Clinical trial results:
Randomized, double-blind, placebo-controlled, multicenter, phase IIb dose finding study of GLPG0634 administered for 24 weeks as monotherapy to subjects with moderately to severely active rheumatoid arthritis who have an inadequate response to methotrexate alone

Summary

EudraCT number	2012-003654-86
Trial protocol	HU DE AT ES LV BG
Global end of trial date	29 May 2015

Results information

Result version number	v1 (current)
This version publication date	14 June 2016
First version publication date	14 June 2016

Trial information

Trial identification

Sponsor protocol code	GLPG0634-CL-204

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01894516
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Galapagos N.V.
Sponsor organisation address	Generaal De Wittelaan L11 A3, 2800, Mechelen, Belgium,
Public contact	Clinical Trial Information Desk, Galapagos N.V., +32 (0)15 342 900, rd@glpg.com
Scientific contact	Clinical Trial Information Desk, Galapagos N.V., +32 (0)15 342 900, rd@glpg.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	29 May 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the efficacy in terms of the percentage of subjects achieving an American College of Rheumatology (ACR)20 response, of different doses of GLPG0634 given once daily compared to placebo at Week 12.

Protection of trial subjects:

Before initiation of the study at each study center, the protocol, the informed consent form (ICF), other written material given to the subjects, and any other relevant study documentation was to be submitted to the appropriate IEC/IRB. Written approval of the study and all relevant study information was to be obtained before the study center could be initiated or the study medication was released to the investigator. Any necessary extensions or renewals of IEC/IRB approval were to be obtained for changes to the study such as modification of the protocol, the ICF or other study documentation. The written approval of the IEC/IRB together with the approved ICF was to be filed in the study files.

The investigator was to promptly report to the IEC/IRB any new information that could have adversely affected the safety of the subjects or the conduct of the study. The investigator was to submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB was to be notified that the study had ended.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 October 2013
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	Mexico: 29
Country: Number of subjects enrolled	Colombia: 18
Country: Number of subjects enrolled	Chile: 17
Country: Number of subjects enrolled	Argentina: 15
Country: Number of subjects enrolled	Guatemala: 9
Country: Number of subjects enrolled	Romania: 5
Country: Number of subjects enrolled	Ukraine: 48
Country: Number of subjects enrolled	Russian Federation: 26
Country: Number of subjects enrolled	Moldova, Republic of: 10
Country: Number of subjects enrolled	United States: 36
Country: Number of subjects enrolled	New Zealand: 2
Country: Number of subjects enrolled	Poland: 33
Country: Number of subjects enrolled	Spain: 5

Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Bulgaria: 4
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Hungary: 21
Country: Number of subjects enrolled	Latvia: 4
Worldwide total number of subjects	287
EEA total number of subjects	77

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)	245
From 65 to 84 years	42
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in Latin America, Europe, United States, and New Zealand. The first participant was screened on 08 October 2013. The last study visit occurred on 29 May 2015.

Pre-assignment

Screening details:

625 participants were screened.

Period 1

Period 1 title	Period 1: Weeks 1-12
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo during Weeks 1-12 and switched to GLPG0634 100 mg QD during Weeks 13-24

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

2 placebo capsules in the morning

Arm title	GLPG0634 50 mg QD

Arm description:

GLPG0634 50 mg once daily during Weeks 1-12; responders (having at least 20% improvement on TJC68 and SJC66) remained on the same treatment while nonresponders switched to 100 mg QD during Weeks 13-24

Arm type	Experimental
Investigational medicinal product name	GLPG0634
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

2 GLPG0634 25 mg capsules once daily in the morning

Arm title	GLPG0634 100 mg QD

Arm description:

GLPG0634 100 mg once daily during Weeks 1-24

Arm type	Experimental

Investigational medicinal product name	GLPG0634
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

2 GLPG0634 50 mg capsules once daily in the morning

Arm title	GLPG0634 200 mg QD

Arm description:

GLPG0634 200 mg once daily during Weeks 1-24

Arm type	Experimental
Investigational medicinal product name	GLPG0634
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

2 GLPG0634 100 mg capsules once daily in the morning

Number of subjects in period 1[1]	Placebo	GLPG0634 50 mg QD	GLPG0634 100 mg QD
Started	72	72	70
Completed	65	67	67
Not completed	7	5	3
Non compliance with the study medication	1	1	-
Withdrawal of the subject's consent	2	3	1
Treatment failure	-	-	1
Adverse event, non-fatal	2	-	-
Other	-	1	1
Adverse event and treatment failure	2	-	-

Number of subjects in period 1[1]	GLPG0634 200 mg QD
Started	69
Completed	66
Not completed	3
Non compliance with the study medication	-
Withdrawal of the subject's consent	2
Treatment failure	-
Adverse event, non-fatal	1
Other	-
Adverse event and treatment failure	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 4 subjects who were enrolled but not treated are not included in the subject disposition table.

Period 2

Period 2 title	Period 2: Weeks 13-24
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo Switch to GLPG0634 100 mg QD

Arm description:

Placebo during Weeks 1-12 and switched to GLPG0634 100 mg QD during Weeks 13-24

Arm type	Experimental
Investigational medicinal product name	GLPG0634
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

2 GLPG0634 50 mg capsules once daily in the morning

Arm title	GLPG0634 50 mg QD Responders

Arm description:

GLPG0634 50 mg once daily during Weeks 1-12; responders remained on the same treatment during Weeks 13-24

Arm type	Experimental
Investigational medicinal product name	GLPG0634
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

2 GLPG0634 25 mg capsules once daily in the morning

Arm title	50 mg QD Switch to GLPG0634 100 mg

Arm description:

Nonresponders from the 50 mg QD group were re-randomized to receive GLPG0634 100 mg during Weeks 13-24

Arm type	Experimental
Investigational medicinal product name	GLPG0634
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

2 GLPG0634 50 mg capsules once daily in the morning

Arm title	GLPG0634 100 mg QD

Arm description:

GLPG0634 100 mg once daily during Weeks 1-24

Arm type	Experimental
Investigational medicinal product name	GLPG0634
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

2 GLPG0634 50 mg capsules once daily in the morning

Arm title	GLPG0634 200 mg QD

Arm description:

GLPG0634 200 mg once daily during Weeks 1-24

Arm type	Experimental
Investigational medicinal product name	GLPG0634
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

2 GLPG0634 100 mg capsules once daily in the morning

Number of subjects in period 2	Placebo Switch to GLPG0634 100 mg QD	GLPG0634 50 mg QD Responders	50 mg QD Switch to GLPG0634 100 mg
Started	65	52	15
Completed	63	50	15
Not completed	2	2	0
Withdrawal of the subject's consent	1	-	-
Adverse event, non-fatal	1	2	-

Number of subjects in period 2	GLPG0634 100 mg QD	GLPG0634 200 mg QD
Started	67	66
Completed	64	65
Not completed	3	1
Withdrawal of the subject's consent	1	-
Adverse event, non-fatal	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo during Weeks 1-12 and switched to GLPG0634 100 mg QD during Weeks 13-24	
Reporting group title	GLPG0634 50 mg QD
Reporting group description:	
GLPG0634 50 mg once daily during Weeks 1-12; responders (having at least 20% improvement on TJC68 and SJC66) remained on the same treatment while nonresponders switched to 100 mg QD during Weeks 13-24	
Reporting group title	GLPG0634 100 mg QD
Reporting group description:	
GLPG0634 100 mg once daily during Weeks 1-24	
Reporting group title	GLPG0634 200 mg QD
Reporting group description:	
GLPG0634 200 mg once daily during Weeks 1-24	

Reporting group values	Placebo	GLPG0634 50 mg QD	GLPG0634 100 mg QD
Number of subjects	72	72	70
Age categorical Units: Subjects			
< 45	19	20	13
≥ 45 to < 65	43	36	48
≥ 65 to < 75	9	13	6
≥ 75	1	3	3
Age continuous Units: years			
arithmetic mean	51.5	52.1	52.8
full range (min-max)	20 to 77	18 to 79	22 to 78
Gender categorical Units: Subjects			
Female	56	62	53
Male	16	10	17
Race Units: Subjects			
Asian	0	1	0
Black or African American	1	1	1
Native Hawaiian or Other Pacific Islander	1	0	0
White	53	53	53
Other	17	17	16
Rheumatoid arthritis (RA) duration Units: years			
arithmetic mean	9.46	8.63	8.57
full range (min-max)	0.7 to 28.9	0.5 to 23.4	0.5 to 33.7
C-reactive protein (CRP) at Baseline Units: mg/L			
arithmetic mean	35.26	24.67	25.55

full range (min-max)	1 to 175	1 to 162.9	1.6 to 244.1
Corrected tender joint count based on 68 joints (TJC68) at Baseline			
68 joints were assessed for tenderness and joints are classified as tender/not tender giving a total possible tender joint count score of 0 to 68.			
Units: units on a scale			
arithmetic mean	25.226	25.58	27.195
full range (min-max)	8 to 63	9 to 64	8 to 65
Corrected swollen joint count based on 66 joints (SJC66) at Baseline			
66 joints were assessed for swelling and joints are classified as swollen/not swollen giving a total possible swollen joint count score of 0 to 66.			
Units: units on a scale			
arithmetic mean	15.98	16.969	18.653
full range (min-max)	7 to 38	7 to 48	6 to 56

Reporting group values	GLPG0634 200 mg QD	Total	
Number of subjects	69	283	
Age categorical			
Units: Subjects			
< 45	18	70	
≥ 45 to < 65	44	171	
≥ 65 to < 75	4	32	
≥ 75	3	10	
Age continuous			
Units: years			
arithmetic mean	51.8		
full range (min-max)	25 to 79	-	
Gender categorical			
Units: Subjects			
Female	60	231	
Male	9	52	
Race			
Units: Subjects			
Asian	0	1	
Black or African American	0	3	
Native Hawaiian or Other Pacific Islander	0	1	
White	54	213	
Other	15	65	
Rheumatoid arthritis (RA) duration			
Units: years			
arithmetic mean	8.68		
full range (min-max)	0.5 to 49.6	-	
C-reactive protein (CRP) at Baseline			
Units: mg/L			
arithmetic mean	23.16		
full range (min-max)	1 to 91.3	-	
Corrected tender joint count based on 68 joints (TJC68) at Baseline			
68 joints were assessed for tenderness and joints are classified as tender/not tender giving a total possible tender joint count score of 0 to 68.			
Units: units on a scale			

arithmetic mean	26.242		
full range (min-max)	8 to 65.94	-	
Corrected swollen joint count based on 66 joints (SJC66) at Baseline			
66 joints were assessed for swelling and joints are classified as swollen/not swollen giving a total possible swollen joint count score of 0 to 66.			
Units: units on a scale			
arithmetic mean	15.74		
full range (min-max)	6 to 46	-	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo during Weeks 1-12 and switched to GLPG0634 100 mg QD during Weeks 13-24	
Reporting group title	GLPG0634 50 mg QD
Reporting group description:	
GLPG0634 50 mg once daily during Weeks 1-12; responders (having at least 20% improvement on TJC68 and SJC66) remained on the same treatment while nonresponders switched to 100 mg QD during Weeks 13-24	
Reporting group title	GLPG0634 100 mg QD
Reporting group description:	
GLPG0634 100 mg once daily during Weeks 1-24	
Reporting group title	GLPG0634 200 mg QD
Reporting group description:	
GLPG0634 200 mg once daily during Weeks 1-24	

Reporting group title	Placebo Switch to GLPG0634 100 mg QD
Reporting group description:	
Placebo during Weeks 1-12 and switched to GLPG0634 100 mg QD during Weeks 13-24	
Reporting group title	GLPG0634 50 mg QD Responders
Reporting group description:	
GLPG0634 50 mg once daily during Weeks 1-12; responders remained on the same treatment during Weeks 13-24	
Reporting group title	50 mg QD Switch to GLPG0634 100 mg
Reporting group description:	
Nonresponders from the 50 mg QD group were re-randomized to receive GLPG0634 100 mg during Weeks 13-24	
Reporting group title	GLPG0634 100 mg QD
Reporting group description:	
GLPG0634 100 mg once daily during Weeks 1-24	

Reporting group title	GLPG0634 200 mg QD
Reporting group description:	
GLPG0634 200 mg once daily during Weeks 1-24	

Primary: Percentage of subjects achieving an ACR20 response at Week 12

End point title	Percentage of subjects achieving an ACR20 response at Week 12

End point description:

The American College of Rheumatology (ACR) response is a measurement of improvement in multiple disease assessment criteria. The ACR20 response was defined as:
1) ≥ 20% improvement from baseline in swollen joint count based on 66 joints (SJC66), and
2) ≥ 20% improvement from baseline in tender joint count based on 68 joints (TJC68), and
3) ≥ 20% improvement from baseline in at least 3 of the following 5 items:
1. Pain visual analog scale (VAS) (taken from the Health Assessment Questionnaire – Disability Index [HAQ-DI]),
2. Patient’s Global Assessment of Disease Activity VAS,
3. Physician's Global Assessment of Disease Activity VAS,
4. Total HAQ-DI score, and
5. C-reactive protein (CRP).

Intent-to-Treat (ITT) Population: all participants in the Safety Population who had post-randomization

data for at least one efficacy parameter.

Non-responder imputation was used (ie, to impute a missing response, the subject was assumed to be a non-responder).

End point type	Primary

End point timeframe:

Week 12

End point values	Placebo	GLPG0634 50 mg QD	GLPG0634 100 mg QD	GLPG0634 200 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72	72	70	69
Units: percentage of subjects				
number (not applicable)	29.2	66.7	65.7	72.5

Statistical analyses

Statistical analysis title	ACR20 Response at Week 12 - Placebo vs 50 mg QD

Statistical analysis description:

Pairwise comparisons of each group vs. the placebo group using a logistic regression model with factors treatment group, geographical region, and prior use of biologics.

Comparison groups	Placebo v GLPG0634 50 mg QD
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [1]
Method	Regression, Logistic
Parameter estimate	Difference in percentage rates
Point estimate	37.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	22.4
upper limit	52.6

Notes:

[1] - P-value has been corrected for multiplicity according to Hommels' closed-testing method.

Statistical analysis title	ACR20 Response at Week 12 - Placebo vs 100 mg QD

Statistical analysis description:

Pairwise comparisons of each group vs. the placebo group using a logistic regression model with factors treatment group, geographical region, and prior use of biologics.

Comparison groups	Placebo v GLPG0634 100 mg QD

Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [2]
Method	Regression, Logistic
Parameter estimate	Difference in percentage rates
Point estimate	36.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.3
upper limit	51.8

Notes:

[2] - P-value has been corrected for multiplicity according to Hommels' closed-testing method.

Statistical analysis title	ACR20 Response at Week 12 - Placebo vs 200 mg QD

Statistical analysis description:

Pairwise comparisons of each group vs. the placebo group using a logistic regression model with factors treatment group, geographical region, and prior use of biologics.

Comparison groups	Placebo v GLPG0634 200 mg QD
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [3]
Method	Regression, Logistic
Parameter estimate	Difference in percentage rates
Point estimate	43.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	28.4
upper limit	58.2

Notes:

[3] - P-value has been corrected for multiplicity according to Hommels' closed-testing method.

Secondary: Percentage of subjects achieving an ACR20 response at Week 24

End point title	Percentage of subjects achieving an ACR20 response at Week 24[4]

End point description:

ACR20 response was defined as:
1) ≥ 20% improvement from baseline in SJC66, and
2) ≥ 20% improvement from baseline in TJC68, and
3) ≥ 20% improvement from baseline in at least 3 of the following 5 items:
1. Pain VAS (taken from the HAQ-DI),
2. Patient’s Global Assessment of Disease Activity VAS,
3. Physician’s Global Assessment of Disease Activity VAS,
4. Total HAQ-DI score, and
5. CRP.

Intent-to-Treat (ITT) Population. Subjects who switched treatment at Week 12 were handled as if they discontinued at Week 12.

Non-responder imputation was used.

End point type	Secondary

End point timeframe:

Week 24

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All placebo subjects switched to GLPG0634 treatment at Week 12 and were not included in the analysis of Week 24.

End point values	GLPG0634 50 mg QD	GLPG0634 100 mg QD	GLPG0634 200 mg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	70	69	
Units: percentage of subjects				
number (not applicable)	56.9	78.6	66.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects achieving an ACR50 response at Weeks 1, 2, 4, 8, 12, and 24

End point title	Percentage of subjects achieving an ACR50 response at Weeks 1, 2, 4, 8, 12, and 24

End point description:

ACR50 response was defined as:
1) ≥ 50% improvement from baseline in SJC66, and
2) ≥ 50% improvement from baseline in TJC68, and
3) ≥ 50% improvement from baseline in at least 3 of the following 5 items:
1. Pain VAS (taken from the HAQ-DI),
2. Patient's Global Assessment of Disease Activity VAS,
3. Physician's Global Assessment of Disease Activity VAS,
4. Total HAQ-DI score, and
5. CRP.

Intent-to-Treat (ITT) Population. Subjects who switched treatment at Week 12 were handled as if they discontinued at Week 12.

Non-responder imputation was used.

Denominator for percentage calculations = total number of subjects per group with a response at that time point.

999 = NA; all placebo subjects switched to GLPG0634 treatment at Week 12 and were not included in the analysis of Week 24.

End point type	Secondary

End point timeframe:

Weeks 1, 2, 4, 8, 12, and 24

End point values	Placebo	GLPG0634 50 mg QD	GLPG0634 100 mg QD	GLPG0634 200 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72[5]	72	70	69
Units: percentage of subjects				
number (not applicable)				
Week 1	1.4	1.4	10	7.2
Week 2	4.2	5.6	7.1	21.7
Week 4	4.2	15.3	18.6	23.2
Week 8	5.6	16.7	25.7	31.9
Week 12	11.1	34.7	37.1	43.5
Week 24	999	33.3	38.6	44.9

Notes:

[5] - Except for at Week 24 (N = 0) because all placebo subjects switched to GLPG0634 at Week 12.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects achieving ACR70 response at Weeks 1, 2, 4, 8, 12, and 24

End point title	Percentage of subjects achieving ACR70 response at Weeks 1, 2, 4, 8, 12, and 24

End point description:

ACR70 response:
1) ≥ 70% improvement from baseline in SJC66, and
2) ≥ 70% improvement from baseline in TJC68, and
3) ≥ 70% improvement from baseline in at least 3 of the following 5 items:
1. Pain VAS (taken from the HAQ-DI),
2. Patient’s Global Assessment of Disease Activity VAS,
3. Physician’s Global Assessment of Disease Activity VAS,
4. Total HAQ-DI score, and
5. CRP.

Intent-to-Treat (ITT) Population. Subjects who switched treatment at Week 12 were handled as if they discontinued at Week 12.

Non-responder imputation was used.

Denominator for percentage calculations = total number of subjects per group with a response at that time point.

999 = NA; all placebo subjects switched to GLPG0634 treatment at Week 12 and were not included in the analysis of Week 24.

End point type	Secondary

End point timeframe:

Weeks 1, 2, 4, 8, 12, and 24

End point values	Placebo	GLPG0634 50 mg QD	GLPG0634 100 mg QD	GLPG0634 200 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72[6]	72	70	69
Units: percentage of subjects				
number (not applicable)				
Week 1	0	0	1.4	1.4

Week 2	2.8	1.4	1.4	4.3
Week 4	1.4	8.3	5.7	11.6
Week 8	2.8	6.9	11.4	17.4
Week 12	2.8	8.3	18.6	13
Week 24	999	19.4	25.7	24.6

Notes:

[6] - Except for at Week 24 (N = 0) because all placebo subjects switched to GLPG0634 at Week 12.

Statistical analyses

No statistical analyses for this end point

Secondary: ACR N% improvement (ACR-N) response at Weeks 1, 2, 4, 8, 12, and 24

End point title	ACR N% improvement (ACR-N) response at Weeks 1, 2, 4, 8, 12, and 24

End point description:

The ACR-N is the smallest percentage improvement in swollen and tender joints and the median of the remaining 5 core parameters, and is expected to be more sensitive to change than the ACR20, ACR50 or ACR70. It is a number varying between 0 and 100, with higher numbers indicating less severity of symptoms.

Intent-to-Treat (ITT) Population. Subjects who switched treatment at Week 12 were handled as if they discontinued at Week 12.

Last observation carried forward (LOCF) algorithm was used (ie, to impute a missing value, the last preceding nonmissing value was used).

999 = NA; all placebo subjects switched to GLPG0634 treatment at Week 12 and were not included in the analysis of Week 24.

End point type	Secondary

End point timeframe:

Weeks 1, 2, 4, 8, 12, and 24

End point values	Placebo	GLPG0634 50 mg QD	GLPG0634 100 mg QD	GLPG0634 200 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72[7]	72	70	69
Units: units on a scale				
arithmetic mean (standard error)				
Week 1	6.79 (± 1.34)	11.66 (± 1.641)	12.84 (± 2.291)	16.84 (± 2.346)
Week 2	10.79 (± 1.917)	17.11 (± 2.362)	16.06 (± 2.261)	27.01 (± 2.776)
Week 4	12.03 (± 2.058)	25 (± 2.852)	24.06 (± 2.898)	32.21 (± 3.172)
Week 8	13.35 (± 2.24)	30.46 (± 2.986)	32.66 (± 3.154)	39.24 (± 3.375)
Week 12	16.28 (± 2.723)	35.03 (± 3.178)	38.35 (± 3.533)	41 (± 3.477)
Week 24	999 (± 999)	38.75 (± 3.748)	46.32 (± 3.295)	46.78 (± 3.648)

Notes:

[7] - Except for at Week 24 (N = 0) because all placebo subjects switched to GLPG0634 at Week 12.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with Disease Activity Score 28 Joints Corrected for CRP (DAS28 (CRP)) European League Against Rheumatism (EULAR) response at Weeks 1, 2, 4, 8, 12, and 24

End point title	Percentage of subjects with Disease Activity Score 28 Joints Corrected for CRP (DAS28 (CRP)) European League Against Rheumatism (EULAR) response at Weeks 1, 2, 4, 8, 12, and 24

End point description:

DAS28 (CRP) was categorized into EULAR response categories (none, moderate, good) as follows:
Good = Actual DAS28 (CRP) ≤ 3.2 AND Improvement in DAS28 (CRP) from baseline > 1.2;
None = Actual DAS28 (CRP) ≤ 3.2, > 3.2 to ≤ 5.1, or > 5.1 AND Improvement in DAS28 (CRP) from baseline ≤ 6.0 or > 0.6 to ≤ 1.2;
Moderate = Actual DAS28 (CRP) ≤ 3.2 AND Improvement in DAS28 (CRP) from baseline > 0.6 to ≤ 1.2, Actual DAS28 (CRP) > 3.2 to ≤ 5.1 or > 5.1 AND Improvement in DAS28 (CRP) from baseline > 1.2, or Actual DAS28 (CRP) > 3.2 to ≤ 5.1 AND Improvement in DAS28 (CRP) from baseline > 0.6 to ≤ 1.2.

Intent-to-Treat (ITT) Population. Subjects who switched treatment at Week 12 were handled as if they discontinued at Week 12.

LOCF algorithm was used.

999 = NA; all placebo subjects switched to GLPG0634 treatment at Week 12 and were not included in the analysis of Week 24.

End point type	Secondary

End point timeframe:

Weeks 1, 2, 4, 8, 12, and 24

End point values	Placebo	GLPG0634 50 mg QD	GLPG0634 100 mg QD	GLPG0634 200 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72[8]	72	70	69
Units: percentage of subjects				
number (not applicable)				
Week 1: None	72	57	63	49
Week 1: Moderate	26	40	31	43
Week 1: Good	1	3	6	7
Week 2: None	67	44	47	26
Week 2: Moderate	31	49	46	64
Week 2: Good	3	7	7	10
Week 4: None	58	38	39	22
Week 4: Moderate	35	47	46	55
Week 4: Good	7	15	16	23
Week 8: None	54	36	24	12
Week 8: Moderate	36	39	54	54
Week 8: Good	10	25	21	35
Week 12: None	49	31	20	14
Week 12: Moderate	38	46	53	41
Week 12: Good	14	24	27	45
Week 24: None	999	28	9	10
Week 24: Moderate	999	36	41	43
Week 24: Good	999	36	50	46

Notes:

[8] - Except for at Week 24 (N = 0) because all placebo subjects switched to GLPG0634 at Week 12.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects achieving ACR/EULAR remission at Weeks 4, 8, 12, and 24

End point title	Percentage of subjects achieving ACR/EULAR remission at Weeks 4, 8, 12, and 24

End point description:

A subject's disease activity status can be defined as being in remission when scores on the TJC28, SJC28, CRP (actual value in mg/dL) and Patient Global Assessment of Disease Activity (cm) are all ≤ 1.

Intent-to-Treat (ITT) Population. Subjects who switched treatment at Week 12 were handled as if they discontinued at Week 12.

Non-responder imputation was used.

Denominator for percentage calculations = total number of subjects per group with a response at that time point.

999 = NA; all placebo subjects switched to GLPG0634 treatment at Week 12 and were not included in the analysis of Week 24.

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, and 24

End point values	Placebo	GLPG0634 50 mg QD	GLPG0634 100 mg QD	GLPG0634 200 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72[9]	72	70	69
Units: percentage of subjects				
number (not applicable)				
Week 4	0	1.4	0	1.4
Week 8	0	0	0	7.2
Week 12	1.4	1.4	4.3	4.3
Week 24	999	8.3	8.6	8.7

Notes:

[9] - Except for at Week 24 (N = 0) because all placebo subjects switched to GLPG0634 at Week 12.

Statistical analyses

No statistical analyses for this end point

Secondary: Simplified Disease Activity Index (SDAI) at baseline and change from baseline at Weeks 1, 2, 4, 8, 12, and 24

End point title	Simplified Disease Activity Index (SDAI) at baseline and change from baseline at Weeks 1, 2, 4, 8, 12, and 24

End point description:

The SDAI is the numerical sum of 5 outcome parameters: TJC28, SJC28, Patient Global Assessment of Disease Activity (in cm), Physician's Global Assessment of Disease Activity (in cm), and CRP (mg/dL).

The SDAI was categorized as follows:
• High disease activity: SDAI > 26
• Moderate disease activity: 11 to 26
• Low disease activity: 3.3 to 11
• Remission: ≤ 3.3.

Intent-to-Treat (ITT) Population. Subjects who switched treatment at Week 12 were handled as if they discontinued at Week 12.

LOCF algorithm was used.

999 = NA; all placebo subjects switched to GLPG0634 treatment at Week 12 and were not included in the analysis of Week 24.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 2, 4, 8, 12, and 24

End point values	Placebo	GLPG0634 50 mg QD	GLPG0634 100 mg QD	GLPG0634 200 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72[10]	72[11]	70	69[12]
Units: units on a scale				
arithmetic mean (standard error)				
Baseline	45.73 (± 1.4789)	43.77 (± 1.5609)	46.608 (± 1.6538)	44.139 (± 1.5079)
Change at Week 1	-7.45 (± 1.5528)	-9.596 (± 1.2567)	-10.886 (± 1.6511)	-14.349 (± 1.4346)
Change at Week 2	-10.022 (± 1.371)	-12.194 (± 1.5982)	-13.172 (± 1.6209)	-18.27 (± 1.6934)
Change at Week 4	-10.927 (± 1.7771)	-17.57 (± 1.7653)	-18.862 (± 1.8073)	-21.288 (± 1.6619)
Change at Week 8	-12.452 (± 1.7748)	-20.144 (± 1.9425)	-23.119 (± 1.8041)	-25.556 (± 1.6949)
Change at Week 12	-12.574 (± 1.984)	-21.413 (± 1.7953)	-25.269 (± 1.9856)	-26.499 (± 1.7534)
Change at Week 24	999 (± 999)	-23.16 (± 1.9364)	-30.983 (± 1.7732)	-29.564 (± 1.8583)

Notes:

[10] - Except at Wk 24 (N=0) because all placebo subjects switched to GLPG0634 at Wk 12; Baseline (N=71)

[11] - Except for at Baseline (N = 70)

[12] - Except for at Baseline (N = 68)

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Disease Activity Index (CDAI) at baseline and change from baseline at Weeks 1, 2, 4, 8, 12, and 24

End point title	Clinical Disease Activity Index (CDAI) at baseline and change from baseline at Weeks 1, 2, 4, 8, 12, and 24

End point description:

The CDAI is the SDAI modified to exclude CRP and is the sum of the 4 outcome parameters: TJC28, SJC28, Patient Global Assessment of Disease Activity (in cm), and Physician's Global Assessment of Disease Activity (in cm).

The CDAI was be categorized as follows:
• High disease activity: > 22
• Moderate disease activity: 10 to 22
• Mild disease activity: 2.8 to 10
• Remission: ≤ 2.8.

Intent-to-Treat (ITT) Population. Subjects who switched treatment at Week 12 were handled as if they discontinued at Week 12.

LOCF algorithm was used.

999 = NA; all placebo subjects switched to GLPG0634 treatment at Week 12 and were not included in the analysis of Week 24.

End point type	Secondary

End point timeframe:

Baseline and Weeks 1, 2, 4, 8, 12, and 24

End point values	Placebo	GLPG0634 50 mg QD	GLPG0634 100 mg QD	GLPG0634 200 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72[13]	72[14]	70	69[15]
Units: units on a scale				
arithmetic mean (standard error)				
Baseline	42.168 (± 1.3272)	41.348 (± 1.4777)	44.052 (± 1.5383)	41.869 (± 1.423)
Change at Week 1	-6.867 (± 1.4538)	-9.226 (± 1.1545)	-9.853 (± 1.5591)	-13.148 (± 1.4085)
Change at Week 2	-9.861 (± 1.1909)	-11.803 (± 1.5275)	-12.306 (± 1.5618)	-16.999 (± 1.702)
Change at Week 4	-10.743 (± 1.7184)	-16.701 (± 1.7003)	-17.654 (± 1.6987)	-20.044 (± 1.6396)
Change at Week 8	-12.071 (± 1.6982)	-19.087 (± 1.8583)	-21.703 (± 1.7491)	-24.228 (± 1.6479)
Change at Week 12	-11.696 (± 1.8752)	-21.019 (± 1.7168)	-24.044 (± 1.9665)	-25.071 (± 1.742)
Change at Week 24	999 (± 999)	-22.278 (± 1.8637)	-29.502 (± 1.6928)	-28.102 (± 1.818)

Notes:

[13] - Except at Wk 24 (N=0) because all placebo subjects switched to GLPG0634 at Wk 12; at Baseline (N=71)

[14] - Except for at Baseline (N = 70)

[15] - Except for at Baseline (N = 68)

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life using the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale at baseline and change from baseline at Weeks 4, 12, and 24

End point title	Quality of Life using the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale at baseline and change

	from baseline at Weeks 4, 12, and 24

End point description:

FACIT-Fatigue scale is a 13-item questionnaire, each scored on a 5-point scale: 0 (Not at all) to 4 (Very much). The larger the subject's response to the questions (with the exception of 2 negatively stated that are scored reversely), the greater the fatigue. The sum of all responses resulted in the FACIT-Fatigue score for a total possible score of 0 (worse score) to 52 (better score), with a higher score indicating a better quality of life.

Intent-to-Treat (ITT) Population. Subjects who switched treatment at Week 12 were handled as if they discontinued at Week 12.

LOCF algorithm was used.

999 = NA; all placebo subjects switched to GLPG0634 treatment at Week 12 and were not included in the analysis of Week 24.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 12, and 24

End point values	Placebo	GLPG0634 50 mg QD	GLPG0634 100 mg QD	GLPG0634 200 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72[16]	72[17]	70	69
Units: units on a scale				
arithmetic mean (standard error)				
Baseline	25.1 (± 1.12)	25.1 (± 1.28)	24.8 (± 1.13)	24.8 (± 1.16)
Change at Week 4	1.4 (± 1.14)	7.2 (± 1.3)	7.2 (± 1.26)	8.5 (± 1.3)
Change at Week 12	3.9 (± 1.23)	9.5 (± 1.43)	10.2 (± 1.21)	11.2 (± 1.44)
Change at Week 24	999 (± 999)	10 (± 1.43)	11.3 (± 1.2)	13.7 (± 1.38)

Notes:

[16] - Except at Wk 24 (N=0) because all placebo subjects switched to GLPG0634 at Wk 12; at Baseline (N=71)
[17] - Except for at Baseline (N = 70)

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life using the Short Form-36 (SF-36) scores at baseline and change from baseline at Weeks 4, 12, and 24

End point title	Quality of Life using the Short Form-36 (SF-36) scores at baseline and change from baseline at Weeks 4, 12, and 24

End point description:

The SF-36 is a 36-item questionnaire measuring 8 domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health). Each domain score ranges from 0 (worst) to 100 (best), with higher scores reflecting better health-related functional status. Two summary scale scores were computed based on weighted combinations of the 8 domain scores: the Physical Component Summary (PCS) and the Mental Component Summary (MCS).

Intent-to-Treat (ITT) Population. Subjects who switched treatment at Week 12 were handled as if they discontinued at Week 12.

LOCF algorithm was used.

999 = NA; all placebo subjects switched to GLPG0634 treatment at Week 12 and were not included in the analysis of Week 24.

End point type	Secondary

End point timeframe:
Baseline and Weeks 4, 12, and 24

End point values	Placebo	GLPG0634 50 mg QD	GLPG0634 100 mg QD	GLPG0634 200 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72[18]	72[19]	70	69
Units: units on a scale				
arithmetic mean (standard error)				
PCS at Baseline	31.1 (± 0.6988)	31.05 (± 0.816)	30.946 (± 0.7631)	31.804 (± 0.8965)
PCS Change at Week 4	2.1 (± 0.72)	5.7 (± 1.04)	5.1 (± 0.92)	6.8 (± 0.92)
PCS Change at Week 12	3 (± 0.89)	7.1 (± 1.11)	7.8 (± 1.04)	8.6 (± 1.09)
PCS Change at Week 24	999 (± 999)	6.9 (± 1.16)	10 (± 1.17)	9.7 (± 1.09)
MCS at Baseline	40.525 (± 1.3053)	42.793 (± 1.3247)	41.185 (± 1.2347)	42.613 (± 1.1674)
MCS Change at Week 4	2.1 (± 1.1)	3.6 (± 1.09)	5.3 (± 1.04)	3.9 (± 1.16)
MCS Change at Week 12	2.7 (± 1.04)	4.9 (± 1.18)	6.9 (± 1.04)	6.8 (± 1.33)
MCS Change at Week 24	999 (± 999)	5.1 (± 1.27)	7.7 (± 1.16)	8.5 (± 1.12)

Notes:

[18] - Except at Wk 24 (N=0) because all placebo subjects switched to GLPG0634 at Wk 12; at Baseline (N=71)

[19] - Except for at Baseline (N = 70)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline through end of study drug treatment (average exposure: 161.0 days)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Adverse events reported in this group includes all subjects randomized to the Placebo group during Weeks 1-12. Subjects who switched treatment at Week 12 were included in the other groups of the same dose for adverse events reported during Weeks 13-24.	
Reporting group title	GLPG0634 50 mg QD
Reporting group description:	
Adverse events reported in this group includes all subjects randomized to the GLPG0634 50 mg QD group during Weeks 1-12 and responders in this group during Weeks 13-24. Subjects who switched treatment at Week 12 were included in the other groups of the same dose for adverse events reported during Weeks 13-24.	
Reporting group title	GLPG0634 100 mg QD
Reporting group description:	
Adverse events reported in this group includes all subjects randomized to the GLPG0634 100 mg QD group during Weeks 1-24 and all nonresponders originally assigned to the GLPG0634 50 mg QD group during Weeks 13-24.	
Reporting group title	GLPG0634 200 mg QD
Reporting group description:	
Adverse events reported in this group includes all subjects randomized to the GLPG0634 200 mg QD group during Weeks 1-24.	

Serious adverse events	Placebo	GLPG0634 50 mg QD	GLPG0634 100 mg QD
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 72 (1.39%)	2 / 72 (2.78%)	3 / 85 (3.53%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 85 (1.18%)
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			
Back pain			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	0 / 85 (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
Osteoarthritis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	0 / 85 (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
Rheumatoid arthritis			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 85 (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			
Cellulitis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 85 (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	0 / 72 (0.00%)	0 / 72 (0.00%)	0 / 85 (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
Pyelonephritis chronic			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 85 (1.18%)
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	GLPG0634 200 mg QD		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 69 (4.35%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rheumatoid arthritis			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			

subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis chronic			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	GLPG0634 50 mg QD	GLPG0634 100 mg QD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 72 (37.50%)	38 / 72 (52.78%)	45 / 85 (52.94%)
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 72 (5.56%)	3 / 72 (4.17%)	1 / 85 (1.18%)
occurrences (all)	4	3	3
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 72 (1.39%)	4 / 72 (5.56%)	1 / 85 (1.18%)
occurrences (all)	1	10	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 85 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	2 / 72 (2.78%)	2 / 72 (2.78%)	4 / 85 (4.71%)
occurrences (all)	2	2	4
Urinary tract infection			

subjects affected / exposed	1 / 72 (1.39%)	3 / 72 (4.17%)	7 / 85 (8.24%)
occurrences (all)	1	4	10
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	3 / 72 (4.17%)	4 / 72 (5.56%)	5 / 85 (5.88%)
occurrences (all)	3	5	5
Hypertriglyceridaemia			
subjects affected / exposed	1 / 72 (1.39%)	2 / 72 (2.78%)	5 / 85 (5.88%)
occurrences (all)	1	2	5

Non-serious adverse events	GLPG0634 200 mg QD		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 69 (47.83%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	4		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	5		
Urinary tract infection			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	6		
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Hypertriglyceridaemia			

subjects affected / exposed occurrences (all)	1 / 69 (1.45%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 April 2013	• Due to the implementation of a new method for CRP measurements carried out by the central laboratory (Quest Diagnostics), the ULN and its fold change that were used to calculate the numeric value for the inclusion criteria were likely to change. Therefore, instead of a numeric value, CRP as inclusion criterion was expressed as a 1.5 fold change ULN. • As adjustments for the body surface area were not going to be carried out (Cockroft- Gault formula), the estimated creatinine clearance was expressed as ml/min/. • In order to reduce the recording burden for patients, the date and time of the taken capsules was recorded on selected visits only and not at every visit. • Size of the SST tubes that were planned to be used for the additional pharmacodynamics assessment, was changed (instead of two 4-ml SST tubes, only one 8.5-ml SST tube was collected).
17 April 2013	Introduced stratification according to the previous use of a biological DMARD in a single clinical study setting, in addition to the stratification according to region. This aimed to obtain equal distribution of subjects who had been previously exposed to a biological DMARD during a single clinical study setting between the study groups, to reduce heterogeneity and therefore be beneficial for results interpretation. Consequently the statistical methods section was adapted accordingly: Cochran-Mantel-Haenszel and logrank tests, both controlling for region, were changed to logistic and proportional hazards regression models in order to include more factors.
02 August 2013	Addressed specific comments received from Competent Authorities and Ethics Committees. In addition, some clarifications were introduced upon request of investigators. Changes introduced included: • The overall benefit/risk assessment was updated in view of recent advances in the product development and the current status of the scientific field for JAK development. • The inclusion/exclusion criteria were refined with further specified and strengthened laboratory test limits, and additional criteria to manage the overall health status at Screening were introduced. • Criteria for individual subject withdrawal were further specified. • An independent DSMB was introduced. • The section on prior and concomitant therapy was updated. Note: Amendment was applicable to all countries apart from the US.
23 May 2014	• The inclusion/exclusion criteria were adjusted to better represent the current RA population without compromising the study objective, including a decrease in entry level for CRP to >0.70xULN. • The individual subject withdrawal criteria were adjusted • The general study procedures (calendar days, re-Screening and retesting guidelines) were refined to provide further guidance to investigators. Note: Amendment was applicable to all countries apart from the US.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported