%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament sprain			
subjects affected / exposed	0 / 644 (0.00%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	0 / 644 (0.00%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	1 / 644 (0.16%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column injury			
subjects affected / exposed	1 / 644 (0.16%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 644 (0.16%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			

subjects affected / exposed	0 / 644 (0.00%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thermal burn			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 644 (0.00%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			

subjects affected / exposed	1 / 644 (0.16%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 644 (0.00%)	0 / 1647 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 644 (0.16%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Burning sensation			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 644 (0.00%)	2 / 1647 (0.12%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	1 / 644 (0.16%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial nerve disorder			
subjects affected / exposed	0 / 644 (0.00%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			

subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Monoplegia			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensorimotor neuropathy			
subjects affected / exposed	0 / 644 (0.00%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 644 (0.16%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tension headache			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	1 / 644 (0.16%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tympanic membrane perforation			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 644 (0.16%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ulcerative			

subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Crohn's disease			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorder			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 644 (0.00%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 644 (0.00%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal polyp			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Alcoholic liver disease			

subjects affected / exposed	0 / 644 (0.00%)	0 / 1647 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stone			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary colic			
subjects affected / exposed	1 / 644 (0.16%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 644 (0.16%)	2 / 1647 (0.12%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 644 (0.16%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic function abnormal			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatotoxicity			
subjects affected / exposed	1 / 644 (0.16%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	1 / 644 (0.16%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis exfoliative			

subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lichenoid keratosis			
subjects affected / exposed	0 / 644 (0.00%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin exfoliation			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus urethral			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric stenosis			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 644 (0.00%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bursitis			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 644 (0.00%)	3 / 1647 (0.18%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 644 (0.00%)	0 / 1647 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess jaw			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiolitis			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Erysipelas			
subjects affected / exposed	0 / 644 (0.00%)	2 / 1647 (0.12%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Giardiasis			
subjects affected / exposed	1 / 644 (0.16%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 644 (0.16%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious mononucleosis			
subjects affected / exposed	0 / 644 (0.00%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pilonidal cyst			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 644 (0.00%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	1 / 644 (0.16%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pseudomonal			

subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 644 (0.00%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 644 (0.00%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 644 (0.00%)	1 / 1647 (0.06%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	1 / 644 (0.16%)	0 / 1647 (0.00%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 644 (0.00%)	2 / 1647 (0.12%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	SAF-TP2: Group 4	SAF-TP2: Group 2	

Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 93 (3.23%)	25 / 662 (3.78%)	
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)			
Anogenital warts			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease			
subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholesteatoma			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer stage II			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma in situ			

subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral fibroma			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin cancer			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid adenoma			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iliac artery occlusion			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Ectopic pregnancy			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Alcohol use			
subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Breast enlargement			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peyronie's disease			
subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			

subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcohol abuse			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety disorder			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase			

increased			
subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone contusion			
subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fracture			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 93 (0.00%)	2 / 662 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column injury			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			

subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 93 (0.00%)	2 / 662 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			

subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Burning sensation			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial nerve disorder			

subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoplegia			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensorimotor neuropathy			
subjects affected / exposed	1 / 93 (1.08%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tension headache			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tympanic membrane perforation			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain upper			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal polyp			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Alcoholic liver disease			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Actinic keratosis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis exfoliative			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lichenoid keratosis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin exfoliation			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus urethral			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric stenosis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders			
Back pain			
subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess jaw			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Erysipelas			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Giardiasis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious mononucleosis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal cyst			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			

subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 93 (1.08%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 662 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoglycaemia			

subjects affected / exposed	0 / 93 (0.00%)	0 / 662 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	SAF-TP2: Group 1	SAF-TP1: Total	SAF-TP2: Group 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	272 / 644 (42.24%)	884 / 1647 (53.67%)	64 / 114 (56.14%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 644 (0.62%)	10 / 1647 (0.61%)	2 / 114 (1.75%)
occurrences (all)	4	10	2
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 644 (0.62%)	8 / 1647 (0.49%)	1 / 114 (0.88%)
occurrences (all)	4	8	1
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	4 / 644 (0.62%)	3 / 1647 (0.18%)	0 / 114 (0.00%)
occurrences (all)	4	3	0
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 644 (1.09%)	55 / 1647 (3.34%)	4 / 114 (3.51%)
occurrences (all)	7	56	5
Nervous system disorders			
Headache			
subjects affected / exposed	31 / 644 (4.81%)	141 / 1647 (8.56%)	6 / 114 (5.26%)
occurrences (all)	38	214	7
Migraine			
subjects affected / exposed	1 / 644 (0.16%)	9 / 1647 (0.55%)	0 / 114 (0.00%)
occurrences (all)	1	13	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 644 (0.78%)	41 / 1647 (2.49%)	0 / 114 (0.00%)
occurrences (all)	5	48	0

Injection site haematoma			
subjects affected / exposed	2 / 644 (0.31%)	18 / 1647 (1.09%)	0 / 114 (0.00%)
occurrences (all)	3	21	0
Pyrexia			
subjects affected / exposed	10 / 644 (1.55%)	36 / 1647 (2.19%)	2 / 114 (1.75%)
occurrences (all)	11	37	4
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 644 (0.31%)	4 / 1647 (0.24%)	1 / 114 (0.88%)
occurrences (all)	2	4	1
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	3 / 644 (0.47%)	6 / 1647 (0.36%)	1 / 114 (0.88%)
occurrences (all)	3	7	1
Eye pruritus			
subjects affected / exposed	0 / 644 (0.00%)	5 / 1647 (0.30%)	0 / 114 (0.00%)
occurrences (all)	0	5	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	16 / 644 (2.48%)	74 / 1647 (4.49%)	4 / 114 (3.51%)
occurrences (all)	18	85	4
Odynophagia			
subjects affected / exposed	4 / 644 (0.62%)	7 / 1647 (0.43%)	1 / 114 (0.88%)
occurrences (all)	4	9	1
Toothache			
subjects affected / exposed	11 / 644 (1.71%)	34 / 1647 (2.06%)	3 / 114 (2.63%)
occurrences (all)	11	37	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 644 (1.71%)	61 / 1647 (3.70%)	3 / 114 (2.63%)
occurrences (all)	11	64	3
Oropharyngeal pain			
subjects affected / exposed	13 / 644 (2.02%)	46 / 1647 (2.79%)	3 / 114 (2.63%)
occurrences (all)	13	52	3
Skin and subcutaneous tissue disorders			

Dermatitis atopic			
subjects affected / exposed	2 / 644 (0.31%)	3 / 1647 (0.18%)	0 / 114 (0.00%)
occurrences (all)	3	3	0
Dermatitis contact			
subjects affected / exposed	4 / 644 (0.62%)	9 / 1647 (0.55%)	0 / 114 (0.00%)
occurrences (all)	4	9	0
Eczema			
subjects affected / exposed	8 / 644 (1.24%)	20 / 1647 (1.21%)	3 / 114 (2.63%)
occurrences (all)	11	24	3
Erythrodermic psoriasis			
subjects affected / exposed	0 / 644 (0.00%)	0 / 1647 (0.00%)	3 / 114 (2.63%)
occurrences (all)	0	0	3
Pruritus			
subjects affected / exposed	9 / 644 (1.40%)	65 / 1647 (3.95%)	2 / 114 (1.75%)
occurrences (all)	9	71	2
Psoriasis			
subjects affected / exposed	12 / 644 (1.86%)	21 / 1647 (1.28%)	11 / 114 (9.65%)
occurrences (all)	12	22	11
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	16 / 644 (2.48%)	50 / 1647 (3.04%)	3 / 114 (2.63%)
occurrences (all)	17	54	3
Arthritis			
subjects affected / exposed	1 / 644 (0.16%)	4 / 1647 (0.24%)	0 / 114 (0.00%)
occurrences (all)	1	4	0
Back pain			
subjects affected / exposed	18 / 644 (2.80%)	64 / 1647 (3.89%)	4 / 114 (3.51%)
occurrences (all)	20	73	4
Infections and infestations			
Bronchitis			
subjects affected / exposed	12 / 644 (1.86%)	23 / 1647 (1.40%)	1 / 114 (0.88%)
occurrences (all)	12	26	1
Cystitis			
subjects affected / exposed	3 / 644 (0.47%)	12 / 1647 (0.73%)	0 / 114 (0.00%)
occurrences (all)	3	14	0
Folliculitis			

subjects affected / exposed	8 / 644 (1.24%)	31 / 1647 (1.88%)	1 / 114 (0.88%)
occurrences (all)	8	35	1
Gastroenteritis			
subjects affected / exposed	10 / 644 (1.55%)	22 / 1647 (1.34%)	3 / 114 (2.63%)
occurrences (all)	10	22	4
Influenza			
subjects affected / exposed	17 / 644 (2.64%)	36 / 1647 (2.19%)	4 / 114 (3.51%)
occurrences (all)	17	39	4
Nasopharyngitis			
subjects affected / exposed	3 / 644 (0.47%)	6 / 1647 (0.36%)	0 / 114 (0.00%)
occurrences (all)	3	6	0
Oral candidiasis			
subjects affected / exposed	9 / 644 (1.40%)	25 / 1647 (1.52%)	0 / 114 (0.00%)
occurrences (all)	9	28	0
Oral herpes			
subjects affected / exposed	12 / 644 (1.86%)	41 / 1647 (2.49%)	3 / 114 (2.63%)
occurrences (all)	16	50	3
Pulpitis dental			
subjects affected / exposed	1 / 644 (0.16%)	4 / 1647 (0.24%)	2 / 114 (1.75%)
occurrences (all)	1	4	3
Rhinitis			
subjects affected / exposed	8 / 644 (1.24%)	52 / 1647 (3.16%)	3 / 114 (2.63%)
occurrences (all)	8	57	3
Sinusitis			
subjects affected / exposed	8 / 644 (1.24%)	22 / 1647 (1.34%)	1 / 114 (0.88%)
occurrences (all)	9	23	1
Tonsillitis			
subjects affected / exposed	8 / 644 (1.24%)	34 / 1647 (2.06%)	2 / 114 (1.75%)
occurrences (all)	8	36	2
Upper respiratory tract infection			
subjects affected / exposed	18 / 644 (2.80%)	65 / 1647 (3.95%)	7 / 114 (6.14%)
occurrences (all)	20	73	7
Urinary tract infection			
subjects affected / exposed	16 / 644 (2.48%)	26 / 1647 (1.58%)	3 / 114 (2.63%)
occurrences (all)	18	29	3
Viral upper respiratory tract infection			

subjects affected / exposed	94 / 644 (14.60%)	368 / 1647 (22.34%)	23 / 114 (20.18%)
occurrences (all)	112	486	32

Non-serious adverse events	SAF-TP2: Group 4	SAF-TP2: Group 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 93 (64.52%)	288 / 662 (43.50%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 93 (4.30%)	6 / 662 (0.91%)	
occurrences (all)	4	6	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 93 (3.23%)	3 / 662 (0.45%)	
occurrences (all)	3	3	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	2 / 93 (2.15%)	4 / 662 (0.60%)	
occurrences (all)	2	4	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 93 (4.30%)	10 / 662 (1.51%)	
occurrences (all)	4	10	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 93 (1.08%)	27 / 662 (4.08%)	
occurrences (all)	1	56	
Migraine			
subjects affected / exposed	2 / 93 (2.15%)	1 / 662 (0.15%)	
occurrences (all)	2	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 93 (0.00%)	2 / 662 (0.30%)	
occurrences (all)	0	2	
Injection site haematoma			
subjects affected / exposed	2 / 93 (2.15%)	1 / 662 (0.15%)	
occurrences (all)	3	1	
Pyrexia			

subjects affected / exposed	1 / 93 (1.08%)	8 / 662 (1.21%)	
occurrences (all)	1	11	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 93 (2.15%)	2 / 662 (0.30%)	
occurrences (all)	2	2	
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	2 / 93 (2.15%)	0 / 662 (0.00%)	
occurrences (all)	2	0	
Eye pruritus			
subjects affected / exposed	3 / 93 (3.23%)	0 / 662 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 93 (0.00%)	22 / 662 (3.32%)	
occurrences (all)	0	22	
Odynophagia			
subjects affected / exposed	3 / 93 (3.23%)	6 / 662 (0.91%)	
occurrences (all)	3	7	
Toothache			
subjects affected / exposed	1 / 93 (1.08%)	11 / 662 (1.66%)	
occurrences (all)	1	14	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 93 (0.00%)	10 / 662 (1.51%)	
occurrences (all)	0	10	
Oropharyngeal pain			
subjects affected / exposed	1 / 93 (1.08%)	17 / 662 (2.57%)	
occurrences (all)	1	19	
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	2 / 93 (2.15%)	1 / 662 (0.15%)	
occurrences (all)	2	2	
Dermatitis contact			

subjects affected / exposed	3 / 93 (3.23%)	1 / 662 (0.15%)	
occurrences (all)	3	1	
Eczema			
subjects affected / exposed	1 / 93 (1.08%)	14 / 662 (2.11%)	
occurrences (all)	2	17	
Erythrodermic psoriasis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 662 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	4 / 93 (4.30%)	11 / 662 (1.66%)	
occurrences (all)	5	11	
Psoriasis			
subjects affected / exposed	8 / 93 (8.60%)	16 / 662 (2.42%)	
occurrences (all)	8	16	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 93 (4.30%)	19 / 662 (2.87%)	
occurrences (all)	4	23	
Arthritis			
subjects affected / exposed	2 / 93 (2.15%)	1 / 662 (0.15%)	
occurrences (all)	2	1	
Back pain			
subjects affected / exposed	1 / 93 (1.08%)	28 / 662 (4.23%)	
occurrences (all)	1	32	
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 93 (3.23%)	6 / 662 (0.91%)	
occurrences (all)	3	8	
Cystitis			
subjects affected / exposed	2 / 93 (2.15%)	3 / 662 (0.45%)	
occurrences (all)	7	3	
Folliculitis			
subjects affected / exposed	2 / 93 (2.15%)	8 / 662 (1.21%)	
occurrences (all)	2	8	
Gastroenteritis			

subjects affected / exposed	2 / 93 (2.15%)	10 / 662 (1.51%)	
occurrences (all)	2	10	
Influenza			
subjects affected / exposed	4 / 93 (4.30%)	19 / 662 (2.87%)	
occurrences (all)	4	20	
Nasopharyngitis			
subjects affected / exposed	2 / 93 (2.15%)	6 / 662 (0.91%)	
occurrences (all)	2	6	
Oral candidiasis			
subjects affected / exposed	3 / 93 (3.23%)	14 / 662 (2.11%)	
occurrences (all)	4	16	
Oral herpes			
subjects affected / exposed	0 / 93 (0.00%)	8 / 662 (1.21%)	
occurrences (all)	0	9	
Pulpitis dental			
subjects affected / exposed	2 / 93 (2.15%)	2 / 662 (0.30%)	
occurrences (all)	2	2	
Rhinitis			
subjects affected / exposed	0 / 93 (0.00%)	12 / 662 (1.81%)	
occurrences (all)	0	14	
Sinusitis			
subjects affected / exposed	2 / 93 (2.15%)	6 / 662 (0.91%)	
occurrences (all)	2	7	
Tonsillitis			
subjects affected / exposed	3 / 93 (3.23%)	9 / 662 (1.36%)	
occurrences (all)	4	11	
Upper respiratory tract infection			
subjects affected / exposed	5 / 93 (5.38%)	16 / 662 (2.42%)	
occurrences (all)	5	17	
Urinary tract infection			
subjects affected / exposed	3 / 93 (3.23%)	8 / 662 (1.21%)	
occurrences (all)	3	11	
Viral upper respiratory tract infection			
subjects affected / exposed	22 / 93 (23.66%)	95 / 662 (14.35%)	
occurrences (all)	28	115	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 June 2015	Amendment 1 was issued to align the requirements for the duration of contraception to be used by patients during the study with the approved European Summary of Product Characteristics. According to the Exclusion criteria of the study protocol, women of childbearing potential had to use effective methods of contraception during dosing of study treatment and for 16 weeks after stopping treatment, in line with phase III AIN457A program study protocols. Therefore, the advice to female patients to prevent pregnancy was amended to cover also the contraception length post treatment requirements of the European Summary of Product Characteristics (20 weeks). In addition, the approved European Summary of Product Characteristics specifies for the pre-filled secukinumab syringe a warning and precaution for use in case a latex sensitivity would be pertinent for a patient. The removable needle cap of the pre-filled syringe contains a derivative of natural rubber latex; at time of the amendment, no natural rubber latex had been detected in the removable needle cap. Nevertheless, the use of pre-filled syringes in latex sensitive individuals had not been studied and therefore a potential risk of hypersensitivity reactions was seen which could not be completely ruled out. The Exclusion criteria of the study protocol had been updated accordingly, as well as the risks and benefits.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported