Clinical trial results:
A randomized, double-blind, parallel-group Phase III study to demonstrate equivalent efficacy and to compare safety & immunogenicity of GP2015 and Enbrel® (EU authorized) in patients with moderate to severe, active rheumatoid arthritis

Summary

EudraCT number	2012-002009-23
Trial protocol	HU CZ LT EE GB SK LV PL DE BG ES
Global end of trial date	12 June 2017

Results information

Result version number	v1 (current)
This version publication date	27 June 2018
First version publication date	27 June 2018

Trial information

Trial identification

Sponsor protocol code	CGP15-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02638259
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	HEXAL AG / Sandoz
Sponsor organisation address	Indistriestr. 25, Holzkirchen, Germany, 83607
Public contact	Sandoz Biopharma Clinical Development - Strategic Planning, Sandoz, 49 0049080244760, biopharma.clinicaltrials@sandoz.com
Scientific contact	Sandoz Biopharma Clinical Development - Strategic Planning, Sandoz, 49 0049080244760, 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	12 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 June 2017
Global end of trial reached?	Yes
Global end of trial date	12 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate equivalence of change in DAS28-CRP score from Baseline to Week 24 between patients treated with GP2015 and patients treated with Enbrel.

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	27 November 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Hungary: 19
Country: Number of subjects enrolled	United States: 49
Country: Number of subjects enrolled	Czech Republic: 31
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Russian Federation: 22
Country: Number of subjects enrolled	Latvia: 8
Country: Number of subjects enrolled	Poland: 92
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Mexico: 9
Country: Number of subjects enrolled	Slovakia: 8
Country: Number of subjects enrolled	Bulgaria: 22
Country: Number of subjects enrolled	Lithuania: 21
Country: Number of subjects enrolled	Serbia: 22
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Estonia: 46
Worldwide total number of subjects	376
EEA total number of subjects	274

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)	300
From 65 to 84 years	76
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

GP2015 : 181 patients completed TP1 and 175 entered TP2. 6 stopped prior to entering TP2 : 3 due to Eligibility, 2 withdrew consent and 1 due to IP delay

TP2 Enbrel GP2015 : 172 patients completed TP1 and 166 entered TP2. 6 stopped prior TP2 : 4 due to Eligibility, 1 withdrew consent and 1 due to adverse event

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	376
Number of subjects completed	376

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	50mg GP2015

Arm description:

Group 1 received treatment with 50mg GP2015 by subcutaneous injection every week up to 24 weeks (Treatment Period 1) after which patients achieving at least a moderate clinical response continued treatment with 50mg GP2015 subcutaneous injection every week up to 48 weeks (Treatment Period 2). GP2015: Enbrel comparator

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

Dosage and administration details:

50 mg subcutaneous injection once weekly

Arm title	50mg EU-authorized Enbrel

Arm description:

Group 2 received treatment with 50mg EU-authorized Enbrel by subcutaneous injection every week up to 24 weeks (Treatment Period 1) after which patients achieving at least a moderate clinical response were switched to 50 mg GP2015 subcutaneous injection every week up to 48 weeks (Treatment Period 2). GP2015: Enbrel comparator

Arm type	Active comparator
Investigational medicinal product name	Enbrel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

50 mg subcutaneous injection once weekly

Number of subjects in period 1	50mg GP2015	50mg EU-authorized Enbrel
Started	186	190
Completed	181	172
Not completed	5	18
Adverse event, serious fatal	-	1
Consent withdrawn by subject	4	6
Adverse event, non-fatal	1	5
Withdrawn per sponsor decision	-	2
Lack of efficacy	-	1
Protocol deviation	-	3

Period 2	
Period 2 title	Treatment Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	50mg GP2015

Arm description:

Group 1 received treatment with 50mg GP2015 by subcutaneous injection every week up to 24 weeks (Treatment Period 1) after which patients achieving at least a moderate clinical response continued treatment with 50mg GP2015 subcutaneous injection every week up to 48 weeks (Treatment Period 2). GP2015: Enbrel comparator

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

Dosage and administration details:

50 mg subcutaneous injection once weekly

Arm title	50mg EU-authorized Enbrel

Arm description:

Group 2 will receive treatment with 50mg EU-authorized Enbrel by subcutaneous injection every week up to 24 weeks (Treatment Period 1) after which patients achieving at least a moderate clinical response will be switched to 50 mg GP2015 subcutaneous injection every week up to 48 weeks (Treatment Period 2). GP2015: Enbrel comparator

Arm type	treatment period 2 : GP2015

No investigational medicinal product assigned in this arm

Number of subjects in period 2[1]	50mg GP2015	50mg EU-authorized Enbrel
Started	175	166
Completed	169	155
Not completed	6	11
Consent withdrawn by subject	1	7
Adverse event, non-fatal	5	4

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 :
TP2 GP2015 : 181 patients completed TP1 and 175 started TP2 (3 did not enter TP2 due to Eligibility, 2 withdrew consent and 1 due to IP delay)
TP2 Enbrel GP2015 : 172 patients completed TP1 and 175 started TP2 (4 due to Eligibility, 1 withdrew consent and 1 due to adverse event)

Baseline characteristics

Reporting groups	
Reporting group title	50mg GP2015
Reporting group description:	
Group 1 received treatment with 50mg GP2015 by subcutaneous injection every week up to 24 weeks (Treatment Period 1) after which patients achieving at least a moderate clinical response continued treatment with 50mg GP2015 subcutaneous injection every week up to 48 weeks (Treatment Period 2). GP2015: Enbrel comparator	
Reporting group title	50mg EU-authorized Enbrel
Reporting group description:	
Group 2 received treatment with 50mg EU-authorized Enbrel by subcutaneous injection every week up to 24 weeks (Treatment Period 1) after which patients achieving at least a moderate clinical response were switched to 50 mg GP2015 subcutaneous injection every week up to 48 weeks (Treatment Period 2). GP2015: Enbrel comparator	

Reporting group values	50mg GP2015	50mg EU-authorized Enbrel	Total
Number of subjects	186	190	376
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)	148	152	300
From 65-84 years	38	38	76
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	55.2	53.1	
standard deviation	± 11.22	± 12.70	-
Sex: Female, Male Units: Subjects			
Female	158	150	308
Male	28	40	68
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	1	2
Asian	0	3	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	5	1	6
White	180	185	365
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Region of Enrollment Units: Subjects			

Hungary|	7	12	19
United States|	23	26	49
Czechia|	16	15	31
United Kingdom|	3	4	7
Spain|	5	5	10
Russia|	12	10	22
Latvia|	6	2	8
Poland|	44	48	92
Italy|	1	0	1
Mexico|	4	5	9
Slovakia|	3	5	8
Bulgaria|	11	11	22
Lithuania|	9	12	21
Serbia|	12	10	22
Germany|	4	5	9
Estonia|	26	20	46

End points

End points reporting groups

Reporting group title	50mg GP2015

Reporting group description:

Group 1 received treatment with 50mg GP2015 by subcutaneous injection every week up to 24 weeks (Treatment Period 1) after which patients achieving at least a moderate clinical response continued treatment with 50mg GP2015 subcutaneous injection every week up to 48 weeks (Treatment Period 2). GP2015: Enbrel comparator

Reporting group title	50mg EU-authorized Enbrel

Reporting group description:

Group 2 received treatment with 50mg EU-authorized Enbrel by subcutaneous injection every week up to 24 weeks (Treatment Period 1) after which patients achieving at least a moderate clinical response were switched to 50 mg GP2015 subcutaneous injection every week up to 48 weeks (Treatment Period 2). GP2015: Enbrel comparator

Reporting group title	50mg GP2015

Reporting group description:

Group 1 received treatment with 50mg GP2015 by subcutaneous injection every week up to 24 weeks (Treatment Period 1) after which patients achieving at least a moderate clinical response continued treatment with 50mg GP2015 subcutaneous injection every week up to 48 weeks (Treatment Period 2). GP2015: Enbrel comparator

Reporting group title	50mg EU-authorized Enbrel

Reporting group description:

Group 2 will receive treatment with 50mg EU-authorized Enbrel by subcutaneous injection every week up to 24 weeks (Treatment Period 1) after which patients achieving at least a moderate clinical response will be switched to 50 mg GP2015 subcutaneous injection every week up to 48 weeks (Treatment Period 2). GP2015: Enbrel comparator

Primary: Safety: Change in DAS28-CRP score from baseline to week 24 in patients treated with GP2015 and patients treated with Enbrel

End point title	Safety: Change in DAS28-CRP score from baseline to week 24 in patients treated with GP2015 and patients treated with Enbrel

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, 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 + 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:

treatment period 1: up to 24 weeks

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	155		
Units: scores on a scale				
least squares mean (standard error)	-2.80 (± 0.113)	-2.73 (± 0.117)		

Statistical analyses

Statistical analysis title	Therapeutic equivalence between GP2015 and Enbrel

Statistical analysis description:

Therapeutic equivalence in terms of change from baseline in DAS28-CRP at week 24 will be concluded if the 95% confidence interval for the LS mean difference between GP2015 and Enbrel 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	50mg GP2015 v 50mg EU-authorized Enbrel
Number of subjects included in analysis	323
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Mean difference (final values)
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	0.12
Variability estimate	Standard error of the mean
Dispersion value	0.097

Secondary: Treatment period 1: Frequency and severity of injection site reactions in GP2015 and Enbrel

End point title	Treatment period 1: Frequency and severity of injection site reactions in GP2015 and Enbrel

End point description:

Frequency of participants with injection site reactions in GP2015 and Enbrel

End point type	Secondary

End point timeframe:

Treatment Period 1, up to 24 weeks

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186	190		
Units: Participants				
All injection site reactions|	13	35		
Moderate injection site reactions|	1	5		
Severe injection site reactions|	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment period 1 - Safety : Immunogenicity by measuring the rate of anti-drug antibody (ADA) positive patients

End point title	Treatment period 1 - Safety : Immunogenicity by measuring the rate of anti-drug antibody (ADA) positive patients

End point description:

Frequency of patients having anti-drug antibody (ADA) during 24 weeks (Treatment Period 1) using 1% false positive rate

End point type	Secondary

End point timeframe:

Treatment Period 1, up to 24 weeks

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186	190		
Units: Participants				
Baseline|	2	0		
Week 2|	2	5		
Week 4|	3	42		
Week 12|	0	5		
Week 24|	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment period 1- DAS28-CRP and DAS28-erythrocyte sedimentation rate (ESR) scores at Baseline and Weeks 4, 12 and 24;

End point title	Treatment period 1- DAS28-CRP and DAS28-erythrocyte sedimentation rate (ESR) scores at Baseline and Weeks 4, 12 and 24;

End point description:

DAS28-CRP is a disease activity score and defined in primary outcome measure. DAS28-ESR is the DAS28 erythrocyte sedimentation rate score. DAS28-CRP and DAS28-ESR: a. best is 0, b. < 2.6 – remission, c. ≥ 2.6 to ≤ 3.2 – low disease activity d. > 3.2 to ≤ 5.1 – moderate disease activity e. > 5.1 – high disease activity DAS28-ESR = 0.56 * sqrt(tender28) + 0.28* sqrt(swollen28) + 0.7 * ln(ESR) + 0.014 * GDA 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) • ESR is erythrocyte sedimentation rate (mm/h) • GDA is the global disease activity measured on a Visual Analogue Scale (VAS) of 100 mm

End point type	Secondary

End point timeframe:

treatment period 1, week 4, 12, 24

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	155		
Units: score on a scale				
arithmetic mean (standard deviation)				
DAS28-CRP baseline|	5.42 (± 0.921)	5.53 (± 0.783)		
DAS28-CRP week 4|	3.81 (± 1.079)	3.82 (± 1.077)		
DAS28-CRP week 12|	3.15 (± 1.045)	3.31 (± 1.088)		
DAS28-CRP week 24|	2.63 (± 0.910)	2.75 (± 0.928)		
DAS28-ESR baseline|	6.34 (± 0.882)	6.41 (± 0.768)		
DAS28-ESR week 4|	4.62 (± 1.183)	4.56 (± 1.204)		
DAS28-ESR week 12|	3.84 (± 1.216)	3.94 (± 1.284)		
DAS28-ESR week 24|	3.24 (± 1.060)	3.32 (± 1.099)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment period 1 - Changes from baseline in DAS28-CRP and DAS-ESR scores to weeks 4, 12 and 24

End point title	Treatment period 1 - Changes from baseline in DAS28-CRP and DAS-ESR scores to weeks 4, 12 and 24

End point description:

End point type	Secondary

End point timeframe:

Treatment period 1, Week 4, week 12, week 24

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	155		
Units: score on a scale				
arithmetic mean (standard deviation)				
DAS28-CRP change from baseline week 4|	-1.59 (± 1.032)	-1.70 (± 1.001)		
DAS28-CRP change from baseline week 12|	-2.23 (± 1.030)	-2.20 (± 1.071)		
DAS28-CRP change from baseline week 24|	-2.78 (± 1.058)	-2.78 (± 1.028)		
DAS28-ESR change from baseline week 4|	-1.72 (± 1.068)	-1.85 (± 1.078)		
DAS28-ESR change from baseline week 12|	-2.50 (± 1.145)	-2.47 (± 1.218)		
DAS28-ESR change from baseline week 24|	-3.10 (± 1.157)	-3.09 (± 1.119)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment period 1- Proportion of patients achieving EULAR response

End point title	Treatment period 1- Proportion of patients achieving EULAR response

End point description:

Proportion of patients achieving European League against Rheumatism (EULAR) good response (defined as DAS28 ≤ 3.2 and DAS28 improvement from Baseline > 1.2) and moderate response (defined as DAS28 ≤ 3.2 and DAS28 improvement > 0.6 and ≤ 1.2, or DAS28 > 3.2 and ≤ 5.1 and DAS28 improvement > 0.6 or DAS28 > 5.1 but DAS28 improvement > 1.2) ;

End point type	Secondary

End point timeframe:

Treatment period 1, week 4, week 12 and week 24

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	155		
Units: Participants				
Good response week 4|	26	21		
Good response week 12|	54	47		
Good response week 24|	88	74		
Moderate response week 4|	95	99		
Moderate response week 12|	103	91		
Moderate response week 24|	76	77		
no response week 4|	46	34		
no response week 12|	11	16		
no response week 24|	4	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment period 1- Proportion of patients achieving DAS28 < 2.6 at Weeks 4, 12 and 24

End point title	Treatment period 1- Proportion of patients achieving DAS28 < 2.6 at Weeks 4, 12 and 24
End point description:	
% patients in DAS28-ESR categories up to week 24	
End point type	Secondary
End point timeframe:	
Treatment period 1, week 4, week 12 and week 24	

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	155		
Units: Participants				
Week 4 - remission (DAS28 <2.6)|	9	7		
Week 12 - remission (DAS28 <2.6)|	21	21		
Week 24 - remission (DAS28 <2.6)|	46	41		

Statistical analyses

No statistical analyses for this end point

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

End point title	Treatment 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 joints/swollen joints ≤ 1 and CRP (mg/dL) ≤ 1 and patient global assessment (1–10) ≤ 1) at Weeks 4, 12 and 24;	
End point type	Secondary
End point timeframe:	
Treatment period 1, week 4, week 12, week 24	

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	155		
Units: participants				
week 4|	1	2		
week 12|	9	8		
week 24|	24	15		

Statistical analyses

No statistical analyses for this end point

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

End point title	Treatment 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: -20% improvement in tender 68 joint-count -20% improvement in swollen 68 joint-count; And 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 (HAQ 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:

Treatment period 1, Week 4, week 12 and week 24

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	155		
Units: participants				
ACR20 response Week 4|	80	83		
ACR20 response Week 12|	131	116		
ACR20 response Week 24|	147	144		
ACR50 response Week 4|	25	28		
ACR50 response Week 12|	55	68		
ACR50 response Week 24|	107	110		
ACR70 response Week 4|	8	7		
ACR70 response Week 12|	21	26		
ACR70 response Week 24|	56	66		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment period 1- ACR-N scores at Weeks 4, 12 and 24;

End point title	Treatment period 1- ACR-N scores at Weeks 4, 12 and 24;

End point description:

ACR-N (American College of Rheumatology percentage of improvement): negative is worsening, positive (up to 100) is an improvement. ACR-N is a single number that characterizes the percentage of improvement from Baseline that a patient has experienced in analogy to ACR20 described above. ACR-N of X (such as 38) means that the patient had achieved an improvement of at least X% (such as 38%) in tender and swollen joints, and an improvement of at least X% (such as 38%) in 3 of the 5 other parameters mentioned above.

End point type	Secondary

End point timeframe:

Treatment period 1, Weeks 4, 12 and 24;

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	155		
Units: score on a scale				
arithmetic mean (standard deviation)				
week 4|	19.9 (± 29.89)	22.6 (± 34.02)		
week 12|	38.3 (± 27.46)	38.7 (± 35.32)		
week 24|	55.4 (± 27.61)	59.4 (± 25.40)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment period 1 - Proportion of patients in each disease activity category as defined by SDAI

End point title	Treatment period 1 - Proportion of patients in each disease activity category as defined by SDAI

End point description:

Proportion of patients in each disease activity category as defined by the Simplified Disease Activity Index (SDAI): high disease activity, SDAI > 26, moderate disease activity, SDAI > 11 to ≤ 26, low disease activity, SDAI > 3.3 to ≤ 11, and remission, SDAI ≤ 3.3 at Weeks 4, 12 and 24; SDAI and CDAI are measures of disease activity in RA. The scores were calculated by numerical summation of the number of tender and swollen joints (using the 28-joint count), and the patient's and physician's global assessment of disease activity.

End point type	Secondary

End point timeframe:

Treatment period 1, Weeks 4, 12 and 24;

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	155		
Units: Participants				
Baseline : Remission (SDAI<=3.3)|	0	0		
Baseline: Low (3.3 < SDAI <= 11)|	0	0		
Baseline : Moderate (11 < SDAI <= 26|	26	19		
Baseline : High (SDAI > 26)|	142	136		
Week 4:Remission (SDAI<=3.3)|	5	4		
Week 4:Low (3.3 < SDAI <= 11)|	35	31		
Week 4: Moderate (11 < SDAI <= 26|	84	82		
Week 4:High (SDAI > 26)|	41	36		
Week 12:Remission (SDAI<=3.3)|	15	13		
Week 12:Low (3.3 < SDAI <= 11)|	61	58		
Week 12: Moderate (11 < SDAI <= 26|	75	68		
Week 12:High (SDAI > 26)|	14	11		
Week 24: Remission (SDAI<=3.3)|	38	31		
Week 24: Low (3.3 < SDAI <= 11)|	83	81		
Week 24 : Moderate (11 < SDAI <= 26|	45	38		
Week 24 :High (SDAI > 26)|	2	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment period 1 - Proportion of patients in each disease activity category as defined by CDAI

End point title	Treatment period 1 - Proportion of patients in each disease activity category as defined by CDAI

End point description:

Proportion of patients in each disease activity category as defined by the Clinical Disease Activity Index (CDAI): high disease activity, CDAI > 22, moderate disease activity, CDAI > 10 to ≤ 22, low disease activity, CDAI > 2.8 to ≤ 10, and remission, CDAI ≤ 2.8 at Weeks 4, 12 and 24; SDAI and CDAI are measures of disease activity in RA. The scores were calculated by numerical summation of the number of tender and swollen joints (using the 28-joint count), and the patient's and physician's global assessment of disease activity.

End point type	Secondary

End point timeframe:

Treatment period 1, Weeks 4, 12 and 24;

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	155		
Units: Participants				
Baseline : Remission (CDAI<=2.8)|	0	0		
Baseline: Low (2.8 < CDAI <= 10)|	0	0		
Baseline : Moderate (10 < CDAI <= 22|	17	7		
Baseline : High (CDAI > 22)|	151	148		
Week 4:Remission(CDAI<=2.8)|	4	3		
Week 4: Low (2.8 < CDAI <= 10)|	33	31		
Week 4: Moderate (10 < CDAI <= 22)|	67	71		
Week 4:High High (CDAI > 22)|	63	49		
Week 12:Remission(CDAI<=2.8)|	14	15		
Week 12: Low (2.8 < CDAI <= 10)|	63	53		
Week 12: Moderate (10 < CDAI <= 22)|	72	63		
Week 12:High (CDAI > 22)|	19	23		
Week 24: Remission (CDAI<=2.8)|	35	31		
Week 24: Low (2.8 < CDAI <= 10)|	81	78		
Week 24 : (10 < CDAI <= 22)|	46	39		
Week 24 :High (CDAI > 22)|	6	7		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Treatment period 1, Weeks 4, 12 and 24;

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	155		
Units: participants				
Baseline|	11	5		
Week 4|	22	30		
Week 12|	40	46		
Week 24|	54	62		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment period 1 - Health assessment questionnaire (HAQ) index at Baseline, Weeks 4, 12 and 24;

End point title	Treatment period 1 - Health assessment questionnaire (HAQ) index at Baseline, Weeks 4, 12 and 24;
End point description:	
Health assessment questionnaire (HAQ) disability index ranges from 0 (best) to 3 (worst)	
End point type	Secondary
End point timeframe:	
Treatment period 1, Baseline, Weeks 4, 12 and 24;	

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	155		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline|	1.44 (± 0.547)	1.47 (± 0.561)		
Week 4|	1.19 (± 0.558)	1.14 (± 0.611)		
Week 12|	1.02 (± 0.560)	0.97 (± 0.599)		
Week 24|	0.88 (± 0.601)	0.80 (± 0.589)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment period 1 - Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue scale relative to Baseline at Weeks 4, 12 and 24;

End point title	Treatment period 1 - Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue scale relative to Baseline at Weeks 4, 12 and 24;
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). A score of less than 30 indicates severe fatigue.	
End point type	Secondary
End point timeframe:	
Treatment period 1, Baseline, Weeks 4, 12 and 24;	

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	155		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline|	27.0 (± 9.67)	25.1 (± 10.33)		
Week 4|	31.6 (± 8.83)	30.9 (± 10.01)		
Week 12|	34.4 (± 8.93)	33.9 (± 9.6)		
Week 24|	36.3 (± 8.94)	36.7 (± 9.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment period 1 - CRP levels at Baseline and Weeks 4, 12 and 24

End point title	Treatment period 1 - CRP levels at Baseline and Weeks 4, 12 and 24

End point description:

End point type	Secondary

End point timeframe:

Treatment period 1, Weeks 4, 12 and 24

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	155		
Units: mg/dL				
arithmetic mean (standard deviation)				
Baseline|	1.19 (± 2.194)	1.10 (± 1.526)		
Week 4|	0.36 (± 0.718)	0.43 (± 0.693)		
Week 12|	0.33 (± 0.772)	0.48 (± 0.850)		
Week 24|	0.44 (± 0.949)	0.35 (± 0.466)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment period 1 - ESR levels at Baseline and Weeks 4, 12 and 24	
End point title	Treatment period 1 - ESR levels at Baseline and Weeks 4, 12 and 24

End point description:

End point type	Secondary

End point timeframe:

Treatment period 1, Weeks 4, 12 and 24

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	155		
Units: mm/h				
arithmetic mean (standard deviation)				
Baseline|	41.4 (± 16.89)	41.8 (± 17.94)		
Week 4|	26.5 (± 16.51)	26.7 (± 17.27)		
Week 12|	23.2 (± 14.67)	23.8 (± 15.41)		
Week 24|	21.4 (± 15.47)	20.8 (± 14.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment period 2: DAS28-CRP and DAS28-ESR scores up to Week 48;	
End point title	Treatment period 2: DAS28-CRP and DAS28-ESR scores up to Week 48;

End point description:

DAS28-CRP and DAS28-ESR: a. best is 0, b. < 2.6 – remission, c. ≥ 2.6 to ≤ 3.2 – low disease activity d. > 3.2 to ≤ 5.1 – moderate disease activity e. > 5.1 – high disease activity

End point type	Secondary

End point timeframe:

Treatment period 1 and 2, week 48

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	131		
Units: score on a scale				
arithmetic mean (standard deviation)				
DAS28-CRP Baseline|	5.45 (± 0.914)	5.57 (± 0.794)		
DAS28-CRP Week 4|	3.89 (± 1.053)	3.79 (± 1.101)		
DAS28-CRP Week 12|	3.20 (± 1.038)	3.27 (± 1.127)		

DAS28-CRP Week 24|	2.64 (± 0.863)	2.67 (± 0.892)		
DAS28-CRP Week 36|	2.65 (± 1.001)	2.74 (± 1.017)		
DAS28-CRP Week 48|	2.57 (± 1.067)	2.74 (± 1.062)		
DAS28-ESR Baseline|	6.39 (± 0.872)	6.43 (± 0.784)		
DAS28-ESR Week 4|	4.70 (± 1.175)	4.49 (± 1.228)		
DAS28-ESR Week 12|	3.90 (± 1.236)	3.85 (± 1.317)		
DAS28-ESR Week 24|	3.23 (± 1.022)	3.19 (± 1.048)		
DAS28-ESR Week 36|	3.25 (± 1.160)	3.28 (± 1.127)		
DAS28-ESR Week 48|	3.20 (± 1.201)	3.30 (± 1.177)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment period 2 : Changes from baseline in DAS28-CRP and DAS28-ESR scores from Week 4 up to Week 48

End point title	Treatment period 2 : Changes from baseline in DAS28-CRP and DAS28-ESR scores from Week 4 up to Week 48

End point description:

End point type	Secondary

End point timeframe:

treatment period 2, up to week 48

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	131		
Units: score on a scale				
arithmetic mean (standard deviation)				
DAS28-CRP change from baseline, week 4|	-1.55 (± 1.014)	-1.76 (± 1.014)		
DAS28-CRP change from baseline, week 12|	-2.22 (± 1.031)	-2.27 (± 1.096)		
DAS28-CRP change from baseline, week 24|	-2.81 (± 1.007)	-2.90 (± 0.988)		
DAS28-CRP change from baseline, week 36|	-2.80 (± 1.087)	-2.82 (± 1.151)		
DAS28-CRP change from baseline, week 48|	-2.88 (± 1.198)	-2.83 (± 1.176)		
DAS28-ESR change from baseline, week 4|	-1.69 (± 1.048)	-1.92 (± 1.087)		
DAS28-ESR change from baseline, week 12|	-2.49 (± 1.152)	-2.57 (± 1.235)		
DAS28-ESR change from baseline, week 24|	-3.16 (± 1.106)	-3.23 (± 1.054)		
DAS28-ESR change from baseline, week 36|	-3.13 (± 1.232)	-3.14 (± 1.154)		
DAS28-ESR change from baseline, week 48|	-3.20 (± 1.297)	-3.14 (± 1.190)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment period 2: proportion of patients achieving EULAR reponse

End point title	Treatment period 2: proportion of patients achieving EULAR reponse

End point description:

Proportion of patients achieving EULAR good response (defined as DAS28 ≤ 3.2 and DAS28 improvement from Baseline > 1.2) and moderate response (defined as DAS28 ≤ 3.2 and DAS28 improvement > 0.6 and ≤ 1.2, or DAS28 > 3.2 and ≤ 5.1 and DAS28 improvement > 0.6 or DAS28 > 5.1 but DAS28 improvement > 1.2) at Weeks 36 and 48;

End point type	Secondary

End point timeframe:

Treatment period 2: Week 36, week 48

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	131		
Units: Participants				
Good response week 4|	20	20		
Good response week 12|	43	43		
Good response week 24|	77	68		
Good response week 36|	82	65		
Good response week 48|	80	67		
Moderate response week 4|	85	82		
Moderate response week 12|	95	75		
Moderate response week 24|	71	63		
Moderate response week 36|	62	64		
Moderate response week 48|	61	57		
no response week 4|	42	28		
no response week 12|	10	12		
no response week 24|	0	0		
no response week 36|	3	2		
no response week 48|	6	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment period 2 : Proportion of patients achieving DAS28 < 2.6 at Weeks 36 and 48;

End point title	Treatment period 2 : Proportion of patients achieving DAS28 < 2.6 at Weeks 36 and 48;
End point description:	
percentage of participants in DAS28-ESR categories up to week 48	
End point type	Secondary
End point timeframe:	
Treatment period 2 : up to week 48	

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	131		
Units: Participants				
Week 36 Remission (DAS28 < 2.6)|	45	38		
Week 48 Remission (DAS28 < 2.6)|	44	35		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment period 2 : Proportion of patients achieving EULAR/ACR Boolean remission criteria

End point title	Treatment period 2 : Proportion of patients achieving EULAR/ACR Boolean remission criteria
End point description:	
Proportion of patients achieving EULAR/ACR Boolean remission criteria (defined as number of tender joints/swollen joints ≤ 1 and CRP (mg/dL) ≤ 1 and patient global assessment (1–10) ≤ 1) at Weeks 36 and 48;	
End point type	Secondary
End point timeframe:	
Treatment period 2 : up to week 48	

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	131		
Units: participants				
Week 4|	0	2		
Week 12|	9	8		
Week 24|	22	13		
Week 36|	25	15		
Week 48|	28	20		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment period 2 : Proportion of patients achieving ACR20/50/70 response at Weeks 36 and 48;

End point title	Treatment period 2 : Proportion of patients achieving ACR20/50/70 response at Weeks 36 and 48;

End point description:

End point type	Secondary

End point timeframe:

Treatment period 2 : up to week 48

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	131		
Units: participants				
ACR20 response Week 36|	128	114		
ACR20 response Week 48|	131	108		
ACR50 response Week 36|	90	83		
ACR50 response Week 48|	93	86		
ACR70 response Week 36|	47	50		
ACR70 response Week 48|	54	55		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment period 2 : ACR-N scores at Weeks 36 and 48;

End point title	Treatment period 2 : ACR-N scores at Weeks 36 and 48;

End point description:

ACR-N: negative is worsening, positive (up to 100) is an improvement

End point type	Secondary

End point timeframe:

Treatment period 2 : up to week 48

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	131		
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 4|	19.7 (± 27.72)	24.9 (± 29.40)		
Week 12|	38.3 (± 27.84)	40.7 (± 34.80)		
Week 24|	56.3 (± 26.58)	60.9 (± 24.79)		
Week 36|	53.8 (± 28.21)	55.7 (± 28.37)		
Week 48|	56.9 (± 29.18)	56.4 (± 30.58)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment period 2 : Proportion of patients in each disease activity category as defined by SDAI

End point title	Treatment period 2 : Proportion of patients in each disease activity category as defined by SDAI

End point description:

Proportion of patients in each disease activity category as defined by the Simplified Disease Activity Index (SDAI): high disease activity, SDAI > 26, moderate disease activity, SDAI > 11 to ≤ 26, low disease activity, SDAI > 3.3 to ≤ 11, and remission, SDAI ≤ 3.3 at Weeks 36 and 48.

End point type	Secondary

End point timeframe:

treatment period 2 : up to week 48

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	131		
Units: Participants				
Baseline : Remission (SDAI <= 3.3)|	0	0		
Baseline : Low (3.3 < SDAI <= 11)|	0	0		
Baseline : Moderate (11 < SDAI <= 26)|	20	16		
Baseline : High (SDAI > 26)|	128	115		
Week 4 : Remission (SDAI <= 3.3)|	2	4		
Week 4 : Low (3.3 < SDAI <= 11)|	29	27		
Week 4 : Moderate (11 < SDAI <= 26|	75	69		
Week 4 : High (SDAI > 26)|	39	29		
Week 12: Remission (SDAI <= 3.3)|	14	12		

Week 12 : Low (3.3 < SDAI <= 11)|	50	51		
Week 12 : Moderate (11 < SDAI <= 26|	69	53		
Week 12 : High (SDAI > 26)|	13	11		
Week 24: Remission (SDAI <= 3.3)|	31	29		
Week 24 : Low (3.3 < SDAI <= 11)|	74	71		
Week 24 : Moderate (11 < SDAI <= 26|	43	29		
Week 24 : High (SDAI > 26)|	0	2		
Week 36: Remission (SDAI <= 3.3)|	34	29		
Week 36 : Low (3.3 < SDAI <= 11|	69	66		
Week 36 : Moderate (11 < SDAI <= 26|	43	30		
Week 36 : High (SDAI > 26)|	1	5		
Week 48: Remission (SDAI <= 3.3)|	39	32		
Week 48 : Low (3.3 < SDAI <= 11|	72	62		
Week 48 : Moderate (11 < SDAI <= 26|	30	29		
Week 48 : High (SDAI > 26)|	6	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment period 2 : Proportion of patients in each disease activity category as defined by CDAI

End point title	Treatment period 2 : Proportion of patients in each disease activity category as defined by CDAI

End point description:

Proportion of patients in each disease activity category as defined by the Clinical Disease Activity Index (CDAI): high disease activity, CDAI > 22, moderate disease activity, CDAI > 10 to ≤ 22, low disease activity, CDAI > 2.8 to ≤ 10, and remission, CDAI ≤ 2.8 at Weeks 36 and 48;

End point type	Secondary

End point timeframe:

treatment period 2 : up to week 48

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	131		
Units: Participants				
Baseline : Remission (CDAI <=2.8)|	0	0		
Baseline : Low (2.8 < CDAI <= 10)|	0	0		
Baseline : Moderate (10 < CDAI <= 22)|	14	6		
Baseline : High (CDAI > 22)|	134	125		
Week 4 : Remission (CDAI <=2.8)|	2	3		
Week 4 : Low (2.8 < CDAI <= 10)|	27	28		
Week 4 : Moderate (11 < SDAI <= 26|	60	60		
Week 4 : High (CDAI > 22)|	58	39		
Week 12: Remission (CDAI <=2.8)|	12	14		

Week 12 : Low (2.8 < CDAI <= 10)|	52	47		
Week 12 : Moderate (10 < CDAI <= 22)|	67	50		
Week 12 : High (CDAI > 22)|	17	19		
Week 24: Remission (CDAI <=2.8)|	29	29		
Week 24 : Low (2.8 < CDAI <= 10)|	71	68		
Week 24 : Moderate (10 < CDAI <= 22)|	45	30		
Week 24 : High (CDAI > 22)|	3	4		
Week 36: Remission (CDAI <=2.8)|	32	29		
Week 36 : Low (2.8 < CDAI <= 10)|	67	63		
Week 36 : Moderate (10 < CDAI <= 22)|	41	32		
Week 36 : High (CDAI > 22)|	7	7		
Week 48: Remission (CDAI <=2.8)|	37	29		
Week 48 : Low (2.8 < CDAI <= 10)|	71	63		
Week 48 : Moderate (10 < CDAI <= 22)|	32	31		
Week 48 : High (CDAI > 22)|	7	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment period 2 :Proportion of patients achieving HAQ index in normal range (≤ 0.5) at Weeks 36 and 48;

End point title	Treatment period 2 :Proportion of patients achieving HAQ index in normal range (≤ 0.5) at Weeks 36 and 48;

End point description:

End point type	Secondary

End point timeframe:

Treatment period 2 : up to week 48

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	131		
Units: participants				
Baseline|	8	4		
Week 4|	17	25		
Week 12|	33	39		
Week 24|	47	51		
Week 36|	46	48		
Week 48|	51	51		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment period 2 :HAQ index at Weeks 36 and 48;

End point title	Treatment period 2 :HAQ index at Weeks 36 and 48;
End point description: HAQ: from 0 (best) to 3 (worst)	
End point type	Secondary
End point timeframe: Treatment period 2 : up to week 48	

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	131		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline|	1.47 (± 0.547)	1.50 (± 0.554)		
Week 4|	1.22 (± 0.554)	1.14 (± 0.620)		
Week 12|	1.04 (± 0.560)	0.97 (± 0.614)		
Week 24|	0.88 (± 0.594)	0.83 (± 0.603)		
Week 36|	0.89 (± 0.584)	0.85 (± 0.651)		
Week 48|	0.85 (± 0.609)	0.84 (± 0.652)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment period 2 : Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue scale relative to Baseline at Weeks 36 and 48;

End point title	Treatment period 2 : Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue scale relative to Baseline at Weeks 36 and 48;
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: Treatment period 2 : up to week 48	

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	131		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline|	26.6 (± 9.71)	25.5 (± 10.78)		
Week 4|	31.5 (± 8.72)	31.3 (± 10.07)		
Week 12|	34.4 (± 8.89)	34.1 (± 9.69)		
Week 24|	36.6 (± 8.75)	36.7 (± 9.05)		
Week 36|	36.9 (± 8.79)	36.4 (± 9.50)		
Week 48|	38.0 (± 8.74)	35.8 (± 9.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment period 2 : CRP levels at week 36 and 48

End point title	Treatment period 2 : CRP levels at week 36 and 48

End point description:

End point type	Secondary

End point timeframe:

Treatment period 2 : up to week 48

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	131		
Units: mg/dL				
arithmetic mean (standard deviation)				
Baseline|	1.21 (± 2.244)	1.17 (± 1.589)		
Week 4|	0.36 (± 0.733)	0.42 (± 0.625)		
Week 12|	0.36 (± 0.817)	0.50 (± 0.910)		
Week 24|	0.44 (± 0.964)	0.36 (± 0.487)		
Week 36|	0.39 (± 0.758)	0.39 (± 0.655)		
Week 48|	0.35 (± 0.623)	0.40 (± 0.878)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment period 2 : ESR levels at week 36 and 48

End point title	Treatment period 2 : ESR levels at week 36 and 48

End point description:

End point type	Secondary

End point timeframe:

Treatment period 2 : up to week 48

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	131		
Units: mm/h				
arithmetic mean (standard deviation)				
Baseline|	42.2 (± 16.99)	41.7 (± 17.99)		
Week 4|	26.8 (± 16.33)	25.3 (± 16.11)		
Week 12|	23.8 (± 15.07)	23.0 (± 15.38)		
Week 24|	21.3 (± 15.66)	19.3 (± 12.66)		
Week 36|	22.1 (± 16.41)	20.3 (± 14.28)		
Week 48|	22.8 (± 16.66)	20.8 (± 14.62)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety - Overall study : Frequency and severity of injection site reactions in GP2015 and Enbrel

End point title	Safety - Overall study : Frequency and severity of injection site reactions in GP2015 and Enbrel

End point description:

Frequency of participants with injection site reactions in GP2015 and Enbrel

End point type	Secondary

End point timeframe:

up to 48 weeks

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186	190		
Units: participants				
participants with at least one ISR|	13	37		
participants with at least one moderate ISR|	1	7		
participants with at least one severe ISR|	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety : Overall study: Immunogenicity by measuring the rate of anti-drug antibody (ADA) positive patients

End point title	Safety : Overall study: Immunogenicity by measuring the rate of anti-drug antibody (ADA) positive patients

End point description:

To assess the immunogenicity of continuous GP2015 treatment versus a treatment transition from Enbrel to GP2015 after 24 weeks of treatment by measuring the rate of ADA positive participants at Weeks 24, 30, 36 and 48. summary of ADA positive data up to week 48 using a 1% false positive cut point

End point type	Secondary

End point timeframe:

up to 48 weeks

End point values	50mg GP2015	50mg EU-authorized Enbrel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186	190		
Units: participants				
Baseline|	2	0		
Week 2|	2	5		
Week 4|	3	42		
Week 12|	0	5		
Week 24|	0	0		
Week 30|	2	0		
Week 36|	0	0		
Week 48|	2	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	19.1

Reporting groups	
Reporting group title	Treatment Period 1 TP1 SAF GP2015
Reporting group description:	
Treatment Period 1 TP1 SAF GP2015	
Reporting group title	Treatment Period 1 TP1 SAF Enbrel
Reporting group description:	
Treatment Period 1 TP1 SAF Enbrel	
Reporting group title	Treatment Period 2 TP2 SAF Continued GP2015
Reporting group description:	
Treatment Period 2 TP2 SAF Continued GP2015	
Reporting group title	Treatment Period 2 TP2 SAF Enbrel switched to GP2015
Reporting group description:	
Treatment Period 2 TP2 SAF Enbrel switched to GP2015	
Reporting group title	Entire study SAF GP2015
Reporting group description:	
Entire study SAF GP2015	
Reporting group title	Entire study SAF Enbrel/GP2015
Reporting group description:	
Entire study SAF Enbrel/GP2015	

Serious adverse events	Treatment Period 1 TP1 SAF GP2015	Treatment Period 1 TP1 SAF Enbrel	Treatment Period 2 TP2 SAF Continued GP2015
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 186 (0.54%)	5 / 190 (2.63%)	4 / 175 (2.29%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 186 (0.00%)	1 / 190 (0.53%)	0 / 175 (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
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Breast cancer			
subjects affected / exposed	0 / 186 (0.00%)	0 / 190 (0.00%)	0 / 175 (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
Colon adenoma			
subjects affected / exposed	0 / 186 (0.00%)	0 / 190 (0.00%)	0 / 175 (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
Lung neoplasm malignant			
subjects affected / exposed	0 / 186 (0.00%)	1 / 190 (0.53%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Injury, poisoning and procedural complications			
Spinal fracture			
subjects affected / exposed	1 / 186 (0.54%)	0 / 190 (0.00%)	0 / 175 (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
Tibia fracture			
subjects affected / exposed	0 / 186 (0.00%)	0 / 190 (0.00%)	1 / 175 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 186 (0.00%)	1 / 190 (0.53%)	0 / 175 (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 failure			
subjects affected / exposed	0 / 186 (0.00%)	0 / 190 (0.00%)	0 / 175 (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
Gastrointestinal disorders			
Salivary gland cyst			

subjects affected / exposed	0 / 186 (0.00%)	0 / 190 (0.00%)	1 / 175 (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
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 186 (0.00%)	0 / 190 (0.00%)	0 / 175 (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
Cholelithiasis			
subjects affected / exposed	0 / 186 (0.00%)	1 / 190 (0.53%)	0 / 175 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Cystitis haemorrhagic			
subjects affected / exposed	0 / 186 (0.00%)	0 / 190 (0.00%)	1 / 175 (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
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	0 / 186 (0.00%)	1 / 190 (0.53%)	0 / 175 (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			
Osteomyelitis			
subjects affected / exposed	0 / 186 (0.00%)	0 / 190 (0.00%)	0 / 175 (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			
subjects affected / exposed	0 / 186 (0.00%)	0 / 190 (0.00%)	1 / 175 (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

Serious adverse events	Treatment Period 2 TP2 SAF Enbrel switched to GP2015	Entire study SAF GP2015	Entire study SAF Enbrel/GP2015
Total subjects affected by serious			

adverse events			
subjects affected / exposed	4 / 166 (2.41%)	5 / 186 (2.69%)	9 / 190 (4.74%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 166 (0.00%)	0 / 186 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 166 (0.60%)	0 / 186 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon adenoma			
subjects affected / exposed	1 / 166 (0.60%)	0 / 186 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 166 (0.00%)	0 / 186 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Injury, poisoning and procedural complications			
Spinal fracture			
subjects affected / exposed	0 / 166 (0.00%)	1 / 186 (0.54%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 166 (0.00%)	1 / 186 (0.54%)	0 / 190 (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			
Atrial fibrillation			

subjects affected / exposed	0 / 166 (0.00%)	0 / 186 (0.00%)	1 / 190 (0.53%)
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	1 / 166 (0.60%)	0 / 186 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Salivary gland cyst			
subjects affected / exposed	0 / 166 (0.00%)	1 / 186 (0.54%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 166 (0.60%)	0 / 186 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 166 (0.00%)	0 / 186 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Cystitis haemorrhagic			
subjects affected / exposed	0 / 166 (0.00%)	1 / 186 (0.54%)	0 / 190 (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			
Rheumatoid arthritis			
subjects affected / exposed	0 / 166 (0.00%)	0 / 186 (0.00%)	1 / 190 (0.53%)
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			
Osteomyelitis			

subjects affected / exposed	1 / 166 (0.60%)	0 / 186 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 186 (0.54%)	0 / 190 (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

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

Non-serious adverse events	Treatment Period 1 TP1 SAF GP2015	Treatment Period 1 TP1 SAF Enbrel	Treatment Period 2 TP2 SAF Continued GP2015
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 186 (27.96%)	64 / 190 (33.68%)	42 / 175 (24.00%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	8 / 186 (4.30%)	4 / 190 (2.11%)	4 / 175 (2.29%)
occurrences (all)	8	4	4
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 186 (1.08%)	2 / 190 (1.05%)	2 / 175 (1.14%)
occurrences (all)	2	2	2
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 186 (0.54%)	1 / 190 (0.53%)	0 / 175 (0.00%)
occurrences (all)	1	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 186 (1.08%)	1 / 190 (0.53%)	2 / 175 (1.14%)
occurrences (all)	3	1	2
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	13 / 186 (6.99%)	35 / 190 (18.42%)	0 / 175 (0.00%)
occurrences (all)	37	155	0
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	3 / 186 (1.61%)	4 / 190 (2.11%)	1 / 175 (0.57%)
occurrences (all)	3	4	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 186 (2.69%)	1 / 190 (0.53%)	3 / 175 (1.71%)
occurrences (all)	5	1	3
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 186 (1.08%)	4 / 190 (2.11%)	2 / 175 (1.14%)
occurrences (all)	2	4	2
Cystitis			
subjects affected / exposed	2 / 186 (1.08%)	4 / 190 (2.11%)	2 / 175 (1.14%)
occurrences (all)	2	4	2
Nasopharyngitis			
subjects affected / exposed	9 / 186 (4.84%)	4 / 190 (2.11%)	13 / 175 (7.43%)
occurrences (all)	9	4	13
Pharyngitis			
subjects affected / exposed	1 / 186 (0.54%)	3 / 190 (1.58%)	2 / 175 (1.14%)
occurrences (all)	1	3	2
Upper respiratory tract infection			
subjects affected / exposed	6 / 186 (3.23%)	7 / 190 (3.68%)	9 / 175 (5.14%)
occurrences (all)	6	7	11
Urinary tract infection			
subjects affected / exposed	8 / 186 (4.30%)	8 / 190 (4.21%)	7 / 175 (4.00%)
occurrences (all)	8	8	7
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 186 (1.08%)	0 / 190 (0.00%)	2 / 175 (1.14%)
occurrences (all)	2	0	2
Metabolism and nutrition disorders			
Hyperuricaemia			
subjects affected / exposed	3 / 186 (1.61%)	1 / 190 (0.53%)	2 / 175 (1.14%)
occurrences (all)	4	1	2

Non-serious adverse events	Treatment Period 2 TP2 SAF Enbrel switched to GP2015	Entire study SAF GP2015	Entire study SAF Enbrel/GP2015
Total subjects affected by non-serious adverse events			

subjects affected / exposed	37 / 166 (22.29%)	79 / 186 (42.47%)	81 / 190 (42.63%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 166 (3.61%)	12 / 186 (6.45%)	8 / 190 (4.21%)
occurrences (all)	6	12	10
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 166 (0.00%)	4 / 186 (2.15%)	2 / 190 (1.05%)
occurrences (all)	0	4	2
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 166 (2.41%)	1 / 186 (0.54%)	5 / 190 (2.63%)
occurrences (all)	4	1	5
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 166 (0.60%)	4 / 186 (2.15%)	2 / 190 (1.05%)
occurrences (all)	1	5	2
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	6 / 166 (3.61%)	13 / 186 (6.99%)	37 / 190 (19.47%)
occurrences (all)	33	37	188
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 166 (1.20%)	4 / 186 (2.15%)	6 / 190 (3.16%)
occurrences (all)	2	4	6
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 166 (0.00%)	8 / 186 (4.30%)	1 / 190 (0.53%)
occurrences (all)	0	8	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 166 (1.20%)	4 / 186 (2.15%)	6 / 190 (3.16%)
occurrences (all)	2	4	6
Cystitis			
subjects affected / exposed	1 / 166 (0.60%)	4 / 186 (2.15%)	5 / 190 (2.63%)
occurrences (all)	1	4	5
Nasopharyngitis			

subjects affected / exposed	9 / 166 (5.42%)	18 / 186 (9.68%)	12 / 190 (6.32%)
occurrences (all)	10	22	14
Pharyngitis			
subjects affected / exposed	1 / 166 (0.60%)	3 / 186 (1.61%)	4 / 190 (2.11%)
occurrences (all)	1	3	4
Upper respiratory tract infection			
subjects affected / exposed	9 / 166 (5.42%)	13 / 186 (6.99%)	15 / 190 (7.89%)
occurrences (all)	10	17	17
Urinary tract infection			
subjects affected / exposed	2 / 166 (1.20%)	13 / 186 (6.99%)	8 / 190 (4.21%)
occurrences (all)	3	15	11
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 166 (1.20%)	4 / 186 (2.15%)	2 / 190 (1.05%)
occurrences (all)	2	4	2
Metabolism and nutrition disorders			
Hyperuricaemia			
subjects affected / exposed	0 / 166 (0.00%)	4 / 186 (2.15%)	1 / 190 (0.53%)
occurrences (all)	0	6	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 September 2015	This amendment contains changes requested by Competent Authorities/Ethics Committees as part of the Voluntary Harmonisation Procedure (VHP) approval process. In addition, minor discrepancies and misspellings were corrected (changes in excl. criteria)
15 February 2016	This amendment contains changes recommended by the health authorities and in reply to the questions related to IND/CTA submission, such as clarification related to the use of DAS28 (based on ESR) for the decision about transition, and change in incl. excl. criteria. In addition, minor discrepancies,misspellings, and organizational details were corrected and clarifications added.

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.

None reported

Notes: