Clinical trial results:
A randomized, double-blind, parallel-group, multicenter study to demonstrate similar efficacy and to compare safety and immunogenicity of GP2017 and Humira in patients with moderate to severe active rheumatoid arthritis

Summary

EudraCT number	2015-003433-10
Trial protocol	CZ GB DE HU RO ES IT
Global end of trial date	26 September 2017

Results information

Result version number	v1 (current)
This version publication date	07 October 2018
First version publication date	07 October 2018

Trial information

Trial identification

Sponsor protocol code	Hexal AG/Sandoz Inc

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02744755
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hexal AG/ Sandoz
Sponsor organisation address	Industriestr. 25, Holzkirchen, Germany, 83807
Public contact	Sandoz Biopharma Clinical Development - Strategic Planning, Sandoz, +49 (0)80244760, biopharma.clinicaltrials@sandoz.com
Scientific contact	Sandoz Biopharma Clinical Development - Strategic Planning, Sandoz, +49 (0)80244760, biopharma.clinicaltrials@sandoz.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	26 September 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to demonstrate similar efficacy of GP2017 and US-licensed Humira in patients with moderate to severe active RA with respect to DAS28-CRP score change from baseline at Week 12.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 March 2016
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	Czech Republic: 42
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Hungary: 17
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Malaysia: 4
Country: Number of subjects enrolled	Mexico: 38
Country: Number of subjects enrolled	Poland: 91
Country: Number of subjects enrolled	Romania: 15
Country: Number of subjects enrolled	Russian Federation: 11
Country: Number of subjects enrolled	Serbia: 11
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	United States: 84
Worldwide total number of subjects	353
EEA total number of subjects	205

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	285
From 65 to 84 years	67
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

353 patients were randomized (1:1)and received at least one dose of study drug; 303 patients completed the study.Eligible patients in the Humira group who completed Study Period 1 (baseline to week 24) with an at least moderate response by DAS28-CRP score were switched to GP2017 treatment during Study Period 2 (Week 24 to week 48).

Pre-assignment

Screening details:

Full analysis set: randomized patients (study drug assigned)
Per protocol set study period 1 (SP1) / study period 2(SP2): patients who completed Week 12 (SP1) / Week 48 (SP2) without major protocol deviations and received at least 5 doses of study drug up to Week 10 (SP1) / 10 doses of IMP from Week 24 to Week 46 (SP2)

Period 1

Period 1 title	Study period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	GP2017

Arm description:

Group 1 received treatment with 40 mg GP2017 in 0.8 mL of solution administered subcutaneously from pre-filled syringes up to 24 weeks (study Period 1) after which patients achieving at least a moderate clinical response continued treatment with 40mg GP2017 subcutaneous injection up to 46 weeks (study Period 2).

Arm type	Experimental
Investigational medicinal product name	GP2017
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen, Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

GP2017 in pre-filled syringes for subcutaneous injection containing 40 mg of active ingredient in 0.8 mL of solution

Arm title	Humira / switched GP2017

Arm description:

Group 2 received treatment with 40 mg Humira in 0.8 mL of solution administered subcutaneously from pre-filled syringes up to 24 weeks (study Period 1) after which patients achieving at least a moderate clinical response were switched to 40mg GP2017 subcutaneous injection up to 46 weeks (study Period 2).

Arm type	Active comparator
Investigational medicinal product name	Humira
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen, Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Humira in pre-filled syringes for subcutaneous injection containing 40 mg of active ingredient in 0.8 mL

of solution

Number of subjects in period 1	GP2017	Humira / switched GP2017
Started	177	176
Completed	163	168
Not completed	14	8
Consent withdrawn by subject	8	4
not defined	-	1
Adverse event, non-fatal	1	1
Pregnancy	1	-
Lost to follow-up	1	1
Protocol deviation	2	1
Lack of efficacy	1	-

Period 2

Period 2 title	Study period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	GP2017

Arm description:

Group 1 received treatment with 40 mg GP2017 in 0.8 mL of solution administered subcutaneously from pre-filled syringes up to 24 weeks (study Period 1) after which patients achieving at least a moderate clinical response continued treatment with 40mg GP2017 subcutaneous injection up to 46 weeks (study Period 2).

Arm type	Experimental
Investigational medicinal product name	GP2017
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

GP2017 in pre-filled syringes for subcutaneous injection containing 40 mg of active ingredient in 0.8 mL of solution

Arm title	Humira / switched GP2017

Arm description:

Group 2 received treatment with 40 mg Humira in 0.8 mL of solution administered subcutaneously from pre-filled syringes up to 24 weeks (study Period 1) after which patients achieving at least a moderate clinical response were switched to 40mg GP2017 subcutaneous injection up to 46 weeks (study Period 2).

Arm type	Switched to Experimental
Investigational medicinal product name	GP2017
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

GP2017 in pre-filled syringes for subcutaneous injection containing 40 mg of active ingredient in 0.8 mL of solution

Number of subjects in period 2[1]	GP2017	Humira / switched GP2017
Started	159	166
Completed	145	158
Not completed	14	8
Consent withdrawn by subject	2	2
not defined	3	2
Adverse event, non-fatal	5	-
Lost to follow-up	-	2
Protocol deviation	1	-
Lack of efficacy	3	2

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: numbers are correct

Baseline characteristics

Reporting groups	
Reporting group title	GP2017
Reporting group description:	
Group 1 received treatment with 40 mg GP2017 in 0.8 mL of solution administered subcutaneously from pre-filled syringes up to 24 weeks (study Period 1) after which patients achieving at least a moderate clinical response continued treatment with 40mg GP2017 subcutaneous injection up to 46 weeks (study Period 2).	
Reporting group title	Humira / switched GP2017
Reporting group description:	
Group 2 received treatment with 40 mg Humira in 0.8 mL of solution administered subcutaneously from pre-filled syringes up to 24 weeks (study Period 1) after which patients achieving at least a moderate clinical response were switched to 40mg GP2017 subcutaneous injection up to 46 weeks (study Period 2).	

Reporting group values	GP2017	Humira / switched GP2017	Total
Number of subjects	177	176	353
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	145	140	285
From 65-84 years	32	35	67
85 years and over	0	1	1
Age Continuous Units: years			
arithmetic mean	52.8	53.8	
standard deviation	± 12.81	± 12.22	-
Sex: Female, Male Units: Subjects			
Female	153	142	295
Male	24	34	58
Race/Ethnicity, Customized Units: Subjects			
White|	152	152	304
American Indian or Alaska Native|	14	15	29
Black or African American|	6	3	9
Asian|	1	3	4
Other|	4	3	7

End points

End points reporting groups

Reporting group title	GP2017

Reporting group description:

Group 1 received treatment with 40 mg GP2017 in 0.8 mL of solution administered subcutaneously from pre-filled syringes up to 24 weeks (study Period 1) after which patients achieving at least a moderate clinical response continued treatment with 40mg GP2017 subcutaneous injection up to 46 weeks (study Period 2).

Reporting group title	Humira / switched GP2017

Reporting group description:

Group 2 received treatment with 40 mg Humira in 0.8 mL of solution administered subcutaneously from pre-filled syringes up to 24 weeks (study Period 1) after which patients achieving at least a moderate clinical response were switched to 40mg GP2017 subcutaneous injection up to 46 weeks (study Period 2).

Reporting group title	GP2017

Reporting group description:

Group 1 received treatment with 40 mg GP2017 in 0.8 mL of solution administered subcutaneously from pre-filled syringes up to 24 weeks (study Period 1) after which patients achieving at least a moderate clinical response continued treatment with 40mg GP2017 subcutaneous injection up to 46 weeks (study Period 2).

Reporting group title	Humira / switched GP2017

Reporting group description:

Group 2 received treatment with 40 mg Humira in 0.8 mL of solution administered subcutaneously from pre-filled syringes up to 24 weeks (study Period 1) after which patients achieving at least a moderate clinical response were switched to 40mg GP2017 subcutaneous injection up to 46 weeks (study Period 2).

Primary: Study period 1: Change in DAS28-CRP score from baseline at week 12 in patients treated with GP2017 and patients treated with Humira

End point title	Study period 1: Change in DAS28-CRP score from baseline at week 12 in patients treated with GP2017 and patients treated with Humira

End point description:

Disease activity score (DAS) 28-CRP is based on 28-joint count (tender and swollen joints), C-reactive protein and patient's assessment of global disease activity (GDA) or general health (GH), values range from 0.96 to 10.0 while higher values mean a higher disease activity. • A DAS28-CRP value >5.1 corresponds to a high disease activity • A DAS28-CRP value between 3.2 and 5.1 corresponds to a moderate disease activity • A DAS28-CRP value between 2.6 and 3.2 corresponds to a low disease activity • A DAS28-CRP value < 2.6 corresponds to remission DAS28-CRP = 0.56 * sqrt(tender28) + 0.28* sqrt(swollen28) + 0.36 * ln(CRP+1) + 0.014 * GDA or GH + 0.96 where • tender28 and swollen28 are the number of tender and swollen joints as assessed using 28-joint count • CRP is C-reactive protein (mg/l) • GDA is the global disease activity measured on a Visual Analogue Scale (VAS) of 100 mm

End point type	Primary

End point timeframe:

Study period 1: week 12

End point values	GP2017	Humira / switched GP2017		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140	144		
Units: scores on a scale				
least squares mean (standard error)	-2.16 (± 0.114)	-2.18 (± 0.110)		

Statistical analyses

Statistical analysis title	equivalence assessment between GP2017 and Humira

Statistical analysis description:

Therapeutic equivalence in terms of change from baseline in DAS28-CRP at week 12 will be concluded if the 95% confidence interval for the LS mean difference between GP2017 and Humira is contained within the interval [-0.6; 0.6]. A mixed-model repeated measures analysis was performed for DAS28-CRP change from baseline including treatment, stratification factors, time, the interaction between time (visits) and treatment all as categorical variables, and baseline DAS28-CRP as a continuous variable.

Comparison groups	GP2017 v Humira / switched GP2017
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	equivalence[1]
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	0.27
Variability estimate	Standard error of the mean
Dispersion value	0.129

Notes:

[1] - A 0.6 change in DAS28-CRP score is considered as no clinically meaningful difference by EULAR criteria and is therefore used as the equivalence margin limits [0.6,-0.6].

Statistical analysis title	equivalence assessment between GP2017 and Humira

Statistical analysis description:

Therapeutic equivalence in terms of change from baseline in DAS28-CRP at week 12 will be concluded if the 90% confidence interval for the LS mean difference between GP2017 and Humira is contained within the interval [-0.6; 0.6]. A mixed-model repeated measures analysis was performed for DAS28-CRP change from baseline including treatment, stratification factors, time, the interaction between time (visits) and treatment all as categorical variables, and baseline DAS28-CRP as a continuous variable.

Comparison groups	GP2017 v Humira / switched GP2017
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	equivalence[2]
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.19
upper limit	0.23

Variability estimate	Standard error of the mean
Dispersion value	0.129

Notes:

[2] - A 0.6 change in DAS28-CRP score is considered as no clinically meaningful difference by EULAR criteria and is therefore used as the equivalence margin limits [0.6,-0.6].

Secondary: Study period 1: time-weighted averaged change from baseline in DAS28-CRP until Week 24 in patients treated with GP2017 and with Humira

End point title	Study period 1: time-weighted averaged change from baseline in DAS28-CRP until Week 24 in patients treated with GP2017 and with Humira

End point description:

Disease activity score (DAS) 28-CRP is based on 28-joint count (tender and swollen joints), C-reactive protein and patient's assessment of global disease activity (GDA) or general health (GH), values range from 0.96 to 10.0 while higher values mean a higher disease activity. • A DAS28-CRP value >5.1 corresponds to a high disease activity • A DAS28-CRP value between 3.2 and 5.1 corresponds to a moderate disease activity • A DAS28-CRP value between 2.6 and 3.2 corresponds to a low disease activity • A DAS28-CRP value < 2.6 corresponds to remission DAS28-CRP = 0.56 * sqrt(tender28) + 0.28* sqrt(swollen28) + 0.36 * ln(CRP+1) + 0.014 * GDA or GH + 0.96 where • tender28 and swollen28 are the number of tender and swollen joints as assessed using 28-joint count • CRP is C-reactive protein (mg/l) • GDA is the global disease activity measured on a Visual Analogue Scale (VAS) of 100 mm

End point type	Secondary

End point timeframe:

Study period 1: week 24

End point values	GP2017	Humira / switched GP2017		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	138		
Units: scores on a scale				
least squares mean (standard error)	-1.85 (± 0.098)	-1.93 (± 0.092)		

Statistical analyses

Statistical analysis title	equivalence assessment between GP2017 and Humira

Statistical analysis description:

ANCOVA model included treatment, body weight as per CRF, prior therapy as per CRF, region as per CRF as fixed effects and baseline DAS28-CRP values as covariate.

Comparison groups	GP2017 v Humira / switched GP2017
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	equivalence[3]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.08

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.27
Variability estimate	Standard error of the mean
Dispersion value	0.096

Notes:

[3] - A 0.6 change in DAS28-CRP score is considered as no clinically meaningful difference by EULAR criteria and is therefore used as the equivalence margin limits [0.6,-0.6].

Statistical analysis title	equivalence assessment between GP2017 and Humira
Comparison groups	GP2017 v Humira / switched GP2017
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	equivalence[4]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.08
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.08
upper limit	0.24
Variability estimate	Standard error of the mean
Dispersion value	0.096

Notes:

[4] - ANCOVA model included treatment, body weight as per CRF, prior therapy as per CRF, region as per CRF
as fixed effects and baseline DAS28-CRP values as covariate.

Secondary: Study period 1- Proportion of patients achieving EULAR criterion for remission

End point title	Study period 1- Proportion of patients achieving EULAR criterion for remission

End point description:

Proportion of patients achieving European League against Rheumatism (EULAR) remission (defined as DAS28 CRP < 2.6)

End point type	Secondary

End point timeframe:

week 4, week 12 and week 24

End point values	GP2017	Humira / switched GP2017		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	138		
Units: Participants				
EULAR remission week 4|	15	7		
EULAR remission week 12|	32	38		
EULAR remission week 24|	49	71		

Statistical analyses

No statistical analyses for this end point

Secondary: Study period 1- Proportion of patients achieving EULAR criterion for good response

End point title	Study period 1- Proportion of patients achieving EULAR criterion for good response

End point description:

Proportion of patients achieving European League against Rheumatism (EULAR) good response (defined as DAS28<=3.2 at post-baseline assessment timepoint(s) with an improvement of >1.2 in DAS28 from baseline.)

End point type	Secondary

End point timeframe:

week 4, week 12 and week 24

End point values	GP2017	Humira / switched GP2017		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	138		
Units: Participants				
Good response week 4|	22	25		
Good response week 12|	51	63		
Good response week 24|	76	93		

Statistical analyses

No statistical analyses for this end point

Secondary: Study period 1- Proportion of patients achieving EULAR criterion for moderate response

End point title	Study period 1- Proportion of patients achieving EULAR criterion for moderate response

End point description:

Proportion of patients achieving European League against Rheumatism (EULAR) moderate response (defined as DAS28<=3.2 at post-baseline assessment timepoint(s) with an improvement of >0.6 to <=1.2 from baseline or DAS28 >3.2 to <=5.1 with an improvement of >0.6 to <=1.2 or of >1.2 from baseline or DAS28 >5.1 with an improvement of >1.2 from baseline) ;

End point type	Secondary

End point timeframe:

week 4, week 12 and week 24

End point values	GP2017	Humira / switched GP2017		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	138		
Units: Participants				
Moderate response week 4|	63	78		
Moderate response week 12|	64	62		
Moderate response week 24|	42	42		

Statistical analyses

No statistical analyses for this end point

Secondary: Study period 1- Proportion of patients achieving EULAR/ACR Boolean remission criteria

End point title	Study period 1- Proportion of patients achieving EULAR/ACR Boolean remission criteria

End point description:

Proportion of patients achieving EULAR/American College of Rheumatology (EULAR/ACR) Boolean remission criteria (defined as number of tender joint count 28 <=1 and swollen joint count 28 <=1, CRP level (mg/dL) <=1 and patient's global assessment <=1 on a scale of 1-10 (corresponding to <=10 on a scale of 1-100).

End point type	Secondary

End point timeframe:

week 4, week 12, week 24

End point values	GP2017	Humira / switched GP2017		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	138		
Units: participants				
week 4|	4	0		
week 12|	8	12		
week 24|	19	26		

Statistical analyses

No statistical analyses for this end point

Secondary: Study period 1: Change in DAS28-CRP and DAS28-ESR scores from baseline to week 24 in patients treated with GP2017 and patients treated with

Humira

End point title	Study period 1: Change in DAS28-CRP and DAS28-ESR scores from baseline to week 24 in patients treated with GP2017 and patients treated with Humira

End point description:

Disease activity score (DAS) 28-CRP is based on 28-joint count (tender and swollen joints), C-reactive protein and patient's assessment of global disease activity (GDA) or general health (GH), values range from 0.96 to 10.0 while higher values mean a higher disease activity. • A DAS28-CRP value >5.1 corresponds to a high disease activity • A DAS28-CRP value between 3.2 and 5.1 corresponds to a moderate disease activity • A DAS28-CRP value between 2.6 and 3.2 corresponds to a low disease activity • A DAS28-CRP value < 2.6 corresponds to remission DAS28-CRP = 0.56 * sqrt(tender28) + 0.28* sqrt(swollen28) + 0.36 * ln(CRP+1) + 0.014 * GDA or GH + 0.96 where • tender28 and swollen28 are the number of tender and swollen joints as assessed using 28-joint count • CRP is C-reactive protein (mg/l) • GDA is the global disease activity measured on a Visual Analogue Scale (VAS) of 100 mm. For DAS-28 ESR, DAS28-ESR = 0.56 * sqrt(TJC28) + 0.28 * sqrt(SJC28) + 0.70 * ln(ESR) + 0.014 * GH

End point type	Secondary

End point timeframe:

study period 1: week 2, 4, 24

End point values	GP2017	Humira / switched GP2017		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	138		
Units: scores on a scale				
least squares mean (standard error)				
DAS28 CRP week 2|	-0.86 (± 0.107)	-0.92 (± 0.101)		
DAS28 CRP week 4|	-1.31 (± 0.112)	-1.36 (± 0.105)		
DAS28 CRP week 24|	-2.61 (± 0.109)	-2.83 (± 0.103)		
DAS28 ESR week 2|	-0.94 (± 0.115)	-0.98 (± 0.109)		
DAS28 ESR week 4|	-1.51 (± 0.124)	-1.51 (± 0.117)		
DAS28 ESR week 24|	-2.97 (± 0.127)	-3.16 (± 0.120)		

Statistical analyses

No statistical analyses for this end point

Secondary: Study period 1- Proportion of patients achieving ACR20/50/70 response at Weeks 4, 12 and 24

End point title	Study period 1- Proportion of patients achieving ACR20/50/70 response at Weeks 4, 12 and 24

End point description:

ACR20 response was defined if a patient fulfilled all 3 criteria below: -at least 20% improvement in tender 68 joint count -at least 20% improvement in swollen 66 joint-count; And at least 20% improvement in at least 3 of the following 5 measures: - Patient’s assessment of RA pain (visual analogue scale (VAS) 100 mm), -Patient’s global assessment of disease activity (VAS 100 mm), -

Physician’s global assessment of disease activity (VAS 100 mm), -Patient self-assessed disability index(HAQ-DI© score), -Acute phase reactant (CRP or ESR). ACR50 and ACR70 responses were defined as ACR20 response replacing “20% improvement” by “50% improvement” and “70% improvement”, respectively.

End point type	Secondary

End point timeframe:

Week 4, week 12 and week 24

End point values	GP2017	Humira / switched GP2017		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	138		
Units: participants				
ACR20 response Week 4|	64	71		
ACR20 response Week 12|	100	106		
ACR20 response Week 24|	111	130		
ACR50 response Week 4|	25	25		
ACR50 response Week 12|	53	67		
ACR50 response Week 24|	78	98		
ACR70 response Week 4|	7	9		
ACR70 response Week 12|	24	35		
ACR70 response Week 24|	48	53		

Statistical analyses

No statistical analyses for this end point

Secondary: Study period 1 - changes from Baseline in Health assessment questionnaire-Disability index (HAQ-DI©) at Weeks 4, 12 and 24;

End point title	Study period 1 - changes from Baseline in Health assessment questionnaire-Disability index (HAQ-DI©) at Weeks 4, 12 and 24;

End point description:

Health assessment questionnaire (HAQ-DI©) disability index ranges from 0 (best) to 3 (worst).The HAQ© was scored in accordance with the recommendation from the developers outlined in the “HAQ PACK” from Stanford University, California. Ramey Dr, Fries JF, Singh G. in B. Spilker Quality of Life and Pharmacoleconomics in Clinical Trials, 2nd ed, The Health Assessment Questionnaire 1995 -- Status and Review. Philadelphia: Lippincott-Raven Pub., 1996, p 227 – 237. Fries JF, Spitz P, Kraines G, Holman H. Measurement of Patient Outcome in Arthritis, Arthritis and Rheumatism, 1980, 23:137-145.

End point type	Secondary

End point timeframe:

Weeks 4, 12 and 24;

End point values	GP2017	Humira / switched GP2017		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	138		
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 4|	-0.32 (± 0.519)	-0.32 (± 0.449)		
Week 12|	-0.50 (± 0.576)	-0.47 (± 0.501)		
Week 24|	-0.63 (± 0.610)	-0.59 (± 0.543)		

Statistical analyses

No statistical analyses for this end point

Secondary: Study period 1- Proportion of patients achieving HAQ-DI© in normal range (≤ 0.5) at Weeks 4, 12 and 24;

End point title	Study period 1- Proportion of patients achieving HAQ-DI© in normal range (≤ 0.5) at Weeks 4, 12 and 24;

End point description:

Health assessment questionnaire disability index (HAQ-DI©) ranges from 0 (best) to 3 (worst)

End point type	Secondary

End point timeframe:

Weeks 4, 12 and 24;

End point values	GP2017	Humira / switched GP2017		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	138		
Units: participants				
Week 4|	27	33		
Week 12|	38	40		
Week 24|	46	50		

Statistical analyses

No statistical analyses for this end point

Secondary: Study period 1- Proportion of patients achieving HAQ-DI© score improvement >0.3 at Weeks 4, 12 and 24

End point title	Study period 1- Proportion of patients achieving HAQ-DI© score improvement >0.3 at Weeks 4, 12 and 24

End point description:

Health assessment questionnaire (HAQ-DI©) disability index ranges from 0 (best) to 3 (worst)

End point type	Secondary

End point timeframe:

Weeks 4, 12 and 24;

End point values	GP2017	Humira / switched GP2017		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	138		
Units: participants				
Week 4|	106	117		
Week 12|	102	109		
Week 24|	91	106		

Statistical analyses

No statistical analyses for this end point

Secondary: Study period 1 - Functional Assessment of Chronic Illness Therapy (FACIT©) Fatigue scale relative to Baseline at Weeks 4, 12 and 24 (change from baseline)

End point title	Study period 1 - Functional Assessment of Chronic Illness Therapy (FACIT©) Fatigue scale relative to Baseline at Weeks 4, 12 and 24 (change from baseline)

End point description:

FACIT© fatigue scale is a 13- item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function, ranging from 0 (worst) to 52 (best).

End point type	Secondary

End point timeframe:

Weeks 4, 12 and 24;

End point values	GP2017	Humira / switched GP2017		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	138		
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 4|	6.59 (± 7.949)	7.25 (± 8.591)		
Week 12|	10.49 (± 9.218)	10.62 (± 9.134)		
Week 24|	12.57 (± 10.760)	12.72 (± 9.451)		

Statistical analyses

No statistical analyses for this end point

Secondary: Study period 1 - CRP and ESR changes from baseline in GP2017 and US-licensed Humira treated patients over time

End point title	Study period 1 - CRP and ESR changes from baseline in GP2017 and US-licensed Humira treated patients over time

End point description:

End point type	Secondary

End point timeframe:

Week 4, week 12, week 24

End point values	GP2017	Humira / switched GP2017		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	138		
Units: score on a scale				
arithmetic mean (standard deviation)				
CRP change from baseline week 4|	-4.79 (± 8.728)	-4.93 (± 12.128)		
CRP change from baseline week 12|	-5.98 (± 11.270)	-5.07 (± 11.791)		
CRP change from baseline week 24|	-2.51 (± 19.176)	-5.30 (± 13.726)		
ESR change from baseline week 4|	-16.17 (± 14.693)	-13.98 (± 15.823)		
ESR change from baseline week 12|	-17.33 (± 16.214)	-15.08 (± 31.150)		
ESR change from baseline week 24|	-19.60 (± 20.494)	-20.49 (± 18.255)		

Statistical analyses

No statistical analyses for this end point

Secondary: Study period 1: Incidence and severity of injection site reactions in GP2017 and Humira

End point title	Study period 1: Incidence and severity of injection site reactions in GP2017 and Humira

End point description:

Incidence of injection site reactions in GP2017 and Humira

End point type	Secondary

End point timeframe:

Treatment Period 1, 24 weeks

End point values	GP2017	Humira / switched GP2017		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	176		
Units: Participants				
incidence of injection site reactions|	7	11		
injection site reactions MILD|	7	7		
injection site reactions MODERATE|	0	4		
injection site reactions SEVERE|	0	0		
Injection site erythema|	2	6		
Injection site pruritus|	2	3		
Injection site pain|	2	1		
Injection site inflammation|	2	0		
Injection site rash|	0	2		
Injection site discolouration|	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Study period 1 - Immunogenicity by measuring the rate of anti-drug antibody (ADA) formation against adalimumab in patients treated with GP2017 or Humira (positive patients)

End point title	Study period 1 - Immunogenicity by measuring the rate of anti-drug antibody (ADA) formation against adalimumab in patients treated with GP2017 or Humira (positive patients)

End point description:

Frequency of patients having anti-drug antibody (ADA) during 24 weeks

End point type	Secondary

End point timeframe:

baseline, week 2, week 4, week 12, week 24

End point values	GP2017	Humira / switched GP2017		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	176		
Units: Participants				
Baseline|	10	6		
Week 2|	12	10		
Week 4|	14	22		
Week 12|	16	23		
Week 24|	23	25		

Statistical analyses

No statistical analyses for this end point

Secondary: Study period 2 - Immunogenicity by measuring the rate of anti-drug antibody (ADA) formation against adalimumab in patients treated with GP2017 who continued GP2017 or switched to GP2017 from Humira (positive patients)

End point title	Study period 2 - Immunogenicity by measuring the rate of anti-drug antibody (ADA) formation against adalimumab in patients treated with GP2017 who continued GP2017 or switched to GP2017 from Humira (positive patients)

End point description:

Frequency of patients having anti-drug antibody (ADA) during 24 weeks

End point type	Secondary

End point timeframe:

week 24, week 36, week 48

End point values	GP2017	Humira / switched GP2017		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	166		
Units: Participants				
Week 24|	22	25		
Week 36|	21	22		
Week 48|	12	12		

Statistical analyses

No statistical analyses for this end point

Secondary: Study period 2 : Proportion of patients achieving ACR20/50/70 response at week 48, in patients treated with GP2017 who continued GP2017 or switched to GP2017 from Humira

End point title	Study period 2 : Proportion of patients achieving ACR20/50/70

	response at week 48, in patients treated with GP2017 who continued GP2017 or switched to GP2017 from Humira

End point description:

End point type	Secondary

End point timeframe:

week 48

End point values	GP2017	Humira / switched GP2017		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	126		
Units: participants				
ACR20 response Week 48|	93	111		
ACR50 response Week 48|	72	81		
ACR70 response Week 48|	49	55		

Statistical analyses

No statistical analyses for this end point

Secondary: Study period 2 - Health Assessment Questionnaire-Disability Index (HAQ-DI©) changes from Week 24 at Week 48 in patients treated continuously with GP2017 and in patients treated with GP2017 after switch from Humira

End point title	Study period 2 - Health Assessment Questionnaire-Disability Index (HAQ-DI©) changes from Week 24 at Week 48 in patients treated continuously with GP2017 and in patients treated with GP2017 after switch from Humira

End point description:

Health assessment questionnaire (HAQ-DI) disability index ranges from 0 (best) to 3 (worst)

End point type	Secondary

End point timeframe:

Weeks 48

End point values	GP2017	Humira / switched GP2017		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	126		
Units: score on a scale				
arithmetic mean (standard deviation)	0.01 (± 0.358)	-0.03 (± 0.427)		

Statistical analyses

No statistical analyses for this end point

Secondary: Study period 2 :Proportion of patients treated continuously with GP2017 and patients treated with GP2017 after switch from Humira achieving HAQ-DI© score in normal range ≤0.5 at Week 48

End point title	Study period 2 :Proportion of patients treated continuously with GP2017 and patients treated with GP2017 after switch from Humira achieving HAQ-DI© score in normal range ≤0.5 at Week 48

End point description:

End point type	Secondary

End point timeframe:

week 48

End point values	GP2017	Humira / switched GP2017		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	126		
Units: participants	45	52		

Statistical analyses

No statistical analyses for this end point

Secondary: Study period 2 : Functional Assessment of Chronic Illness Therapy (FACIT©) Fatigue scale changes from Week 24 at Week 48 in patients treated continuously with GP2017 and in patients treated with GP2017 after switch from Humira

End point title	Study period 2 : Functional Assessment of Chronic Illness Therapy (FACIT©) Fatigue scale changes from Week 24 at Week 48 in patients treated continuously with GP2017 and in patients treated with GP2017 after switch from Humira

End point description:

FACIT©: from 0 (worst) to 52 (best), a score of less than 30 indicates severe fatigue

End point type	Secondary

End point timeframe:

week 48

End point values	GP2017	Humira / switched GP2017		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	126		
Units: score on a scale				
arithmetic mean (standard deviation)	-0.65 (± 7.421)	-0.85 (± 7.476)		

Statistical analyses

No statistical analyses for this end point

Secondary: Study period 2: Changes from Week 24 at Week 48 in DAS28-CRP and DAS28-ESR scores in patients treated continuously with GP2017 and in patients treated with GP2017 after switch from Humira

End point title	Study period 2: Changes from Week 24 at Week 48 in DAS28-CRP and DAS28-ESR scores in patients treated continuously with GP2017 and in patients treated with GP2017 after switch from Humira

End point description:

Disease activity score (DAS) 28-CRP is based on 28-joint count (tender and swollen joints), C-reactive protein and patient's assessment of global disease activity (GDA) or general health (GH), values range from 0.96 to 10.0 while higher values mean a higher disease activity. • A DAS28-CRP value >5.1 corresponds to a high disease activity • A DAS28-CRP value between 3.2 and 5.1 corresponds to a moderate disease activity • A DAS28-CRP value between 2.6 and 3.2 corresponds to a low disease activity • A DAS28-CRP value < 2.6 corresponds to remission DAS28-CRP = 0.56 * sqrt(tender28) + 0.28* sqrt(swollen28) + 0.36 * ln(CRP+1) + 0.014 * GDA or GH + 0.96 where • tender28 and swollen28 are the number of tender and swollen joints as assessed using 28-joint count • CRP is C-reactive protein (mg/l) • GDA is the global disease activity measured on a Visual Analogue Scale (VAS) of 100 mm. For DAS-28 ESR, DAS28-ESR = 0.56 * sqrt(TJC28) + 0.28 * sqrt(SJC28) + 0.70 * ln(ESR) + 0.014 * GH

End point type	Secondary

End point timeframe:

week 48

End point values	GP2017	Humira / switched GP2017		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	126		
Units: score on a scale				
arithmetic mean (standard deviation)				
DAS28-CRP Week 48, change from week 24|	-0.10 (± 0.893)	0.00 (± 0.941)		
DAS28-ESR Week 48, change from week 24|	-0.04 (± 1.015)	0.00 (± 1.025)		

Statistical analyses

No statistical analyses for this end point

Secondary: Study period 2: Incidence of injection site reactions in patients treated continuously with GP2017 and in patients treated with GP2017 after switch from Humira

End point title	Study period 2: Incidence of injection site reactions in patients treated continuously with GP2017 and in patients treated with GP2017 after switch from Humira

End point description:

Incidence of injection site reactions

End point type	Secondary

End point timeframe:

up to 48 weeks

End point values	GP2017	Humira / switched GP2017		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	166		
Units: participants				
Number of patients with ISRs|	1	2		
Injection site erythema|	1	2		
Injection site pruritus|	0	1		
Injection site pain|	0	0		
Injection site inflammation|	0	0		
Injection site rash|	0	0		
Injection site discolouration|	0	0		
injection site reactions MILD|	1	1		
injection site reactions MODERATE|	0	1		
injection site reactions SEVERE|	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Timeframe for AE	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Study Period 1 SP1 SAF GP2017
Reporting group description:	
Study Period 1 SP1 SAF GP2017	
Reporting group title	Study Period 1 SP1 SAF Humira
Reporting group description:	
Study Period 1 SP1 SAF Humira	
Reporting group title	Study Period 2 SP2 SAF Continued GP2017
Reporting group description:	
Study Period 2 SP2 SAF Continued GP2017	
Reporting group title	Study Period 2 SP2 SAF Humira to GP2017
Reporting group description:	
Study Period 2 SP2 SAF Humira to GP2017	
Reporting group title	Entire study SP1 SAF GP2017
Reporting group description:	
Entire study SP1 SAF GP2017	
Reporting group title	Entire study SP1 SAF Humira/Switched GP2017
Reporting group description:	
Entire study SP1 SAF Humira/Switched GP2017	

Serious adverse events	Study Period 1 SP1 SAF GP2017	Study Period 1 SP1 SAF Humira	Study Period 2 SP2 SAF Continued GP2017
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 177 (2.82%)	4 / 176 (2.27%)	4 / 159 (2.52%)
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)			
Brain neoplasm benign			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			

subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 177 (0.00%)	0 / 176 (0.00%)	1 / 159 (0.63%)
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			
Angina pectoris			
subjects affected / exposed	0 / 177 (0.00%)	0 / 176 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 177 (0.00%)	0 / 176 (0.00%)	1 / 159 (0.63%)
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 / 177 (0.00%)	1 / 176 (0.57%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemianopia homonymous			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial pressure increased			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 177 (0.00%)	0 / 176 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 177 (0.00%)	0 / 176 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Uterine prolapse			
subjects affected / exposed	0 / 177 (0.00%)	0 / 176 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 177 (0.00%)	0 / 176 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 177 (0.00%)	0 / 176 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 177 (0.00%)	0 / 176 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 177 (0.00%)	0 / 176 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Study Period 2 SP2 SAF Humira to GP2017	Entire study SP1 SAF GP2017	Entire study SP1 SAF Humira/Switched GP2017
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 166 (3.61%)	7 / 177 (3.95%)	10 / 176 (5.68%)
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)			
Brain neoplasm benign			

subjects affected / exposed	0 / 166 (0.00%)	0 / 177 (0.00%)	1 / 176 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 166 (0.00%)	0 / 177 (0.00%)	1 / 176 (0.57%)
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			
Humerus fracture			
subjects affected / exposed	0 / 166 (0.00%)	0 / 177 (0.00%)	1 / 176 (0.57%)
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 / 166 (0.00%)	1 / 177 (0.56%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 166 (0.60%)	0 / 177 (0.00%)	1 / 176 (0.57%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 166 (0.00%)	1 / 177 (0.56%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 166 (0.00%)	0 / 177 (0.00%)	1 / 176 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemianopia homonymous			
subjects affected / exposed	0 / 166 (0.00%)	0 / 177 (0.00%)	1 / 176 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Intracranial pressure increased			
subjects affected / exposed	0 / 166 (0.00%)	0 / 177 (0.00%)	1 / 176 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 166 (0.00%)	1 / 177 (0.56%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 166 (0.60%)	0 / 177 (0.00%)	1 / 176 (0.57%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 166 (0.60%)	0 / 177 (0.00%)	1 / 176 (0.57%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 166 (0.00%)	0 / 177 (0.00%)	1 / 176 (0.57%)
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			
Uterine prolapse			
subjects affected / exposed	1 / 166 (0.60%)	0 / 177 (0.00%)	1 / 176 (0.57%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 177 (0.56%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			

subjects affected / exposed	0 / 166 (0.00%)	1 / 177 (0.56%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 166 (0.00%)	1 / 177 (0.56%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 177 (0.00%)	1 / 176 (0.57%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 177 (0.56%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 166 (1.20%)	0 / 177 (0.00%)	2 / 176 (1.14%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 166 (0.00%)	1 / 177 (0.56%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 166 (0.60%)	0 / 177 (0.00%)	1 / 176 (0.57%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Study Period 1 SP1 SAF GP2017	Study Period 1 SP1 SAF Humira	Study Period 2 SP2 SAF Continued GP2017
Total subjects affected by non-serious adverse events			
subjects affected / exposed	83 / 177 (46.89%)	74 / 176 (42.05%)	28 / 159 (17.61%)
Investigations			
Transaminases increased			
subjects affected / exposed	0 / 177 (0.00%)	3 / 176 (1.70%)	1 / 159 (0.63%)
occurrences (all)	0	3	1
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 177 (1.13%)	3 / 176 (1.70%)	0 / 159 (0.00%)
occurrences (all)	2	3	0
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 177 (2.82%)	3 / 176 (1.70%)	2 / 159 (1.26%)
occurrences (all)	5	3	2
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 177 (3.95%)	5 / 176 (2.84%)	2 / 159 (1.26%)
occurrences (all)	7	5	2
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	2 / 177 (1.13%)	0 / 176 (0.00%)	2 / 159 (1.26%)
occurrences (all)	2	0	2
Neutropenia			
subjects affected / exposed	3 / 177 (1.69%)	0 / 176 (0.00%)	2 / 159 (1.26%)
occurrences (all)	3	0	2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 177 (2.82%)	0 / 176 (0.00%)	0 / 159 (0.00%)
occurrences (all)	5	0	0
Injection site erythema			
subjects affected / exposed	2 / 177 (1.13%)	6 / 176 (3.41%)	1 / 159 (0.63%)
occurrences (all)	3	17	1
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	4 / 177 (2.26%)	7 / 176 (3.98%)	0 / 159 (0.00%)
occurrences (all)	4	7	0
Nausea			
subjects affected / exposed	5 / 177 (2.82%)	1 / 176 (0.57%)	0 / 159 (0.00%)
occurrences (all)	6	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 177 (1.13%)	1 / 176 (0.57%)	3 / 159 (1.89%)
occurrences (all)	2	1	3
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 177 (0.00%)	3 / 176 (1.70%)	0 / 159 (0.00%)
occurrences (all)	0	3	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 177 (4.52%)	0 / 176 (0.00%)	2 / 159 (1.26%)
occurrences (all)	8	0	2
Rheumatoid arthritis			
subjects affected / exposed	3 / 177 (1.69%)	1 / 176 (0.57%)	5 / 159 (3.14%)
occurrences (all)	4	1	5
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 177 (2.26%)	8 / 176 (4.55%)	1 / 159 (0.63%)
occurrences (all)	4	9	1
Gastroenteritis			
subjects affected / exposed	2 / 177 (1.13%)	4 / 176 (2.27%)	1 / 159 (0.63%)
occurrences (all)	2	4	1
Influenza			
subjects affected / exposed	3 / 177 (1.69%)	5 / 176 (2.84%)	1 / 159 (0.63%)
occurrences (all)	4	5	1
Oral herpes			
subjects affected / exposed	4 / 177 (2.26%)	3 / 176 (1.70%)	1 / 159 (0.63%)
occurrences (all)	6	3	1
Pharyngitis			
subjects affected / exposed	9 / 177 (5.08%)	10 / 176 (5.68%)	1 / 159 (0.63%)
occurrences (all)	11	11	1

Sinusitis			
subjects affected / exposed	5 / 177 (2.82%)	3 / 176 (1.70%)	0 / 159 (0.00%)
occurrences (all)	5	3	0
Upper respiratory tract infection			
subjects affected / exposed	12 / 177 (6.78%)	7 / 176 (3.98%)	4 / 159 (2.52%)
occurrences (all)	14	9	4
Urinary tract infection			
subjects affected / exposed	4 / 177 (2.26%)	6 / 176 (3.41%)	2 / 159 (1.26%)
occurrences (all)	4	6	2
Viral upper respiratory tract infection			
subjects affected / exposed	26 / 177 (14.69%)	16 / 176 (9.09%)	4 / 159 (2.52%)
occurrences (all)	28	18	4
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	3 / 177 (1.69%)	3 / 176 (1.70%)	2 / 159 (1.26%)
occurrences (all)	3	3	2

Non-serious adverse events	Study Period 2 SP2 SAF Humira to GP2017	Entire study SP1 SAF GP2017	Entire study SP1 SAF Humira/Switched GP2017
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 166 (15.66%)	94 / 177 (53.11%)	80 / 176 (45.45%)
Investigations			
Transaminases increased			
subjects affected / exposed	1 / 166 (0.60%)	1 / 177 (0.56%)	4 / 176 (2.27%)
occurrences (all)	1	1	4
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 166 (0.60%)	2 / 177 (1.13%)	4 / 176 (2.27%)
occurrences (all)	1	2	4
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 166 (0.60%)	6 / 177 (3.39%)	4 / 176 (2.27%)
occurrences (all)	1	7	4
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 166 (1.20%)	8 / 177 (4.52%)	7 / 176 (3.98%)
occurrences (all)	2	9	7

Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 166 (0.00%)	4 / 177 (2.26%)	0 / 176 (0.00%)
occurrences (all)	0	4	0
Neutropenia			
subjects affected / exposed	0 / 166 (0.00%)	5 / 177 (2.82%)	0 / 176 (0.00%)
occurrences (all)	0	5	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 166 (0.60%)	5 / 177 (2.82%)	1 / 176 (0.57%)
occurrences (all)	1	5	1
Injection site erythema			
subjects affected / exposed	2 / 166 (1.20%)	3 / 177 (1.69%)	6 / 176 (3.41%)
occurrences (all)	2	4	19
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 166 (0.00%)	4 / 177 (2.26%)	7 / 176 (3.98%)
occurrences (all)	0	4	7
Nausea			
subjects affected / exposed	0 / 166 (0.00%)	5 / 177 (2.82%)	1 / 176 (0.57%)
occurrences (all)	0	6	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 166 (0.00%)	5 / 177 (2.82%)	1 / 176 (0.57%)
occurrences (all)	0	5	1
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 166 (0.60%)	0 / 177 (0.00%)	4 / 176 (2.27%)
occurrences (all)	1	0	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 166 (0.00%)	10 / 177 (5.65%)	0 / 176 (0.00%)
occurrences (all)	0	10	0
Rheumatoid arthritis			
subjects affected / exposed	2 / 166 (1.20%)	6 / 177 (3.39%)	3 / 176 (1.70%)
occurrences (all)	2	9	3

Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 166 (2.41%)	4 / 177 (2.26%)	12 / 176 (6.82%)
occurrences (all)	4	5	13
Gastroenteritis			
subjects affected / exposed	0 / 166 (0.00%)	3 / 177 (1.69%)	4 / 176 (2.27%)
occurrences (all)	0	3	4
Influenza			
subjects affected / exposed	0 / 166 (0.00%)	4 / 177 (2.26%)	5 / 176 (2.84%)
occurrences (all)	0	5	5
Oral herpes			
subjects affected / exposed	0 / 166 (0.00%)	5 / 177 (2.82%)	3 / 176 (1.70%)
occurrences (all)	0	7	3
Pharyngitis			
subjects affected / exposed	3 / 166 (1.81%)	10 / 177 (5.65%)	10 / 176 (5.68%)
occurrences (all)	3	12	14
Sinusitis			
subjects affected / exposed	2 / 166 (1.20%)	5 / 177 (2.82%)	5 / 176 (2.84%)
occurrences (all)	2	5	5
Upper respiratory tract infection			
subjects affected / exposed	3 / 166 (1.81%)	14 / 177 (7.91%)	9 / 176 (5.11%)
occurrences (all)	3	18	12
Urinary tract infection			
subjects affected / exposed	3 / 166 (1.81%)	6 / 177 (3.39%)	8 / 176 (4.55%)
occurrences (all)	3	6	9
Viral upper respiratory tract infection			
subjects affected / exposed	4 / 166 (2.41%)	29 / 177 (16.38%)	19 / 176 (10.80%)
occurrences (all)	4	32	22
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	0 / 166 (0.00%)	5 / 177 (2.82%)	3 / 176 (1.70%)
occurrences (all)	0	5	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 November 2015	Amendment 1 mainly provided further clarification of some inclusion and exclusion criteria and the blood sampling schedule.
15 February 2016	Amendment 2 introduced the following changes: The patients' HIV seronegativity was to be confirmed at the study eligibility screening. The ranges for clinically notable sodium and calcium values were amended in line with CTCAE version 4.
01 February 2017	Amendment 3 introduced the following substantial changes: The originally planned analysis and reporting of Week 12 data was removed. Instead all data were to be analyzed at the end of the study and reported in a single study report. The already collected serum samples that were left over after the assessment of adalimumab trough concentration and testing for ADAs were not to be destroyed (as originally planned) but to be stored for later additional exploratory research, if the patient agreed. The amended protocol and the additional Informed Consent to be signed by the affected patients had to be approved by or notified to the respective local authorities.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

NA

Notes: