Clinical trial results:
A Confirmatory (Phase 3) Randomized, Double-blind, Multicenter Study to Evaluate Efficacy, Safety, and Immunogenicity of M923 (a Proposed Adalimumab Biosimilar) and Humira® in Subjects with Moderate to Severe Chronic Plaque-type Psoriasis

Summary

EudraCT number	2015-001751-76
Trial protocol	SK CZ DE LV EE HU PL
Global end of trial date	04 April 2017

Results information

Result version number	v1 (current)
This version publication date	24 August 2018
First version publication date	24 August 2018

Trial information

Trial identification

Sponsor protocol code	911401

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02581345
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Momenta Pharmaceuticals, Inc.
Sponsor organisation address	675 West Kendall Street, Cambridge, United States, 02142
Public contact	Clinical Trial Information Desk, Momenta Pharmaceuticals, Inc., clinicaltrialinformationdesk@momentapharma.com
Scientific contact	Clinical Trial Information Desk, Momenta Pharmaceuticals, Inc., clinicaltrialinformationdesk@momentapharma.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	04 April 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to demonstrate equivalence in measures of efficacy between M923 (test) and European Union (EU)-licensed Humira (referred to as the EU Reference Protein Product (EU RPP)) in participants with moderate to severe chronic plaque-type psoriasis.

Protection of trial subjects:

This study was conducted in accordance with the protocol, the International Council for Harmonization Guideline for Good Clinical Practice E6 (ICH GCP, April 1996), Title 21 of the US Code of Federal Regulations (US CFR), the European Clinical Trial Directive (2001/20/EC and 2005/28/EC), and applicable national and local regulatory requirements. Aspects of the study concerned with the investigational medicinal product (IMP) met the requirements of EU Good Manufacturing Practice (GMP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 September 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	Slovakia: 11
Country: Number of subjects enrolled	Bulgaria: 35
Country: Number of subjects enrolled	Czech Republic: 90
Country: Number of subjects enrolled	Estonia: 58
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Latvia: 35
Country: Number of subjects enrolled	Poland: 180
Country: Number of subjects enrolled	Canada: 74
Country: Number of subjects enrolled	United States: 74
Worldwide total number of subjects	572
EEA total number of subjects	424

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	531
From 65 to 84 years	41
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 572 participants were enrolled and randomized equally into M923 and European Union reference protein product (EU RPP) arms. One participant in each arm did not receive any treatment. The 263 participants completing EU RPP treatment in Part 1 were randomized to 1 of 2 treatment arms in Part 2 (Transition and Continuous).

Period 1

Period 1 title	Part 1: up to Week 16
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1: M923

Arm description:

Participants received 80 milligrams (mg) M923 (recombinant human immunoglobulin G subclass 1 [IgG1] monoclonal antibody specific for human tumor necrosis factor–alpha [TNF-α]) at Baseline (Week 0) and 40 mg every 2 weeks from Week 1 to Week 16 as a subcutaneous injection.

Arm type	Experimental
Investigational medicinal product name	M923
Investigational medicinal product code	
Other name	Adalimumab
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received 80 milligrams (mg) M923 at Baseline (Week 0) and 40 mg every 2 weeks from Week 1 to Week 16 as a subcutaneous injection.

Arm title	Part 1: EU RPP

Arm description:

Participants received 80 mg European Union Reference Protein Product (EU RPP) at Baseline (Week 0) and 40 mg every 2 weeks from Week 1 to Week 16 as a subcutaneous injection.

Arm type	Active comparator
Investigational medicinal product name	EU RPP
Investigational medicinal product code	
Other name	Humira, Adalimumab
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received 80 mg EU RPP at Baseline (Week 0) and 40 mg every 2 weeks from Week 1 to Week 16 as a subcutaneous injection.

Number of subjects in period 1	Part 1: M923	Part 1: EU RPP
Started	286	286
Completed	271	263
Not completed	15	23
Physician decision	2	4
Consent withdrawn by subject	4	7
Adverse event, non-fatal	3	8
Unspecified reason	3	3
Did not receive treatment	1	1
Lost to follow-up	2	-

Period 2

Period 2 title	Part 2: Week 17 to Week 47
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 2: M923

Arm description:

Participants who received M923 in Part 1 continued to receive 40 mg M923 every 2 weeks from Week 17 to Week 48 (last dose at Week 47) as a subcutaneous injection.

Arm type	Experimental
Investigational medicinal product name	M923
Investigational medicinal product code	
Other name	Adalimumab
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received 40 mg M923 every 2 weeks from Week 17 to Week 48 (last dose at Week 47) as a subcutaneous injection.

Arm title	Part 2: Transition EU RPP

Arm description:

At Week 17, participants who received EU RPP in Part 1 transitioned from EU RPP to M923 (40 mg every 2 weeks), then to EU RPP at Week 25 (40 mg every 2 weeks), and then to M923 at Week 37 (last dose at Week 47).

Arm type	M923 and EU RPP
Investigational medicinal product name	EU RPP
Investigational medicinal product code	
Other name	Humira, Adalimumab
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received 40 mg EU RPP every 2 weeks from Week 25 to Week 36 as a subcutaneous injection.

Investigational medicinal product name	M923
Investigational medicinal product code	
Other name	Adalimumab
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received 40 mg M923 every 2 weeks from Week 17 to Week 24 and Week 37 to Week 48 (last dose at Week 47) as a subcutaneous injection.

Arm title	Part 2: Continuous EU RPP

Arm description:

Participants who received M923 in Part 1 continued to receive 40 mg M923 every 2 weeks from Week 17 to Week 48 (last dose at Week 47) as a subcutaneous injection.

Arm type	Experimental
Investigational medicinal product name	EU RPP
Investigational medicinal product code	
Other name	Humira, Adalimumab
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received 40 mg EU RPP every 2 weeks from Week 17 to Week 48 (last dose at Week 47) as a subcutaneous injection.

Number of subjects in period 2	Part 2: M923	Part 2: Transition EU RPP	Part 2: Continuous EU RPP
Started	271	132	131
Completed	242	117	119
Not completed	29	15	12
Physician decision	3	2	1
Consent withdrawn by subject	9	7	5
Adverse event, non-fatal	5	2	2
Failure to achieve at least a PASI 50	8	3	2
Unspecified reason	2	1	1
Lost to follow-up	2	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Part 1: M923
Reporting group description:	
Participants received 80 milligrams (mg) M923 (recombinant human immunoglobulin G subclass 1 [IgG1] monoclonal antibody specific for human tumor necrosis factor–alpha [TNF-α]) at Baseline (Week 0) and 40 mg every 2 weeks from Week 1 to Week 16 as a subcutaneous injection.	
Reporting group title	Part 1: EU RPP
Reporting group description:	
Participants received 80 mg European Union Reference Protein Product (EU RPP) at Baseline (Week 0) and 40 mg every 2 weeks from Week 1 to Week 16 as a subcutaneous injection.	

Reporting group values	Part 1: M923	Part 1: EU RPP	Total
Number of subjects	286	286	572
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	44.6	45.5	
standard deviation	± 12.4	± 12.9	-
Gender categorical			
Units: Subjects			
Female	95	100	195
Male	191	186	377
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	2	1	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	1	4
White	281	282	563
More than one race	0	0	0
Unknown or Not Reported	0	1	1
Number of Participants with the indicated Static Physician's Global Assessment (sPGA) Score			
The sPGA is a 6-point scale ranging from 0 (clear) to 5 (very severe) used to measure the severity of disease (induration, scaling, and erythema). Analysis was conducted using the Modified Intent-to-treat (mITT) Analysis Set including all consenting subjects randomized to study treatment (Arm A or Arm B) and contributed post-baseline data for at least one efficacy endpoint.			
Units: Subjects			
Moderate	170	182	352
Severe	103	91	194
Very Severe	12	12	24
Missing	1	1	2
Clear	0	0	0
Almost Clear	0	0	0
Mild	0	0	0

Psoriasis Area and Severity Index (PASI) Score			
The PASI measures the average redness (erythema), thickness (induration), and scaliness [each graded on a scale of 0 (no disease) to 4 (very severe)] of psoriasis lesions, weighted by the area of involvement. The total PASI score ranges from 0 to 72. The higher the total score, the more severe the disease. Analysis was conducted using the mITT Analysis Set.			
Units: Units on a scale			
arithmetic mean	21.24	20.16	
standard deviation	± 9.27	± 8.16	-

End points

End points reporting groups

Reporting group title	Part 1: M923
Reporting group description:	
Participants received 80 milligrams (mg) M923 (recombinant human immunoglobulin G subclass 1 [IgG1] monoclonal antibody specific for human tumor necrosis factor–alpha [TNF-α]) at Baseline (Week 0) and 40 mg every 2 weeks from Week 1 to Week 16 as a subcutaneous injection.	
Reporting group title	Part 1: EU RPP
Reporting group description:	
Participants received 80 mg European Union Reference Protein Product (EU RPP) at Baseline (Week 0) and 40 mg every 2 weeks from Week 1 to Week 16 as a subcutaneous injection.	
Reporting group title	Part 2: M923
Reporting group description:	
Participants who received M923 in Part 1 continued to receive 40 mg M923 every 2 weeks from Week 17 to Week 48 (last dose at Week 47) as a subcutaneous injection.	
Reporting group title	Part 2: Transition EU RPP
Reporting group description:	
At Week 17, participants who received EU RPP in Part 1 transitioned from EU RPP to M923 (40 mg every 2 weeks), then to EU RPP at Week 25 (40 mg every 2 weeks), and then to M923 at Week 37 (last dose at Week 47).	
Reporting group title	Part 2: Continuous EU RPP
Reporting group description:	
Participants who received M923 in Part 1 continued to receive 40 mg M923 every 2 weeks from Week 17 to Week 48 (last dose at Week 47) as a subcutaneous injection.	
Subject analysis set title	Part 1: M923
Subject analysis set type	Per protocol
Subject analysis set description:	
The Participants received 80 milligrams (mg) M923 (recombinant human immunoglobulin G subclass 1 [IgG1] monoclonal antibody specific for human tumor necrosis factor–alpha [TNF-α]) at Baseline (Week 0) and 40 mg every 2 weeks from Week 1 to Week 16 as a subcutaneous injection. The analysis was performed using Per Protocol (PP) Analysis Set defined as a subgroup of the Intent-To-Treat (ITT) Analysis Set that included all participants who did not have any deviations from the protocol deemed significant enough for exclusion from the efficacy analysis and received at least 1 dose of study drug.	
Subject analysis set title	Part 1: EU RPP
Subject analysis set type	Per protocol
Subject analysis set description:	
Participants received 80 mg European Union Reference Protein Product (EU RPP) at Baseline (Week 0) and 40 mg every 2 weeks from Week 1 to Week 16 as a subcutaneous injection. The analysis was performed using PP Analysis Set.	
Subject analysis set title	Part 2: M923
Subject analysis set type	Per protocol
Subject analysis set description:	
Participants who received M923 in Part 1 continued to receive 40 mg M923 every 2 weeks from Week 17 to Week 48 (last dose at Week 47) as a subcutaneous injection. The analysis was performed using PP Analysis Set.	
Subject analysis set title	Part 2: Transition EU RPP
Subject analysis set type	Per protocol
Subject analysis set description:	
Participants who received EU RPP in Part 1 transitioned from EU RPP to M923 (40 mg every 2 weeks) at Week 17, then to EU RPP at Week 25 (40 mg every 2 weeks), and then to M923 at Week 37 (last dose at Week 47). The analysis was performed using PP Analysis Set.	
Subject analysis set title	Part 2: Continuous EU RPP
Subject analysis set type	Per protocol
Subject analysis set description:	
Participants who received EU RPP in Part 1 continued to receive EU RPP (40 mg every 2 weeks) from	

Week 17 to Week 48 (last dose at Week 47). The analysis was performed using PP Analysis Set.

Subject analysis set title	Part 1: M923
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received 80 mg M923 at Baseline (Week 0) and 40 mg every 2 weeks from Week 1 to Week 16 as a subcutaneous injection. The analysis was performed using Safety Analysis Set (SAS), which included all participants who received at least 1 dose of study drug.

Subject analysis set title	Part 1: EU RPP
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received 80 mg European Union Reference Protein Product (EU RPP) at Baseline (Week 0) and 40 mg every 2 weeks from Week 1 to Week 16 as a subcutaneous injection. The analysis was performed using SAS.

Subject analysis set title	Part 2: M923
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants who received M923 in Part 1 continued to receive 40 mg M923 every 2 weeks from Week 17 to Week 48 (last dose at Week 47) as a subcutaneous injection. The analysis was performed using SAS.

Subject analysis set title	Part 1 and Part 2: M923
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received 80 mg M923 at Baseline (Week 0) and 40 mg every 2 weeks from Week 1 to Week 48 as a subcutaneous injection. The analysis was performed using SAS.

Subject analysis set title	Part 2: Transition EU RPP
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants who received EU RPP in Part 1 transitioned from EU RPP to M923 (40 mg every 2 weeks) at Week 17, then to EU RPP at Week 25 (40 mg every 2 weeks), and then to M923 at Week 37 (last dose at Week 47). The analysis was performed using SAS.

Subject analysis set title	Part 2: Continuous EU RPP
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants who received EU RPP in Part 1 continued to receive EU RPP (40 mg every 2 weeks) from Week 17 to Week 48 (last dose at Week 47). The analysis was performed using SAS.

Subject analysis set title	Part 1: M923
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received 80 mg M923 at Baseline (Week 0) and 40 mg every 2 weeks from Week 1 to Week 16 as a subcutaneous injection. The analysis was performed using Pharmacokinetic (PK) Analysis Set, which included all participants who received at least 1 dose of study drug and had at least 1 measured concentration at a scheduled PK time point after start of dosing. Only participants with available data were analyzed.

Subject analysis set title	Part 1: EU RPP
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received 80 mg EU RPP at Baseline (Week 0) and 40 mg every 2 weeks from Week 1 to Week 16 as a subcutaneous injection. The analysis was performed using PK Analysis Set.

Subject analysis set title	Part 2: M923
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who received M923 in Part 1 continued to receive 40 mg M923 every 2 weeks from Week 17 to Week 48 (last dose at Week 47) as a subcutaneous injection. The analysis was performed using PK Analysis Set.

Subject analysis set title	Part 2: Transition EU RPP
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who received EU RPP in Part 1 transitioned from EU RPP to M923 (40 mg every 2 weeks) At Week 17, then to EU RPP at Week 25 (40 mg every 2 weeks), and then to M923 at Week 37 (last dose at Week 47). The analysis was performed using PK Analysis Set.

Subject analysis set title	Part 2: Continuous EU RPP
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who received EU RPP in Part 1 continued to receive EU RPP (40 mg every 2 weeks) from Week 17 to Week 48 (last dose at Week 47). The analysis was performed using PK Analysis Set.

Primary: Percentage of Participants Who Achieved a 75% Reduction in Psoriasis Area and Severity Index (PASI) (PASI 75) Scores at Week 16

End point title	Percentage of Participants Who Achieved a 75% Reduction in Psoriasis Area and Severity Index (PASI) (PASI 75) Scores at Week 16

End point description:

The PASI combines assessments of the extent of body surface involvement in 4 anatomical regions (head, arms, trunk, and legs) and the severity of scaling, redness, and thickness in each region, yielding an overall score of 0 for no disease to 72 for the most severe disease. Each of the body areas was scored by itself, and then the 4 scores were combined into the final PASI score. Participants achieving PASI 75 are defined as having an improvement (reduction) of at least 75% in the Week 16 PASI score compared to the score at Baseline. The analysis was performed using PP Analysis Set.

End point type	Primary

End point timeframe:

Baseline; Week 16

End point values	Part 1: M923	Part 1: EU RPP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	267	271		
Units: Percentage of participants				
number (confidence interval 95%)	80.1 (74.9 to 84.8)	79.0 (73.6 to 83.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part 1: M923 v Part 1: EU RPP
Number of subjects included in analysis	538
Analysis specification	Pre-specified
Analysis type	equivalence[1]
Parameter estimate	Difference in proportion (M923 - EU RPP)
Point estimate	0.014
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.043
upper limit	0.072

Notes:

[1] - Per Food and Drug Administration (FDA), the equivalence testing was made using 90% confidence interval and an equivalence margin of 18%.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Part 1: M923 v Part 1: EU RPP
Number of subjects included in analysis	538
Analysis specification	Pre-specified
Analysis type	equivalence[2]
Parameter estimate	Difference in proportion (M923 - EU RPP)
Point estimate	0.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.054
upper limit	0.082

Notes:

[2] - Per European Medicines Agency (EMA), the equivalence testing was made using 95% confidence interval and an equivalence margin of 15%.

Secondary: Percentage of Participants With a Response of Clear or Almost Clear on the Static Physician Global Assessment (sPGA) at Week 16

End point title	Percentage of Participants With a Response of Clear or Almost Clear on the Static Physician Global Assessment (sPGA) at Week 16

End point description:

The sPGA response rate was defined as the percentage of participants who had achieved a clear or almost clear response on the 6-point sPGA scale. The sPGA was the physician’s determination of the participant’s psoriasis lesions overall at a given time point. Overall lesions were categorized by descriptions for induration, erythema, and scaling. For the analysis of responses, the participant’s psoriasis was assessed at a given time point on a 6-point scale on which 0 = cleared, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe, and 5 = very severe. Analysis was performed using PP Analysis Set.

End point type	Secondary

End point timeframe:

Week 16

End point values	Part 1: M923	Part 1: EU RPP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	267	271		
Units: Percentage of participants				
number (confidence interval 95%)	68.9 (63.0 to 74.4)	66.1 (60.1 to 71.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part 1: M923 v Part 1: EU RPP

Number of subjects included in analysis	538
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Difference in proportion (M923 - EU RPP)
Point estimate	0.031
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.048
upper limit	0.11

Notes:

[3] - No formal hypothesis testing of equivalence was performed for the comparison between M923 and EU RPP using the secondary efficacy outcome measures. Confidence Interval for difference in proportion in original scale was calculated using stratified Newcombe method.

Secondary: Number of Participants Achieving PASI 50 Response at Week 16

End point title	Number of Participants Achieving PASI 50 Response at Week 16

End point description:

The PASI combines assessments of the extent of body surface involvement in 4 anatomical regions (head, arms, trunk, and legs) and the severity of scaling, redness, and thickness in each region, yielding an overall score of 0 for no disease to 72 for the most severe disease. Each of the body areas was scored by itself, and then the 4 scores were combined into the final PASI score. Participants achieving PASI 50 are defined as having an improvement (reduction) of at least 50% compared to Baseline. Analysis was performed using PP Analysis Set.

End point type	Secondary

End point timeframe:

Baseline; Week 16

End point values	Part 1: M923	Part 1: EU RPP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	267	271		
Units: Participants	243	253		

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Comparison groups	Part 1: M923 v Part 1: EU RPP
Number of subjects included in analysis	538
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	Difference in proportion (M923 - EU RPP)
Point estimate	-0.022
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.069
upper limit	0.024

Notes:

[4] - No formal hypothesis testing of equivalence was performed for the comparison between M923 and EU RPP using the secondary efficacy outcome measures. Confidence Interval for difference in proportion in original scale calculated using stratified Newcombe method. Protocol defined margins are: [-0.15;+0.15] for 95% confidence interval.

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part 1: EU RPP v Part 1: M923
Number of subjects included in analysis	538
Analysis specification	Pre-specified
Analysis type	other[5]
Parameter estimate	Difference in proportion (M923 - EU RPP)
Point estimate	-0.022
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.061
upper limit	0.016

Notes:

[5] - No formal hypothesis testing of equivalence was performed for the comparison between M923 and EU RPP using the secondary efficacy outcome measures. Confidence Interval for difference in proportion in original scale calculated using stratified Newcombe method. Protocol defined margins are: [-0.18;+0.18] for 90% confidence interval.

Secondary: Number of Participants Achieving PASI 50 Response at Week 52 (Follow-Up Visit)

End point title	Number of Participants Achieving PASI 50 Response at Week 52 (Follow-Up Visit)

End point description:

The PASI combines assessments of the extent of body surface involvement in 4 anatomical regions (head, arms, trunk, and legs) and the severity of scaling, redness, and thickness in each region, yielding an overall score of 0 for no disease to 72 for the most severe disease. Each of the body areas was scored by itself, and then the 4 scores were combined into the final PASI score. Participants achieving PASI 50 are defined as having an improvement (reduction) of at least 50% compared to Baseline. Analysis was performed using PP Analysis Set. Only those participants contributing data at Week 52 were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 52

End point values	Part 2: M923	Part 2: Transition EU RPP	Part 2: Continuous EU RPP	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	258	130	129	
Units: Participants	228	111	113	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving PASI 75 Response at Week 16

End point title	Number of Participants Achieving PASI 75 Response at Week 16

End point description:

The PASI combines assessments of the extent of body surface involvement in 4 anatomical regions (head, arms, trunk, and legs) and the severity of scaling, redness, and thickness in each region, yielding an overall score of 0 for no disease to 72 for the most severe disease. Each of the body areas was scored by itself, and then the 4 scores were combined into the final PASI score. Participants achieving PASI 75 are defined as having an improvement (reduction) of at least 75% compared to Baseline. Analysis was performed using PP Analysis Set.

End point type	Secondary

End point timeframe:

Baseline; Week 16

End point values	Part 1: M923	Part 1: EU RPP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	267	271		
Units: Participants	214	214		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving PASI 75 Response at Week 52 (Follow-Up Visit)

End point title	Number of Participants Achieving PASI 75 Response at Week 52 (Follow-Up Visit)

End point description:

The PASI combines assessments of the extent of body surface involvement in 4 anatomical regions (head, arms, trunk, and legs) and the severity of scaling, redness, and thickness in each region, yielding an overall score of 0 for no disease to 72 for the most severe disease. Each of the body areas was scored by itself, and then the 4 scores were combined into the final PASI score. Participants achieving PASI 75 are defined as having an improvement (reduction) of at least 75% compared to Baseline. Analysis was performed using PP Analysis Set. Only those participants contributing data at Week 52 were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 52

End point values	Part 2: M923	Part 2: Transition EU RPP	Part 2: Continuous EU RPP	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	258	130	129	
Units: Participants	202	96	101	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving PASI 90 Response at Week 16

End point title	Number of Participants Achieving PASI 90 Response at Week 16

End point description:

The PASI combines assessments of the extent of body surface involvement in 4 anatomical regions (head, arms, trunk, and legs) and the severity of scaling, redness, and thickness in each region, yielding an overall score of 0 for no disease to 72 for the most severe disease. Each of the body areas was scored by itself, and then the 4 scores were combined into the final PASI score. Participants achieving PASI 90 are defined as having an improvement (reduction) of at least 90% compared to Baseline. Analysis was performed using PP Analysis Set.

End point type	Secondary

End point timeframe:

Baseline; Week 16

End point values	Part 1: M923	Part 1: EU RPP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	267	271		
Units: Participants	165	147		

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Comparison groups	Part 1: M923 v Part 1: EU RPP
Number of subjects included in analysis	538
Analysis specification	Pre-specified
Analysis type	other[6]
Parameter estimate	Difference in proportion (M923 - EU RPP)
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.004
upper limit	0.162

Notes:

[6] - No formal hypothesis testing of equivalence was performed for the comparison between M923 and EU RPP using the secondary efficacy outcome measures. Confidence Interval for difference in proportion in original scale calculated using stratified Newcombe method. Protocol defined margins are: [-0.15;+0.15] for 95% confidence interval.

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part 1: M923 v Part 1: EU RPP
Number of subjects included in analysis	538
Analysis specification	Pre-specified
Analysis type	other[7]
Parameter estimate	Difference in proportion (M923 - EU RPP)
Point estimate	0.08
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.01
upper limit	0.149

Notes:

[7] - No formal hypothesis testing of equivalence was performed for the comparison between M923 and EU RPP using the secondary efficacy outcome measures. Confidence Interval for difference in proportion in original scale calculated using stratified Newcombe method. Protocol defined margins are: [-0.18;+0.18] for 90% confidence interval.

Secondary: Number of Participants Achieving PASI 90 Response at Week 52 (Follow-Up Visit)

End point title	Number of Participants Achieving PASI 90 Response at Week 52 (Follow-Up Visit)

End point description:

The PASI combines assessments of the extent of body surface involvement in 4 anatomical regions (head, arms, trunk, and legs) and the severity of scaling, redness, and thickness in each region, yielding an overall score of 0 for no disease to 72 for the most severe disease. Each of the body areas was scored by itself, and then the 4 scores were combined into the final PASI score. Participants achieving PASI 90 are defined as having an improvement (reduction) of at least 90% compared to Baseline. Analysis was performed using PP Analysis Set. Only those participants contributing data at Week 52 were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 52

End point values	Part 2: M923	Part 2: Transition EU RPP	Part 2: Continuous EU RPP	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	258	130	129	
Units: Participants	159	71	77	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute PASI Score at Baseline

End point title	Absolute PASI Score at Baseline

End point description:

The PASI combines assessments of the extent of body surface involvement in 4 anatomical regions (head, arms, trunk, and legs) and the severity of scaling, redness, and thickness in each region, yielding an overall score of 0 for no disease to 72 for the most severe disease. Each of the body areas was scored by itself, and then the 4 scores were combined into the final PASI score. Analysis was performed using PP Analysis Set including participants with evaluable data for part 1 and part 2 of the study.

End point type	Secondary

End point timeframe:

Baseline

End point values	Part 1: M923	Part 1: EU RPP	Part 2: M923	Part 2: Transition EU RPP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	267	271	258	130
Units: Units on a scale				
arithmetic mean (standard deviation)	21.34 (± 9.268)	20.29 (± 8.266)	21.21 (± 9.100)	19.93 (± 8.255)

End point values	Part 2: Continuous EU RPP			
Subject group type	Subject analysis set			
Number of subjects analysed	129			
Units: Units on a scale				
arithmetic mean (standard deviation)	21.00 (± 8.511)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute PASI Score at Week 16

End point title	Absolute PASI Score at Week 16

End point description:

The PASI combines assessments of the extent of body surface involvement in 4 anatomical regions (head, arms, trunk, and legs) and the severity of scaling, redness, and thickness in each region, yielding an overall score of 0 for no disease to 72 for the most severe disease. Each of the body areas was scored by itself, and then the 4 scores were combined into the final PASI score. Analysis was performed using PP Analysis Set. Only those participants contributing data at Week 16 were analyzed.

End point type	Secondary

End point timeframe:

Week 16

End point values	Part 1: M923	Part 1: EU RPP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	261	263		
Units: Units on a scale				
arithmetic mean (standard deviation)	2.58 (± 4.092)	2.50 (± 3.098)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute PASI Score at Week 52 (Follow-Up Visit)

End point title	Absolute PASI Score at Week 52 (Follow-Up Visit)

End point description:

The PASI combines assessments of the extent of body surface involvement in 4 anatomical regions (head, arms, trunk, and legs) and the severity of scaling, redness, and thickness in each region, yielding an overall score of 0 for no disease to 72 for the most severe disease. Each of the body areas was scored by itself, and then the 4 scores were combined into the final PASI score. Analysis was performed using PP Analysis Set. Only those participants contributing data at Week 52 were analyzed.

End point type	Secondary

End point timeframe:

Week 52

End point values	Part 2: M923	Part 2: Transition EU RPP	Part 2: Continuous EU RPP	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	246	120	124	
Units: Units on a scale				
arithmetic mean (standard deviation)	2.76 (± 4.768)	2.85 (± 4.913)	2.67 (± 3.919)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in PASI Score at Week 16

End point title	Percent Change From Baseline in PASI Score at Week 16

End point description:

The PASI combines assessments of the extent of body surface involvement in 4 anatomical regions (head, arms, trunk, and legs) and the severity of scaling, redness, and thickness in each region, yielding an overall score of 0 for no disease to 72 for the most severe disease. Each of the body areas was scored by itself, and then the 4 scores were combined into the final PASI score. Percent change from Baseline was calculated as: (post-Baseline value – Baseline value) / (Baseline value) * 100. Analysis was performed using PP Analysis Set. Only those participants contributing data at Week 16 were

analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 16

End point values	Part 1: M923	Part 1: EU RPP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	261	263		
Units: Percent change				
arithmetic mean (standard deviation)	-86.21 (± 20.065)	-86.79 (± 15.756)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in PASI Score at Week 52 (Follow-Up Visit)

End point title	Percent Change From Baseline in PASI Score at Week 52 (Follow-Up Visit)

End point description:

The PASI combines assessments of the extent of body surface involvement in 4 anatomical regions (head, arms, trunk, and legs) and the severity of scaling, redness, and thickness in each region, yielding an overall score of 0 for no disease to 72 for the most severe disease. Each of the body areas was scored by itself, and then the 4 scores were combined into the final PASI score. Percent change from Baseline was calculated as: (post-Baseline value – Baseline value) / (Baseline value) * 100. Analysis was performed using PP Analysis Set. Only those participants contributing data at Week 52 were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 52

End point values	Part 2: M923	Part 2: Transition EU RPP	Part 2: Continuous EU RPP	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	246	120	124	
Units: Percent change				
arithmetic mean (standard deviation)	-86.43 (± 22.570)	-85.53 (± 21.771)	-85.64 (± 20.968)	

Statistical analyses

No statistical analyses for this end point

Secondary: Health-Related Quality of Life During Treatment: Dermatology Life Quality Index (DLQI) Score at Baseline

End point title	Health-Related Quality of Life During Treatment: Dermatology Life Quality Index (DLQI) Score at Baseline

End point description:

The DLQI score was calculated by summing the individual scores of each question at a given time point, resulting in a maximum score of 30 and a minimum score of 0. The higher the score, the more quality of life is impaired. For the analysis of responses, the participant's results were assessed on a scoring scale on which 3 = very much or yes (applicable to question 7 only), 2 = a lot, 1 = a little, 0 = not at all or not relevant. Interpretation of DLQI scoring can be taken as 0 – 1 = no effect at all on participant's life, 2 – 5 = small effect on participant's life, 6 – 10 = moderate effect on participant's life, 11 – 20 = very large effect on participant's life, and 21 – 30 = extremely large effect on participant's life. Analysis was performed using PP Analysis Set including participants with evaluable data for part 1 and part 2 of the study.

End point type	Secondary

End point timeframe:

Baseline

End point values	Part 1: M923	Part 1: EU RPP	Part 2: M923	Part 2: Transition EU RPP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	267	271	267	130
Units: Units on a scale				
arithmetic mean (standard deviation)	12.5 (± 7.13)	10.5 (± 6.71)	12.5 (± 7.13)	10.1 (± 6.57)

End point values	Part 2: Continuous EU RPP			
Subject group type	Subject analysis set			
Number of subjects analysed	141			
Units: Units on a scale				
arithmetic mean (standard deviation)	10.9 (± 6.83)			

Statistical analyses

No statistical analyses for this end point

Secondary: Health-Related Quality of Life During Treatment: DLQI Score at Week 16

End point title	Health-Related Quality of Life During Treatment: DLQI Score at Week 16

End point description:

The DLQI score was calculated by summing the individual scores of each question at a given time point, resulting in a maximum score of 30 and a minimum score of 0. The higher the score, the more quality of life is impaired. For the analysis of responses, the participant's results were assessed on a scoring scale on which 3 = very much or yes (applicable to question 7 only), 2 = a lot, 1 = a little, 0 = not at all or

not relevant. Interpretation of DLQI scoring can be taken as 0 – 1 = no effect at all on participant's life, 2 – 5 = small effect on participant's life, 6 – 10 = moderate effect on participant's life, 11 – 20 = very large effect on participant's life, and 21 – 30 = extremely large effect on participant's life. Analysis was performed using PP Analysis Set. Only those participants contributing data at Week 16 were analyzed.

End point type	Secondary

End point timeframe:

Week 16

End point values	Part 1: M923	Part 1: EU RPP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	258	259		
Units: Units on a scale				
arithmetic mean (standard deviation)	2.4 (± 4.04)	2.1 (± 3.50)		

Statistical analyses

No statistical analyses for this end point

Secondary: Health-Related Quality of Life During Treatment: DLQI Score at Week 48 (Completion/Termination Visit)

End point title	Health-Related Quality of Life During Treatment: DLQI Score at Week 48 (Completion/Termination Visit)

End point description:

The DLQI score was calculated by summing the individual scores of each question at a given time point, resulting in a maximum score of 30 and a minimum score of 0. The higher the score, the more quality of life is impaired. For the analysis of responses, the participant's results were assessed on a scoring scale on which 3 = very much or yes (applicable to question 7 only), 2 = a lot, 1 = a little, 0 = not at all or not relevant. Interpretation of DLQI scoring can be taken as 0 – 1 = no effect at all on participant's life, 2 – 5 = small effect on participant's life, 6 – 10 = moderate effect on participant's life, 11 – 20 = very large effect on participant's life, and 21 – 30 = extremely large effect on participant's life. Analysis was performed using PP Analysis Set from Part 2 of the study. Only those participants contributing data at Week 48 were analyzed.

End point type	Secondary

End point timeframe:

Week 48

End point values	Part 2: M923	Part 2: Transition EU RPP	Part 2: Continuous EU RPP	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	232	115	117	
Units: Units on a scale				
arithmetic mean (standard deviation)	2.1 (± 3.77)	1.6 (± 2.83)	2.1 (± 3.97)	

Statistical analyses

No statistical analyses for this end point

Secondary: Health-Related Quality of Life During Treatment: EuroQoL 5-Dimension Health Status Questionnaire (EQ-5D-5L) at Baseline

End point title	Health-Related Quality of Life During Treatment: EuroQoL 5-Dimension Health Status Questionnaire (EQ-5D-5L) at Baseline

End point description:

The EQ-5D-5L health score was measured on a Visual Analog Scale (VAS) anchored by 0 = "worst health you can imagine" and 100 = "best health you can imagine". Baseline was defined as the last scheduled observation prior to dosing, typically Day 1, predose. Analysis was performed using PP Analysis Set including participants with evaluable data for part 1 and part 2 of the study.

End point type	Secondary

End point timeframe:

Baseline

End point values	Part 1: M923	Part 1: EU RPP	Part 2: M923	Part 2: Transition EU RPP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	267	271	258	130
Units: Units on a scale				
arithmetic mean (standard deviation)	71.3 (± 18.70)	72.5 (± 20.27)	71.4 (± 18.71)	71.2 (± 20.43)

End point values	Part 2: Continuous EU RPP			
Subject group type	Subject analysis set			
Number of subjects analysed	129			
Units: Units on a scale				
arithmetic mean (standard deviation)	73.5 (± 19.84)			

Statistical analyses

No statistical analyses for this end point

Secondary: Health-Related Quality of Life During Treatment: EQ-5D-5L at Week 16

End point title	Health-Related Quality of Life During Treatment: EQ-5D-5L at Week 16

End point description:

The EQ-5D-5L health score was measured on a Visual Analog Scale (VAS) anchored by 0 = "worst health you can imagine" and 100 = "best health you can imagine". Analysis was performed using PP Analysis Set. Only those participants contributing data at Week 16 were analyzed.

End point type	Secondary

End point timeframe:

Week 16

End point values	Part 1: M923	Part 1: EU RPP	Part 2: M923	Part 2: Transition EU RPP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	258	259	257	130
Units: Units on a scale				
arithmetic mean (standard deviation)	83.7 (± 12.38)	83.4 (± 13.92)	83.8 (± 12.22)	82.7 (± 14.85)

End point values	Part 2: Continuous EU RPP			
Subject group type	Subject analysis set			
Number of subjects analysed	129			
Units: Units on a scale				
arithmetic mean (standard deviation)	84.1 (± 12.94)			

Statistical analyses

No statistical analyses for this end point

Secondary: Health-Related Quality of Life During Treatment: EQ-5D-5L at Week 48 (Completion/Termination Visit)

End point title	Health-Related Quality of Life During Treatment: EQ-5D-5L at Week 48 (Completion/Termination Visit)

End point description:

The EQ-5D-5L health score was measured on a Visual Analog Scale (VAS) anchored by 0 = "worst health you can imagine" and 100 = "best health you can imagine". Analysis was performed using PP Analysis Set. Only those participants contributing data at Week 48 were analyzed.

End point type	Secondary

End point timeframe:

Week 48

End point values	Part 2: M923	Part 2: Transition EU RPP	Part 2: Continuous EU RPP	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	232	115	117	
Units: Units on a scale				
arithmetic mean (standard deviation)	85.3 (± 13.83)	83.9 (± 14.92)	84.2 (± 12.98)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Meaningful Changes in Vital Signs

End point title	Number of Participants With Clinically Meaningful Changes in Vital Signs

End point description:

Vital signs included body temperature, respiratory rate, pulse rate, systolic and diastolic blood pressure, and weight. Clinically meaningful changes were classified as such by the Investigator and reported as adverse events. The analysis was performed using SAS.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Part 1: M923	Part 1: EU RPP	Part 2: M923	Part 2: Transition EU RPP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	285	285	271	132
Units: Participants	0	0	0	0

End point values	Part 2: Continuous EU RPP			
Subject group type	Subject analysis set			
Number of subjects analysed	131			
Units: Participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Meaningful Changes in Laboratory Results at Baseline

End point title	Number of Participants With Clinically Meaningful Changes in Laboratory Results at Baseline

End point description:

Laboratory results included hematology [Hemoglobin, Hematocrit, Platelet count, Mean cell volume, White blood cell count (total leucocytes), Neutrophils absolute, Neutrophils, Lymphocytes absolute, Lymphocytes, Monocytes, Eosinophils absolute, and Eosinophils], chemistry (Aspartate transaminase, Alanine transaminase, Gamma glutamyl transferase, Creatine kinase, C-reactive protein, Cholesterol, Triglycerides, Total protein, Potassium, Urea, Creatinine, Phosphate, Glucose, and Uric acid) and urinalysis [Specific Gravity] parameters. Laboratory results of a few hematology (Red Blood Cell Count and Monocytes absolute), chemistry (Alkaline Phosphatase, Total bilirubin, Sodium, Chloride, and Albumin), and urinalysis (pH) parameters were not assessed at Baseline and Week 16. Clinically meaningful changes were classified as such by the Investigator and reported as adverse events.

End point type	Secondary

End point timeframe:
Baseline

End point values	Part 1: M923	Part 1: EU RPP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285	285		
Units: Participants				
Hemoglobin	0	0		
Hematocrit	0	0		
Platelet count	0	0		
Mean cell volume	0	0		
White blood cell count (total leucocytes)	1	1		
Neutrophils absolute	2	1		
Neutrophils	1	0		
Lymphocytes absolute	1	1		
Lymphocytes	1	1		
Monocytes	0	0		
Eosinophils absolute	0	0		
Eosinophils	0	0		
Aspartate transaminase	0	0		
Alanine transaminase	1	1		
Gamma glutamyl transferase	1	4		
Creatine kinase	2	0		
C-reactive protein	6	2		
Cholesterol	2	4		
Triglycerides	3	2		
Total protein	0	1		
Potassium	1	0		
Urea	1	0		
Creatinine	0	0		
Phosphate	0	0		
Glucose	1	2		
Uric acid	2	0		
Specific Gravity	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Meaningful Changes in Laboratory Results at Week 16

End point title	Number of Participants With Clinically Meaningful Changes in Laboratory Results at Week 16

End point description:

Laboratory results included hematology [Hemoglobin, Hematocrit, Platelet count, Mean cell volume, White blood cell count (total leucocytes), Neutrophils absolute, Neutrophils, Lymphocytes absolute, Lymphocytes, Monocytes, Eosinophils absolute, and Eosinophils], chemistry (Aspartate transaminase,

Alanine transaminase, Gamma glutamyl transferase, Creatine kinase, C-reactive protein, Cholesterol, Triglycerides, Total protein, Potassium, Urea, Creatinine, Phosphate, Glucose, and Uric acid) and urinalysis [Specific Gravity] parameters. Laboratory results of a few hematology (Red Blood Cell Count and Monocytes absolute), chemistry (Alkaline Phosphatase, Total bilirubin, Sodium, Chloride, and Albumin), and urinalysis (pH) parameters were not assessed at Baseline and Week 16. Clinically meaningful changes were classified as such by the Investigator and reported as adverse events.

End point type	Secondary

End point timeframe:

Week 16

End point values	Part 1: M923	Part 1: EU RPP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285	285		
Units: Participants				
Hemoglobin	1	1		
Hematocrit	1	1		
Platelet count	0	0		
Mean cell volume	0	1		
White blood cell count (total leucocytes)	2	0		
Neutrophils absolute	1	0		
Neutrophils	0	0		
Lymphocytes absolute	0	1		
Lymphocytes	0	1		
Monocytes	0	0		
Eosinophils absolute	1	0		
Eosinophils	1	0		
Aspartate transaminase	2	0		
Alanine transaminase	3	1		
Gamma glutamyl transferase	3	2		
Creatine kinase	2	0		
C-reactive protein	1	0		
Cholesterol	4	3		
Triglycerides	5	3		
Total protein	0	1		
Potassium	1	0		
Urea	0	0		
Creatinine	0	0		
Phosphate	0	0		
Glucose	2	3		
Uric acid	1	1		
Specific Gravity	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Meaningful Changes in Laboratory

Results at Week 48 (Completion/Termination Visit)

End point title	Number of Participants With Clinically Meaningful Changes in Laboratory Results at Week 48 (Completion/Termination Visit)

End point description:

Laboratory results included hematology [Red Blood Cell Count, Hemoglobin, Hematocrit, Platelet count, Mean cell volume, White blood cell count (total leucocytes), Neutrophils absolute, Neutrophils, Lymphocytes absolute, Lymphocytes, Monocytes absolute, Monocytes, Eosinophils absolute, and Eosinophils], chemistry (Aspartate transaminase, Alanine transaminase, Alkaline Phosphatase, Gamma glutamyl transferase, Total bilirubin, Creatine kinase, C-reactive protein, Cholesterol, Triglycerides, Total protein, Sodium, Potassium, Chloride, Urea, Creatinine, Albumin, Phosphate, Glucose, and Uric acid) and urinalysis [pH and Specific Gravity] parameters. Clinically meaningful changes were classified as such by the Investigator and reported as adverse events.

End point type	Secondary

End point timeframe:

Week 48

End point values	Part 2: M923	Part 2: Transition EU RPP	Part 2: Continuous EU RPP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	271	132	131	
Units: Participants				
Red Blood Cell Count	1	0	1	
Hemoglobin	1	0	1	
Hematocrit	1	0	1	
Platelet count	1	0	0	
Mean cell volume	0	0	1	
White blood cell count (total leucocytes)	2	1	1	
Neutrophils absolute	3	1	2	
Neutrophils	3	0	0	
Lymphocytes absolute	0	0	1	
Lymphocytes	1	0	0	
Monocytes absolute	0	0	0	
Monocytes	1	0	0	
Eosinophils absolute	0	0	0	
Eosinophils	2	0	0	
Aspartate transaminase	2	0	1	
Alanine transaminase	5	0	3	
Alkaline Phosphatase	0	0	0	
Gamma glutamyl transferase	3	0	3	
Total bilirubin	1	0	1	
Creatine kinase	0	1	1	
C-reactive protein	3	0	0	
Cholesterol	7	3	2	
Triglycerides	11	4	2	
Total protein	0	0	0	
Sodium	0	0	0	
Potassium	0	0	0	
Chloride	0	0	0	
Urea	0	0	0	
Creatinine	0	0	0	

Albumin	0	0	0	
Phosphate	0	0	0	
Glucose	5	3	0	
Uric acid	1	3	3	
pH	1	1	0	
Specific Gravity	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Significant Abnormalities in Electrocardiogram Parameters at Baseline

End point title	Number of Participants With Clinically Significant Abnormalities in Electrocardiogram Parameters at Baseline

End point description:

Clinically significant abnormalities were classified as such by the Investigator and reported as adverse events. The analysis was performed using SAS.

End point type	Secondary

End point timeframe:

Baseline

End point values	Part 1: M923	Part 1: EU RPP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	285	285		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Significant Abnormalities in Electrocardiogram Parameters at Week 16

End point title	Number of Participants With Clinically Significant Abnormalities in Electrocardiogram Parameters at Week 16

End point description:

Clinically significant abnormalities were classified as such by the Investigator and reported as adverse events. The analysis was performed using SAS.

End point type	Secondary

End point timeframe:

Week 16

End point values	Part 1: M923	Part 1: EU RPP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	285	285		
Units: Participants	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Significant Abnormalities in Electrocardiogram Parameters at Week 48 (Completion/Termination Visit)

End point title	Number of Participants With Clinically Significant Abnormalities in Electrocardiogram Parameters at Week 48 (Completion/Termination Visit)

End point description:

Clinically significant abnormalities were classified as such by the Investigator and reported as adverse events. The analysis was performed using SAS.

End point type	Secondary

End point timeframe:

Week 48

End point values	Part 2: M923	Part 2: Transition EU RPP	Part 2: Continuous EU RPP	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	271	132	131	
Units: Participants	3	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Treatment-emergent Adverse Events (TEAEs)

End point title	Number of participants with Treatment-emergent Adverse Events (TEAEs)

End point description:

TEAEs are adverse events that occurred during or after study drug administration. For more details on adverse events please refer the safety section. Analysis was performed using SAS.

End point type	Secondary

End point timeframe:

From first administration of study drug until study completion or discontinuation i.e. up to approximately 52 weeks

End point values	Part 1: M923	Part 1: EU RPP	Part 2: M923	Part 2: Transition EU RPP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	285	285	271	132
Units: Participants	169	194	199	99

End point values	Part 2: Continuous EU RPP			
Subject group type	Subject analysis set			
Number of subjects analysed	131			
Units: Participants	103			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Serum Concentrations by Treatment

End point title	Pharmacokinetics: Serum Concentrations by Treatment

End point description:

Serum samples were collected at Baseline (Week 0, perdose), approximately 1 week (peak) after IP administration (Weeks 8 and 16), and 2 weeks after dose administration as a trough sample collected prior to the next dose administration (Weeks 17, 21, 25, 29, 37, 41).

End point type	Secondary

End point timeframe:

Baseline (Week 0), Week 8, 16, 17, 21, 25, 29, 37, and 41

End point values	Part 1: M923	Part 1: EU RPP	Part 2: M923	Part 2: Transition EU RPP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	282	281	282	149
Units: nanograms per milliter (ng/mL)				
arithmetic mean (standard deviation)				
Baseline (Week 0)/Predose; n = 279, 279, 0, 0, 0	302 (± 16.5)	301 (± 9.69)	0 (± 0)	0 (± 0)
Week 8/Peak; n = 277, 272, 0, 0, 0	9100 (± 5450)	7640 (± 4370)	0 (± 0)	0 (± 0)
Week 16/Peak; n = 268, 261, 0, 0, 0	8580 (± 5700)	6990 (± 5100)	0 (± 0)	0 (± 0)
Week 17/Trough; n = 0, 0, 267, 130, 129	0 (± 0)	0 (± 0)	6900 (± 5270)	5340 (± 4050)
Week 21/Trough; n = 0, 0, 257, 127, 130	0 (± 0)	0 (± 0)	6630 (± 4960)	5100 (± 4040)

Week 25/Trough; 0, 0, 252, 126, 127	0 (± 0)	0 (± 0)	6790 (± 5210)	4970 (± 3870)
Week 29/Trough; n = 0, 0, 248, 125, 124	0 (± 0)	0 (± 0)	5990 (± 4020)	4840 (± 3480)
Week 37/Trough; n = 0, 0, 245, 121, 120	0 (± 0)	0 (± 0)	6120 (± 4220)	4830 (± 3680)
Week 41/Trough; n = 0, 0, 241, 119, 117	0 (± 0)	0 (± 0)	5950 (± 4230)	4740 (± 3710)

End point values	Part 2: Continuous EU RPP			
Subject group type	Subject analysis set			
Number of subjects analysed	132			
Units: nanograms per milliter (ng/mL)				
arithmetic mean (standard deviation)				
Baseline (Week 0)/Predose; n = 279, 279, 0, 0, 0	0 (± 0)			
Week 8/Peak; n = 277, 272, 0, 0, 0	0 (± 0)			
Week 16/Peak; n = 268, 261, 0, 0, 0	0 (± 0)			
Week 17/Trough; n = 0, 0, 267, 130, 129	5840 (± 4840)			
Week 21/Trough; n = 0, 0, 257, 127, 130	6260 (± 4960)			
Week 25/Trough; 0, 0, 252, 126, 127	6320 (± 5260)			
Week 29/Trough; n = 0, 0, 248, 125, 124	5330 (± 4000)			
Week 37/Trough; n = 0, 0, 245, 121, 120	5250 (± 4190)			
Week 41/Trough; n = 0, 0, 241, 119, 117	5480 (± 4140)			

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity: Number of Participants With Anti-Drug Antibodies (ADA) at Baseline

End point title	Immunogenicity: Number of Participants With Anti-Drug Antibodies (ADA) at Baseline

End point description:

The M923 confirmation assay was evaluated only if the EU Humira confirmation assay was negative. Overall Result: a participant was considered to be positive if a confirmed positive result was observed at any assay (including predose; if a participant had either a negative result in the screening assay or a positive result at screening followed by a negative result in all confirmation tiers, the overall result was negative. Overall Status: a participant was considered to have developed ADA or neutralizing ADAs if a confirmed positive result was observed at any time during the treatment period inclusive of the predose results; the designation of negative required either a negative screening assay or a negative confirmation result at each sampling time. The same convention applied for the neutralizing assay results. The analysis was performed using SAS.

End point type	Secondary

End point timeframe:

Baseline

End point values	Part 1: M923	Part 1: EU RPP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	285	285		
Units: Participants				
EU Humera	15	11		
M923	1	2		
Overall Results	16	13		
Neutralizing ADA	4	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity: Number of Participants With ADA at Week 16

End point title	Immunogenicity: Number of Participants With ADA at Week 16

End point description:

The M923 confirmation assay was evaluated only if the EU Humira confirmation assay was negative. Overall Result: a participant was considered to be positive if a confirmed positive result was observed at any assay (including predose; if a participant had either a negative result in the screening assay or a positive result at screening followed by a negative result in all confirmation tiers, the overall result was negative. Overall Status: a participant was considered to have developed ADA or neutralizing ADAs if a confirmed positive result was observed at any time during the treatment period inclusive of the predose results; the designation of negative required either a negative screening assay or a negative confirmation result at each sampling time. The same convention applied for the neutralizing assay results. The analysis was performed using SAS.

End point type	Secondary

End point timeframe:

Week 16

End point values	Part 1: M923	Part 1: EU RPP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	285	285		
Units: Participants				
EU Humera	135	144		
M923	4	8		
Overall Results	139	152		
Neutralizing ADA	28	30		

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity: Number of Participants With ADA at Week 25

End point title	Immunogenicity: Number of Participants With ADA at Week 25

End point description:

The M923 confirmation assay was evaluated only if the EU Humira confirmation assay was negative. Overall Result: a participant was considered to be positive if a confirmed positive result was observed at any assay (including predose; if a participant had either a negative result in the screening assay or a positive result at screening followed by a negative result in all confirmation tiers, the overall result was negative. Overall Status: a participant was considered to have developed ADA or neutralizing ADAs if a confirmed positive result was observed at any time during the treatment period inclusive of the predose results; the designation of negative required either a negative screening assay or a negative confirmation result at each sampling time. The same convention applied for the neutralizing assay results. The analysis was performed using SAS.

End point type	Secondary

End point timeframe:

Week 25

End point values	Part 2: M923	Part 2: Transition EU RPP	Part 2: Continuous EU RPP	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	271	132	131	
Units: Participants				
EU Humera	144	80	92	
M923	12	5	5	
Overall result	156	85	97	
Neutralizing ADA	55	25	32	

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity: Number of Participants With ADA at Week 52 (Completion/Termination Visit)

End point title	Immunogenicity: Number of Participants With ADA at Week 52 (Completion/Termination Visit)

End point description:

The M923 confirmation assay was evaluated only if the EU Humira confirmation assay was negative. Overall Result: a participant was considered to be positive if a confirmed positive result was observed at any assay (including predose; if a participant had either a negative result in the screening assay or a positive result at screening followed by a negative result in all confirmation tiers, the overall result was negative. Overall Status: a participant was considered to have developed ADA or neutralizing ADAs if a confirmed positive result was observed at any time during the treatment period inclusive of the predose results; the designation of negative required either a negative screening assay or a negative confirmation result at each sampling time. The same convention applied for the neutralizing assay results. The analysis was performed using SAS.

End point type	Secondary

End point timeframe:

Week 52

End point values	Part 2: M923	Part 2: Transition EU RPP	Part 2: Continuous EU RPP	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	271	132	131	
Units: Participants				
EU Humera	131	73	80	
M923	10	6	7	
Overall result	141	79	87	
Neutralizing ADA	40	28	23	

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity: Number of Participants With ADA and nADA by Titer at Baseline

End point title	Immunogenicity: Number of Participants With ADA and nADA by Titer at Baseline

End point description:

The M923 confirmation assay was evaluated only if the EU Humira confirmation assay was negative. Overall Result: a participant was considered to be positive if a confirmed positive result was observed at any assay (including predose); if a participant had either a negative result in the screening assay or a positive result at screening followed by a negative result in all confirmation tiers, the overall result was negative. Overall Status: a participant was considered to have developed ADA or neutralizing ADAs if a confirmed positive result was observed at any time during the treatment period inclusive of the predose results; the designation of negative required either a negative screening assay or a negative confirmation result at each sampling time. In confirmed positive samples, an assay was used to determine the relative titer of the ADA; a subsequent neutralizing antibodies assay was used to determine the presence of neutralizing antibodies. The analysis was performed using SAS.

End point type	Secondary

End point timeframe:

Baseline (Week 0)

End point values	Part 1: M923	Part 1: EU RPP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	285	285		
Units: Participants				
No positive result	266	271		
Predose positive result	16	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity: Number of Participants With ADA and nADA by Titer at Week 16

End point title	Immunogenicity: Number of Participants With ADA and nADA by Titer at Week 16

End point description:

The M923 confirmation assay was evaluated only if the EU Humira confirmation assay was negative. Overall Result: a participant was considered to be positive if a confirmed positive result was observed at any assay (including predose); if a participant had either a negative result in the screening assay or a positive result at screening followed by a negative result in all confirmation tiers, the overall result was negative. Overall Status: a participant was considered to have developed ADA or neutralizing ADAs if a confirmed positive result was observed at any time during the treatment period inclusive of the predose results; the designation of negative required either a negative screening assay or a negative confirmation result at each sampling time. In confirmed positive samples, an assay was used to determine the relative titer of the ADA; a subsequent neutralizing antibodies assay was used to determine the presence of neutralizing antibodies. The analysis was performed using SAS.

End point type	Secondary

End point timeframe:

Week 16

End point values	Part 1: M923	Part 1: EU RPP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	285	285		
Units: Participants				
Titers ≤ 1:16 (postdose positive ADAs)	16	26		
Titers ≤ 1:16 (postdose positive nADAs)	2	2		
Titers > 1:16 to ≤ 1:128 (postdose positive ADAs)	90	73		
Titers > 1:16 to ≤ 1:128 (postdose positive nADAs)	17	6		
Titers >1:128 to ≤ 1:152 (postdose positive ADAs)	27	40		
Titers >1:128 to ≤ 1:152 (postdose positive nADAs)	3	11		
Titers >1:152 (postdose positive ADAs)	6	13		
Titers >1:152 (postdose positive nADAs)	6	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity: Number of Participants With ADA and nADA by Titer at Week 25

End point title	Immunogenicity: Number of Participants With ADA and nADA by Titer at Week 25

End point description:

The M923 confirmation assay was evaluated only if the EU Humira confirmation assay was negative. Overall Result: a participant was considered to be positive if a confirmed positive result was observed at any assay (including predose); if a participant had either a negative result in the screening assay or a positive result at screening followed by a negative result in all confirmation tiers, the overall result was negative. Overall Status: a participant was considered to have developed ADA or neutralizing ADAs if a confirmed positive result was observed at any time during the treatment period inclusive of the predose results; the designation of negative required either a negative screening assay or a negative confirmation result at each sampling time. In confirmed positive samples, an assay was used to determine the relative titer of the ADA; a subsequent neutralizing antibodies assay was used to

determine the presence of neutralizing antibodies. The analysis was performed using SAS.

End point type	Secondary

End point timeframe:

Week 25

End point values	Part 1 and Part 2: M923	Part 2: Transition EU RPP	Part 2: Continuous EU RPP	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	285	132	131	
Units: Participants				
Titers ≤ 1:16 (postdose positive ADAs)	24	19	21	
Titers ≤ 1:16 (postdose positive nADAs)	6	2	4	
Titers > 1:16 to ≤ 1:128 (postdose positive ADAs)	86	37	42	
Titers > 1:16 to ≤ 1:128 (postdose positive nADAs)	17	4	7	
Titers >1:128 to ≤ 1:152 (postdose positive ADAs)	28	14	22	
Titers >1:128 to ≤ 1:152 (postdose positive nADAs)	16	6	10	
Titers >1:152 (postdose positive ADAs)	18	15	12	
Titers >1:152 (postdose positive nADAs)	16	13	11	

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity: Number of Participants With ADA and nADA by Titer at Week 52 (Completion/Termination Visit)

End point title	Immunogenicity: Number of Participants With ADA and nADA by Titer at Week 52 (Completion/Termination Visit)

End point description:

The M923 confirmation assay was evaluated only if the EU Humira confirmation assay was negative. Overall Result: a participant was considered to be positive if a confirmed positive result was observed at any assay (including predose); if a participant had either a negative result in the screening assay or a positive result at screening followed by a negative result in all confirmation tiers, the overall result was negative. Overall Status: a participant was considered to have developed ADA or neutralizing ADAs if a confirmed positive result was observed at any time during the treatment period inclusive of the predose results; the designation of negative required either a negative screening assay or a negative confirmation result at each sampling time. In confirmed positive samples, an assay was used to determine the relative titer of the ADA; a subsequent neutralizing antibodies assay was used to determine the presence of neutralizing antibodies. The analysis was performed using SAS.

End point type	Secondary

End point timeframe:

Week 52

End point values	Part 1 and Part 2: M923	Part 2: Transition EU RPP	Part 2: Continuous EU RPP	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	285	132	131	
Units: Participants				
Titers ≤ 1:16 (postdose positive ADAs)	26	11	17	
Titers ≤ 1:16 (postdose positive nADAs)	0	2	3	
Titers > 1:16 to ≤ 1:128 (postdose positive ADAs)	62	37	38	
Titers > 1:16 to ≤ 1:128 (postdose positive nADAs)	13	6	5	
Titers >1:128 to ≤ 1:152 (postdose positive ADAs)	23	12	15	
Titers >1:128 to ≤ 1:152 (postdose positive nADAs)	9	6	2	
Titers >1:152 (postdose positive ADAs)	13	7	10	
Titers >1:152 (postdose positive nADAs)	11	6	7	

Statistical analyses

No statistical analyses for this end point

Secondary: Median Time to Seroconversion

End point title	Median Time to Seroconversion

End point description:

Time to seroconversion (in days) was defined as the time to the observation of the first confirmed positive ADA response. Participants with confirmed positive ADA response at baseline (Week 0 predose) were excluded. The analysis was performed using SAS. Only those participants who had a postdose seroconversion time were analyzed.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Part 1 and Part 2: M923	Part 2: Transition EU RPP	Part 2: Continuous EU RPP	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	216	120	106	
Units: Days				
median (full range (min-max))	113 (52 to 372)	113 (51 to 375)	112 (54 to 373)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 52

Adverse event reporting additional description:

Adverse events were collected in members of the Safety Analysis Set (SAS), comprised of all participants who received at least 1 dose of study drug (M923 or European Union reference protein product [EU RPP]).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Part 1: M923

Reporting group description:

Participants received 80 milligrams (mg) M923 (recombinant human immunoglobulin G subclass 1 [IgG1] monoclonal antibody specific for human tumor necrosis factor–alpha [TNF-α]) at Baseline (Week 0) and 40 mg every 2 weeks from Week 1 to Week 16 as a subcutaneous injection.

Reporting group title	Part 2: M923

Reporting group description:

Participants who received M923 in Part 1 continued to receive 40 mg M923 every 2 weeks from Week 17 to Week 48 (last dose at Week 47) as a subcutaneous injection.

Reporting group title	Part 2: Transition EU RRP

Reporting group description:

At Week 17, participants who received EU RPP in Part 1 transitioned from EU RPP to M923 (40 mg every 2 weeks), then to EU RPP at Week 25 (40 mg every 2 weeks), and then to M923 at Week 37 (last dose at Week 47).

Reporting group title	Part 1: EU RPP

Reporting group description:

Participants received 80 mg European Union Reference Protein Product (EU RPP) at Baseline (Week 0) and 40 mg every 2 weeks from Week 1 to Week 16 as a subcutaneous injection.

Reporting group title	Part 2: Continuous EU RRP

Reporting group description:

Participants who received EU RPP in Part 1 continued to receive EU RPP (40 mg every 2 weeks) from Week 17 to Week 48 (last dose at Week 47).

Serious adverse events	Part 1: M923	Part 2: M923	Part 2: Transition EU RRP
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 285 (1.40%)	10 / 271 (3.69%)	10 / 132 (7.58%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign ovarian tumour			

subjects affected / exposed	0 / 285 (0.00%)	1 / 271 (0.37%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder papilloma			
subjects affected / exposed	1 / 285 (0.35%)	0 / 271 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 285 (0.35%)	0 / 271 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric adenoma			
subjects affected / exposed	1 / 285 (0.35%)	0 / 271 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningioma			
subjects affected / exposed	0 / 285 (0.00%)	1 / 271 (0.37%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nodular melanoma			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	0 / 285 (0.00%)	1 / 271 (0.37%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 285 (0.35%)	0 / 271 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral vascular disorder			

subjects affected / exposed	0 / 285 (0.00%)	1 / 271 (0.37%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial hyperplasia			
subjects affected / exposed	0 / 285 (0.00%)	1 / 271 (0.37%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Genital prolapse			
subjects affected / exposed	0 / 285 (0.00%)	1 / 271 (0.37%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Nasal septum deviation			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicide attempt			

subjects affected / exposed	0 / 285 (0.00%)	1 / 271 (0.37%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device loosening			
subjects affected / exposed	0 / 285 (0.00%)	1 / 271 (0.37%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 285 (0.35%)	0 / 271 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Brain contusion			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial bones fracture			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint injury			

subjects affected / exposed	1 / 285 (0.35%)	0 / 271 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fractured base			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 285 (0.00%)	1 / 271 (0.37%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 285 (0.00%)	1 / 271 (0.37%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy			
subjects affected / exposed	0 / 285 (0.00%)	1 / 271 (0.37%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive cardiomyopathy			

subjects affected / exposed	0 / 285 (0.00%)	1 / 271 (0.37%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 285 (0.00%)	1 / 271 (0.37%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical myelopathy			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	0 / 285 (0.00%)	1 / 271 (0.37%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 285 (0.35%)	0 / 271 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pustular psoriasis			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash generalised			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovitis			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	1 / 132 (0.76%)
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			
Appendicitis			
subjects affected / exposed	0 / 285 (0.00%)	1 / 271 (0.37%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis bacterial			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonsillar abscess			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 285 (0.00%)	0 / 271 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part 1: EU RPP	Part 2: Continuous EU RRP	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 285 (2.46%)	8 / 131 (6.11%)	
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)			
Benign ovarian tumour			
subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder papilloma			
subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric adenoma			
subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodular melanoma			
subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arteriosclerosis			

subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 285 (0.35%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 285 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial hyperplasia			
subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital prolapse			

subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Nasal septum deviation			
subjects affected / exposed	1 / 285 (0.35%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device loosening			
subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	0 / 285 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Brain contusion			
subjects affected / exposed	1 / 285 (0.35%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			

subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 285 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 285 (0.35%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 285 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fractured base			
subjects affected / exposed	1 / 285 (0.35%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 285 (0.35%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			

subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	0 / 285 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive cardiomyopathy			
subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	0 / 285 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 285 (0.35%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 285 (0.35%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical myelopathy			
subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			

subjects affected / exposed	1 / 285 (0.35%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 285 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 285 (0.35%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pustular psoriasis			
subjects affected / exposed	1 / 285 (0.35%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 285 (0.35%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rash generalised			
subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 285 (0.35%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	0 / 285 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovitis			
subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 285 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			

subjects affected / exposed	0 / 285 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 285 (0.00%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Part 1: M923	Part 2: M923	Part 2: Transition EU RRP
Total subjects affected by non-serious adverse events			
subjects affected / exposed	92 / 285 (32.28%)	96 / 271 (35.42%)	47 / 132 (35.61%)
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 285 (3.16%)	2 / 271 (0.74%)	7 / 132 (5.30%)
occurrences (all)	11	7	11
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	68 / 285 (23.86%)	27 / 271 (9.96%)	15 / 132 (11.36%)
occurrences (all)	256	116	79
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	8 / 285 (2.81%)	28 / 271 (10.33%)	14 / 132 (10.61%)
occurrences (all)	10	32	18
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	19 / 285 (6.67%)	40 / 271 (14.76%)	16 / 132 (12.12%)
occurrences (all)	20	55	20
Upper respiratory tract infection			
subjects affected / exposed	9 / 285 (3.16%)	15 / 271 (5.54%)	6 / 132 (4.55%)
occurrences (all)	9	18	7

Non-serious adverse events	Part 1: EU RPP	Part 2: Continuous EU RRP	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	104 / 285 (36.49%)	63 / 131 (48.09%)	

Nervous system disorders Headache subjects affected / exposed occurrences (all)	 10 / 285 (3.51%) 13	 5 / 131 (3.82%) 5	
General disorders and administration site conditions Injection site reaction subjects affected / exposed occurrences (all)	 79 / 285 (27.72%) 261	 19 / 131 (14.50%) 70	
Skin and subcutaneous tissue disorders Psoriasis subjects affected / exposed occurrences (all)	 8 / 285 (2.81%) 8	 21 / 131 (16.03%) 25	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	 17 / 285 (5.96%) 19 6 / 285 (2.11%) 7	 20 / 131 (15.27%) 25 11 / 131 (8.40%) 13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 July 2015	Summary of Significant Changes Adopted with Protocol Amendment 1 •Clarified that the European Union reference protein product (EU RPP) is not an approved product in the United States. •In response to Food and Drug Administration (FDA) feedback/guidance: -Primary endpoint analysis revised to occur at Week 16 instead of Week 13 -Treatment Arm C eliminated -Efficacy, safety, Pharmacokinetic (PK), and immunogenicity objectives were revised to reflect the examination of the transitions between M923 and EU RPP, rather than interchangeability -The PK sub-study was removed -The use of the terms "similar/biosimilar/or comparable" were removed or revised to adhere to FDA guidance regarding conclusory statements in the study protocol •The study drug injection parameters were revised to reflect a 2-hour observation period after Weeks 0, 1, 17, 25, and 37, and a 30 minute observation period after injections at Weeks 19, 21, 27, and 39 •The biostatistical analysis was revised to reflect the change in primary efficacy from Week 13 to Week 16, to clarify the response rate justification, and to apply the change in equivalence margin to include 18% (Confidence Interval [CI] 90%) for the US FDA and 15% (CI 95%) for the EU EMA •Timing of the following assessments was revised: Dermatology Life Quality Index (DLQI) and EuroQoL-5 dimensions Health Status Questionnaire (EQ 5D 5L); physical examination; 12 lead electrocardiogram (ECG); urinalysis, PK and immunogenicity; laboratory assessments; urine pregnancy tests; study drug injections onsite and at home; injection site evaluation, and post injection monitoring.
08 October 2015	Summary of Significant Change Adopted with Protocol Amendment 2 •The use of the terms "similar/biosimilar/comparable" were removed/revised in order to adhere to FDA guidance regarding conclusory statements in the study protocol or Investigator's Brochure.

04 August 2016	•To clarify the study objectives: -The primary objective was changed from "to demonstrate equivalent efficacy between M923 (test) and EU RPP (reference) in participants with moderate to severe chronic plaque type psoriasis" to "to demonstrate equivalence in measures of efficacy between M923 (test) and EU RPP (reference) in participants with moderate to severe chronic plaque type psoriasis" -The secondary objective was changed from "Evaluate the safety, immunogenicity, and tolerability of M923 compared with EU RPP" to "Evaluate the continued efficacy, safety, immunogenicity, and tolerability of M923 compared with EU RPP" -The secondary objective was changed from "Evaluate exposure of EU RPP and M923" to "Evaluate concentration summaries over time" •Changes were made to Section 8.4, Outcome Measures to clarify the outcome measures and how they were to be measured •Changes to study entry criteria were made: -To clarify the maximum period where male partners should use a condom -To clarify that the subject must have had no major deviations regarding concomitant medication -To clarify the type of imaging exam acceptable for this study (i.e., "a radiograph or comparable imaging with negative finding for TB or other similar infections") •To clarify all non-permitted treatments, topical treatments containing acetylsalicylic acid were included in the list of treatments not permitted during the course of the study •It was added that after the discontinuation visit, if the subject agreed, a Follow-up Visit was to be conducted 5 weeks after last IP dose •It was clarified that the interim analysis was to be done for the first randomized subjects and would analyze primary endpoint data, PK, and safety up through Week 25. It was also clarified that the final analysis was to be carried out in all subjects recruited (n=572). Note: The summary of change is not all-inclusive.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported