Clinical trial results:
A comparative Study to Assess the Efficacy, Safety and Immunogenicity of YLB113 and Enbrel for the Treatment of Rheumatoid Arthritis

Summary

EudraCT number	2015-002809-12
Trial protocol	HU LV CZ ES BG
Global end of trial date	02 August 2017

Results information

Result version number	v1 (current)
This version publication date	17 August 2018
First version publication date	17 August 2018

Trial information

Trial identification

Sponsor protocol code	YLB113-002

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	YL Biologics Ltd
Sponsor organisation address	Gat No. 1156, Village Ghotwade, Mulshi Taluke, Pune, India, 412 115
Public contact	Head - Regulatory , YL Biologics Ltd, 91 2066549816, akshayaodak@lupin.com
Scientific contact	Head - Regulatory , YL Biologics Ltd, 91 2066549816, akshayaodak@lupin.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 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 August 2017
Global end of trial reached?	Yes
Global end of trial date	02 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to compare the efficacy of dosing and safety, 20% improvement according to American College of Rheumatology criteria (ACR20) at Week 24 of treatment with YLB113 50 mg or Enbrel 50 mg given once a week as a subcutaneous (SC) injection along with methotrexate (MTX) in patients with moderate to severe RA and to evaluate the long-term safety and immunogenicity, of YLB113 administration in comparison to Enbrel

Protection of trial subjects:

The study was conducted in accordance with the protocol, the ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, and applicable laws and regulations. The study was also conducted in accordance with the Japanese GCP in Japan and in accordance with ICH-GCP and/or local regulatory GCP in European Union (EU) and India. An ICF approved by each study center's IRB/IEC was signed by the subject or their legally authorized representative (according to the regulatory and legal requirements of the participating country). The ICF contained all relevant information to be conveyed to the prospective subject in order to assist him/her in making informed decision about participating in the study. Subjects were required to continue MTX, (Note: Reduction in the MTX dose was allowed for safety considerations only). Dosing with folic acid was allowed so as to prevent toxicity associated with MTX administration. For pain and rescue therapy, single-agent NSAIDs were allowed, (Note: Reduction in the dose of NSAIDs was allowed for safety considerations only). Oral corticosteroids (≤10 mg prednisone per day or equivalent corticosteroid) were allowed, (Note: Reduction in the dose of prednisolone was allowed for safety considerations only). Ongoing non-drug therapy started prior to obtaining informed consent (eg, physical therapy) for the purpose of treating the RA affected parts was allowed. A change to the type of such therapy or discontinuation based on an improvement in RA disease activity was allowed.

Background therapy:

Essential Medications (MTX)
Subjects were required to continue MTX (6 to 25 mg/week) provided that the dose of MTX was stable for at least 6 weeks prior to screening and remained stable for the duration of the study, except during the follow-up period (Note: Reduction in the MTX dose was allowed for safety considerations only).

Evidence for comparator:

YLB113 (developed by YL Biologics Co., Ltd. hereinafter referred to as YLB) is an investigational biosimilar of Enbrel® (manufactured and marketed by Pfizer, Inc. which has the active ingredient Etanercept. YLB113 is found to be biosimilar to Enbrel based on analytical similarity and preclinical studies conducted to compare with Enbrel. For the development of biosimilars it is necessary to establish the similarity in quality characteristics and to demonstrate equivalence in efficacy and safety with the innovator drug as the control group. YLB113 has demonstrated excellent similarity to Enbrel in terms of quality (CMC) parameters as well as comparability in non-clinical studies. Two comparative Phase I studies, conducted one each in Japan and India, has demonstrated bioequivalence between YLB113 and Enbrel at 25 mg and 50 mg doses, respectively. The current Phase III study was planned to further demonstrate therapeutic equivalence between YLB113 and Enbrel in terms of efficacy, long-term safety and immunogenicity in RA subjects.

Actual start date of recruitment	25 August 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Spain: 25
Country: Number of subjects enrolled	Bulgaria: 48
Country: Number of subjects enrolled	Czech Republic: 45
Country: Number of subjects enrolled	Hungary: 70
Country: Number of subjects enrolled	Latvia: 16
Country: Number of subjects enrolled	Ukraine: 28
Country: Number of subjects enrolled	Japan: 262
Country: Number of subjects enrolled	India: 33
Worldwide total number of subjects	528
EEA total number of subjects	205

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	445
From 65 to 84 years	83
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 874 subjects were screened, and 528 subjects were randomized to YLB113 and Enbrel arms in a 1:1 ratio.

Pre-assignment

Screening details:

Screening period consisted of 28 days during which patients were to undergo an eligibility assessment. All Screening assessments were to be completed within 28 days prior to baseline.

Period 1

Period 1 title	Stage A double-blind phase (24 weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

All eligible subjects were randomly assigned the study medication, after all the requiredscreening procedures were completed and all required data were submitted to the interactive web response system (IWRS) system. Subjects who qualified for study randomization received a unique randomization number by IWRS. The IWRS assigned subjects to a treatment group based on a predefined randomization list.

Arms

Are arms mutually exclusive?	Yes
Arm title	YLB113 (Lupin Etanercept) - stage A

Arm description:

Eligible subjects randomly assigned to receive YLB113 50 mg once a week as a SC injection for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	YLB113
Investigational medicinal product code	YLB113
Other name	INN ETANERCEPT, CAS 185243-69-0, EV substance code SUB01984MIG
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

YLB113 50 mg prefilled syringe 1.0 mL for SC injection

Arm title	Enbrel - stage A

Arm description:

Eligible subjects randomly assigned to receive Enbrel 50 mg once a week as a SC injection for 24 weeks.

Arm type	Active comparator
Investigational medicinal product name	Enbrel
Investigational medicinal product code	Enbrel
Other name	INN ETANERCEPT, CAS 185243-69-0, EV substance code SUB01984MIG
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Enbrel 50 mg prefilled syringe 1.0 mL for SC injection

Number of subjects in period 1	YLB113 (Lupin Etanercept) - stage A	Enbrel - stage A
Started	266	262
Completed	247	250
Not completed	19	12
Consent withdrawn by subject	8	2
Physician decision	1	1
Adverse event, non-fatal	2	5
Ineligible of patient	3	1
Other	1	-
Pregnancy	1	-
Not dosed	2	2
Protocol deviation	1	1

Period 2

Period 2 title	Stage B double-blind phase (28 weeks)
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	YLB113 (Lupin Etanercept) - stage B

Arm description:

Subjects administered with YLB113 50 mg who completed evaluations for Week 24 in Stage A and were willing to continue in Stage B, and tolerated the study medications administered in Stage A with no serious adverse events (SAEs), or unresolved Grade 3 or higher AEs related to study medication. The subjects were administered the same drug as Stage A once a week as a SC injection for 28 weeks in this multicenter, comparative study.

Arm type	Experimental
Investigational medicinal product name	YLB113
Investigational medicinal product code	YLB113
Other name	INN ETANERCEPT, CAS 185243-69-0, EV substance code SUB01984MIG
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

YLB113 50 mg prefilled syringe 1.0 mL for SC injection

Arm title	Enbrel - stage B

Arm description:

Subjects administered with Enbrel 50 mg who completed evaluations for Week 24 in Stage A and were

willing to continue in Stage B, and tolerated the study medications administered in Stage A with no serious adverse events (SAEs), or unresolved Grade 3 or higher AEs related to study medication. The subjects were administered the same drug as Stage A once a week as a SC injection for 28 weeks in this multicenter, comparative study.

Arm type	Active comparator
Investigational medicinal product name	Enbrel
Investigational medicinal product code	Enbrel
Other name	INN ETANERCEPT, CAS 185243-69-0, EV substance code SUB01984MIG
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Enbrel 50 mg prefilled syringe 1.0 mL for SC injection

Number of subjects in period 2[1]	YLB113 (Lupin Etanercept) - stage B	Enbrel - stage B
Started	236	235
Completed	227	227
Not completed	9	8
Physician decision	2	2
Consent withdrawn by subject	3	1
Adverse event, non-fatal	4	4
RA symptoms exacerbation	-	1

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: A total of 497 subjects completed Stage A (247 in YLB113 arm and 250 in Enbrel arm). Of these 497 subjects, 471 subjects entered in Stage B, 18 in Stage C while 8 subjects did not opt for either stage. Out of the 471 subjects that entered in Stage B, FAS population consisted of 464 subjects. All 18 subjects that entered in Stage C were part of FAS population.

Period 3

Period 3 title	Stage C double-blind phase (28 weeks)
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	Enbrel - stage C

Arm description:

Subjects who received Enbrel 50 mg in Stage A, demonstrated reduction in their baseline DAS28 score by ≥0.6 at Week 12 and/or Week 24 and completed the 24-week period of Stage A, and tolerated the study medications administered in Stage A with no SAEs or unresolved Grade 3 or higher AEs related to study medication were eligible to enter Stage C were crossed over to receive YLB113 50 mg in Stage C

Arm type	Experimental

Investigational medicinal product name	YLB113
Investigational medicinal product code	YLB113
Other name	INN ETANERCEPT, CAS 185243-69-0, EV substance code SUB01984MIG
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

YLB113 50 mg prefilled syringe 1.0 mL for SC injection

Arm title	YLB113 (Lupin Etanercept) - stage C

Arm description:

Subjects who received YLB113 50 mg in Stage A, demonstrated reduction in their baseline DAS28 score by ≥0.6 at Week 12 and/or Week 24 and completed the 24-week period of Stage A, and tolerated the study medications administered in Stage A with no SAEs or unresolved Grade 3 or higher AEs related to study medication were eligible to enter Stage C were crossed over to receive Enbrel 50 mg in Stage C.

Arm type	Active comparator
Investigational medicinal product name	Enbrel
Investigational medicinal product code	Enbrel
Other name	INN ETANERCEPT, CAS 185243-69-0, EV substance code SUB01984MIG
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Enbrel 50 mg prefilled syringe 1.0 mL for SC injection.

Number of subjects in period 3[2]	Enbrel - stage C	YLB113 (Lupin Etanercept) - stage C
Started	8	10
Completed	8	9
Not completed	0	1
RA symptoms exacerbation	-	1

Notes:

[2] - 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: A total of 497 subjects completed Stage A (247 in YLB113 arm and 250 in Enbrel arm). Of these 497 subjects, 471 subjects entered in Stage B, 18 in Stage C while 8 subjects did not opt for either stage. Out of the 471 subjects that entered in Stage B, FAS population consisted of 464 subjects. All 18 subjects that entered in Stage C were part of FAS population.

Baseline characteristics

Reporting groups

Reporting group title	YLB113 (Lupin Etanercept) - stage A

Reporting group description:

Eligible subjects randomly assigned to receive YLB113 50 mg once a week as a SC injection for 24 weeks.

Reporting group title	Enbrel - stage A

Reporting group description:

Eligible subjects randomly assigned to receive Enbrel 50 mg once a week as a SC injection for 24 weeks.

Reporting group values	YLB113 (Lupin Etanercept) - stage A	Enbrel - stage A	Total
Number of subjects	266	262	528
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)	224	221	445
From 65-84 years	42	41	83
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	52.0	52.6	
standard deviation	± 12.46	± 11.46	-
Gender categorical Units: Subjects			
Female	202	210	412
Male	64	52	116
Region Units: Subjects			
Japan	132	130	262
India	16	17	33
Europe	118	115	233
Acute Phase Reactant selected for patient in calculating for ACR20 and DAS28 Units: Subjects			
CRP	103	90	193
ESR	163	172	335
ACR Global Functional Status of RA Units: Subjects			
Class I	38	41	79

Class II	183	177	360
Class III	45	44	89
Class IV	0	0	0
Tender joint counts (TJC) at Baseline			
68 Total Score			
Units: rating scale			
arithmetic mean	18.1	18.9	
standard deviation	± 10.02	± 10.38	-
Tender joint counts (TJC) at Baseline			
28 Total Score			
Units: rating scale			
arithmetic mean	12.7	12.6	
standard deviation	± 6.36	± 6.06	-
Swollen joint counts (SJC) at Baseline			
66 Total Score			
Units: rating scale			
arithmetic mean	13.3	14.2	
standard deviation	± 7.07	± 7.17	-
Swollen joint counts (SJC) at Baseline			
28 Total Score			
Units: rating scale			
arithmetic mean	10.3	10.5	
standard deviation	± 4.92	± 4.93	-
Patient global assessment of disease activity (Visual Analog Scale) at Baseline			
Units: rating scale			
arithmetic mean	61.3	63.4	
standard deviation	± 21.47	± 21.60	-
Patient assessment of pain (VAS) at Baseline			
Units: rating scale			
arithmetic mean	60.6	63.1	
standard deviation	± 22.26	± 21.76	-
Physician global assessment of disease activity (Visual Analog Scale) at Baseline			
Units: rating scale			
arithmetic mean	59.8	60.6	
standard deviation	± 19.13	± 19.71	-
Health Assessment Questionnaire(HAQ) at Baseline			
Units: rating scale			
arithmetic mean	1.06	1.13	
standard deviation	± 0.712	± 0.685	-
Disease Activity (DAS28) score at Baseline based on investigator chosen patient specific Acute Phase			
Units: rating scale			
arithmetic mean	5.756	5.771	
standard deviation	± 1.1112	± 1.0448	-
Disease Activity (DAS28) score at Baseline based on patient-specific Acute Phase reactant			
DAS28-CRP			

Units: rating scale			
arithmetic mean	5.191	5.237	
standard deviation	± 1.0013	± 0.9222	-
Disease Activity (DAS28) score at Baseline based on patient-specific Acute Phase reactant			
DAS28-ESR			
Units: rating scale			
arithmetic mean	6.108	6.057	
standard deviation	± 1.0306	± 0.9955	-
Erythrocyte Sedimentation Rate(ESR) results (mm/hr)			
Units: rating scale			
arithmetic mean	35.5	32.8	
standard deviation	± 21.45	± 20.60	-
C-reactive protein (CRP) (mg/dl)			
Units: rating scale			
arithmetic mean	1.299	1.015	
standard deviation	± 2.0762	± 1.4559	-
MTX dose at Baseline			
Units: rating scale			
arithmetic mean	11.37	11.82	
standard deviation	± 3.967	± 4.021	-
Body Mass Index (kg/m2)			
Units: rate scaling			
arithmetic mean	24.8	25.0	
standard deviation	± 5.24	± 5.14	-

End points

End points reporting groups

Reporting group title	YLB113 (Lupin Etanercept) - stage A

Reporting group description:

Eligible subjects randomly assigned to receive YLB113 50 mg once a week as a SC injection for 24 weeks.

Reporting group title	Enbrel - stage A

Reporting group description:

Eligible subjects randomly assigned to receive Enbrel 50 mg once a week as a SC injection for 24 weeks.

Reporting group title	YLB113 (Lupin Etanercept) - stage B

Reporting group description:

Subjects administered with YLB113 50 mg who completed evaluations for Week 24 in Stage A and were willing to continue in Stage B, and tolerated the study medications administered in Stage A with no serious adverse events (SAEs), or unresolved Grade 3 or higher AEs related to study medication. The subjects were administered the same drug as Stage A once a week as a SC injection for 28 weeks in this multicenter, comparative study.

Reporting group title	Enbrel - stage B

Reporting group description:

Subjects administered with Enbrel 50 mg who completed evaluations for Week 24 in Stage A and were willing to continue in Stage B, and tolerated the study medications administered in Stage A with no serious adverse events (SAEs), or unresolved Grade 3 or higher AEs related to study medication. The subjects were administered the same drug as Stage A once a week as a SC injection for 28 weeks in this multicenter, comparative study.

Reporting group title	Enbrel - stage C

Reporting group description:

Subjects who received Enbrel 50 mg in Stage A, demonstrated reduction in their baseline DAS28 score by ≥0.6 at Week 12 and/or Week 24 and completed the 24-week period of Stage A, and tolerated the study medications administered in Stage A with no SAEs or unresolved Grade 3 or higher AEs related to study medication were eligible to enter Stage C were crossed over to receive YLB113 50 mg in Stage C

Reporting group title	YLB113 (Lupin Etanercept) - stage C

Reporting group description:

Subjects who received YLB113 50 mg in Stage A, demonstrated reduction in their baseline DAS28 score by ≥0.6 at Week 12 and/or Week 24 and completed the 24-week period of Stage A, and tolerated the study medications administered in Stage A with no SAEs or unresolved Grade 3 or higher AEs related to study medication were eligible to enter Stage C were crossed over to receive Enbrel 50 mg in Stage C.

Primary: ACR20 response rate at week 24 between YLB113 and Enbrel

End point title	ACR20 response rate at week 24 between YLB113 and Enbrel

End point description:

Estimate and Confidence Intervals for Differences in ACR20 Response Rate at Week 24

End point type	Primary

End point timeframe:

The ACR20 respose rate was determined at week24

End point values	YLB113 (Lupin Etanercept) - stage A	Enbrel - stage A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	254		
Units: response rate	263	254		

Statistical analyses

Statistical analysis title	Differences in ACR20 Response Rate at Week 24

Statistical analysis description:

Statistical analysis description: ACR20 response rate after the first 24 weeks of treatment (Stage A) was the primary endpoint to assess equivalence between YLB113 and Enbrel®. Therapeutic equivalence in terms of ACR20 could be concluded if the exact 95% confidence interval for the difference in the ACR20 rates is completely contained within the interval [−15%; 15%]. A binomial regression model was to be employed.

Comparison groups	YLB113 (Lupin Etanercept) - stage A v Enbrel - stage A
Number of subjects included in analysis	517
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	< 0.025
Method	Binomial Regression
Parameter estimate	95% CI for the difference in ACR20
Point estimate	-5.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.6
upper limit	0.5

Notes:

[1] - The analysis of the primary variable was based on the FAS.

Secondary: ACR20 Response Rate by Visit (Week) between YLB113 and Enbrel

End point title	ACR20 Response Rate by Visit (Week) between YLB113 and Enbrel

End point description:

Estimate and Confidence Intervals for Differences in ACR20 Response Rate by Visit (Week)

End point type	Secondary

End point timeframe:

At each visit (Week) Day 29 (Week 4) - Day 57 (Week 8) - Day 85 (Week 12)

End point values	YLB113 (Lupin Etanercept) - stage A	Enbrel - stage A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	254		
Units: Response to treatment at each Visit-Week				
Week 4	263	254		

Week 57	263	254		
Week 12	263	254		

Statistical analyses

Statistical analysis title	Differences in ACR20 Response Rate at Week 4

Statistical analysis description:

ACR20 response rate in each treatment group (Stage A) at Week 4 was one of the secondary endpoint. A binomial regression model was to be employed to calculate 95% CI.

Comparison groups	YLB113 (Lupin Etanercept) - stage A v Enbrel - stage A
Number of subjects included in analysis	517
Analysis specification	Pre-specified
Analysis type	equivalence[2]
P-value	< 0.025
Method	binomial regression model
Parameter estimate	95% CI for the difference in ACR20
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	10.2

Notes:

[2] - The analysis of this secondary variable was based on the FAS.

Statistical analysis title	Differences in ACR20 Response Rate at Week 8

Statistical analysis description:

ACR20 response rate in each treatment group (Stage A) at Week 8 was one of the secondary endpoint. A binomial regression model was to be employed to calculate 95% CI.

Comparison groups	YLB113 (Lupin Etanercept) - stage A v Enbrel - stage A
Number of subjects included in analysis	517
Analysis specification	Pre-specified
Analysis type	equivalence[3]
P-value	< 0.025
Method	binomial regression model
Parameter estimate	95% CI for the difference in ACR20
Point estimate	-6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.2
upper limit	1.2

Notes:

[3] - The analysis of this secondary variable was based on the FAS.

Statistical analysis title	Differences in ACR20 Response Rate at Week 12

Statistical analysis description:

ACR20 response rate in each treatment group (Stage A) at Week 12 was one of the secondary endpoint.

A binomial regression model was to be employed to calculate 95% CI.

Comparison groups	YLB113 (Lupin Etanercept) - stage A v Enbrel - stage A
Number of subjects included in analysis	517
Analysis specification	Pre-specified
Analysis type	equivalence[4]
P-value	< 0.025
Method	binomial regression model
Parameter estimate	95% CI for the difference in ACR20
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10
upper limit	3.1

Notes:

[4] - The analysis of this secondary variable was based on the FAS.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During Stage A (up to 24 weeks)
During Stage B and C (up to 28 weeks)

Adverse event reporting additional description:

AEs collected from date of informed consent until completion of the final visit (28 days follow up visit) and SAEs occurring after the time of informed consent until the final visit (28 days follow up visit) have been reported. SAEs occurring after end of study should be reported if PI considers that there is a casual relationship with study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Stage A YLB113

Reporting group description:

Patient receiving at least one dose of experimental drug YLB113 during stage A

Reporting group title	Stage A Enbrel

Reporting group description:

Patient receiving at least one dose of comparator Enbrel during stage A

Reporting group title	Stage B YLB113

Reporting group description:

Patient receiving at least one dose of experimental drug YLB113 during stage B

Reporting group title	Stage B Enbrel

Reporting group description:

Patient receiving at least one dose of comparator drug Enbrel during stage B

Reporting group title	Stage C YLB113

Reporting group description:

Patient receiving at least one dose of experimental drug YLB113 during stage C

Reporting group title	Stage C Enbrel

Reporting group description:

Patient receiving at least one dose of comparator drug Enbrel during stage C

Serious adverse events	Stage A YLB113	Stage A Enbrel	Stage B YLB113
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 263 (3.04%)	4 / 254 (1.57%)	8 / 235 (3.40%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lobular breast carcinoma in situ			
subjects affected / exposed	1 / 263 (0.38%)	0 / 254 (0.00%)	0 / 235 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Metastases to liver			
subjects affected / exposed	0 / 263 (0.00%)	0 / 254 (0.00%)	1 / 235 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lung			
subjects affected / exposed	0 / 263 (0.00%)	0 / 254 (0.00%)	1 / 235 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma			
subjects affected / exposed	0 / 263 (0.00%)	0 / 254 (0.00%)	1 / 235 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine cancer			
subjects affected / exposed	0 / 263 (0.00%)	0 / 254 (0.00%)	0 / 235 (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
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 263 (0.38%)	0 / 254 (0.00%)	0 / 235 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 263 (0.00%)	0 / 254 (0.00%)	1 / 235 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 263 (0.00%)	0 / 254 (0.00%)	0 / 235 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			

subjects affected / exposed	0 / 263 (0.00%)	0 / 254 (0.00%)	1 / 235 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIth nerve paresis			
subjects affected / exposed	0 / 263 (0.00%)	0 / 254 (0.00%)	0 / 235 (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
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 263 (0.00%)	0 / 254 (0.00%)	1 / 235 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 254 (0.39%)	0 / 235 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	1 / 263 (0.38%)	0 / 254 (0.00%)	0 / 235 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	1 / 263 (0.38%)	0 / 254 (0.00%)	1 / 235 (0.43%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleurisy			
subjects affected / exposed	1 / 263 (0.38%)	0 / 254 (0.00%)	0 / 235 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural cyst			

subjects affected / exposed	0 / 263 (0.00%)	0 / 254 (0.00%)	1 / 235 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Still's disease adult onset			
subjects affected / exposed	1 / 263 (0.38%)	0 / 254 (0.00%)	0 / 235 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Escherichia urinary tract infection			
subjects affected / exposed	1 / 263 (0.38%)	0 / 254 (0.00%)	0 / 235 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 263 (0.38%)	1 / 254 (0.39%)	0 / 235 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 263 (0.38%)	2 / 254 (0.79%)	0 / 235 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 263 (0.00%)	0 / 254 (0.00%)	0 / 235 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 263 (0.00%)	0 / 254 (0.00%)	1 / 235 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal abscess			
subjects affected / exposed	0 / 263 (0.00%)	0 / 254 (0.00%)	0 / 235 (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

Rhinitis			
subjects affected / exposed	0 / 263 (0.00%)	0 / 254 (0.00%)	1 / 235 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 263 (0.00%)	0 / 254 (0.00%)	1 / 235 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Stage B Enbrel	Stage C YLB113	Stage C Enbrel
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 229 (2.18%)	0 / 10 (0.00%)	0 / 8 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lobular breast carcinoma in situ			
subjects affected / exposed	0 / 229 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Metastases to liver			
subjects affected / exposed	0 / 229 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Metastases to lung			
subjects affected / exposed	0 / 229 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Pancreatic carcinoma			
subjects affected / exposed	0 / 229 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Uterine cancer			

subjects affected / exposed	1 / 229 (0.44%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 229 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 229 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 229 (0.44%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 229 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
VIth nerve paresis			
subjects affected / exposed	1 / 229 (0.44%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 229 (0.00%)	0 / 10 (0.00%)	0 / 8 (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			
Gastritis			

subjects affected / exposed	0 / 229 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	0 / 229 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	0 / 229 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Pleurisy			
subjects affected / exposed	0 / 229 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Pleural cyst			
subjects affected / exposed	0 / 229 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Musculoskeletal and connective tissue disorders			
Still's disease adult onset			
subjects affected / exposed	0 / 229 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Infections and infestations			
Escherichia urinary tract infection			
subjects affected / exposed	0 / 229 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Pneumocystis jirovecii pneumonia			

subjects affected / exposed	0 / 229 (0.00%)	0 / 10 (0.00%)	0 / 8 (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 / 229 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Herpes zoster			
subjects affected / exposed	1 / 229 (0.44%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 229 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Renal abscess			
subjects affected / exposed	1 / 229 (0.44%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinitis			
subjects affected / exposed	0 / 229 (0.00%)	0 / 10 (0.00%)	0 / 8 (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
Sinusitis			
subjects affected / exposed	0 / 229 (0.00%)	0 / 10 (0.00%)	0 / 8 (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

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

Non-serious adverse events	Stage A YLB113	Stage A Enbrel	Stage B YLB113
Total subjects affected by non-serious adverse events			
subjects affected / exposed	144 / 263 (54.75%)	166 / 254 (65.35%)	120 / 235 (51.06%)
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 263 (0.00%)	0 / 254 (0.00%)	0 / 235 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	5 / 263 (1.90%)	25 / 254 (9.84%)	0 / 235 (0.00%)
occurrences (all)	5	25	0
Injection site reaction			
subjects affected / exposed	10 / 263 (3.80%)	35 / 254 (13.78%)	0 / 235 (0.00%)
occurrences (all)	10	35	0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 263 (0.00%)	0 / 254 (0.00%)	0 / 235 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	0 / 263 (0.00%)	0 / 254 (0.00%)	0 / 235 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	30 / 263 (11.41%)	25 / 254 (9.84%)	35 / 235 (14.89%)
occurrences (all)	30	25	35
Respiratory tract infection viral			
subjects affected / exposed	0 / 263 (0.00%)	0 / 254 (0.00%)	0 / 235 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 263 (0.00%)	0 / 254 (0.00%)	0 / 235 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Stage B Enbrel	Stage C YLB113	Stage C Enbrel
Total subjects affected by non-serious adverse events			
subjects affected / exposed	143 / 229 (62.45%)	3 / 10 (30.00%)	3 / 8 (37.50%)
Cardiac disorders			

Atrioventricular block first degree			
subjects affected / exposed	0 / 229 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	0 / 229 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Injection site reaction			
subjects affected / exposed	0 / 229 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 229 (0.00%)	1 / 10 (10.00%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	0 / 229 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	44 / 229 (19.21%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	44	0	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 229 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	0 / 229 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 June 2015	Protocol Version 1.0 was submitted to the PMDA. Protocol Version 1.0 was the first protocol approved by the IRB. It was implemented only in Japan.
16 July 2015	Protocol Amendment Version 1.1 was an amendment of Protocol Version 1.0, which was modified as per the PMDA advice. It was implemented only in Japan.
29 July 2015	Protocol Amendment Version 1.1.1 was an amendment of Protocol Version 1.1, and was implemented in Europe and India, but not in Japan. This amendment concerned the changes of washout period of auranofin and hydroxychloroquine (annexure 15 of the protocol), from 5 months and 8 months, respectively, to 4 weeks for both, based on reconsideration of their maximum half-lives.
10 February 2016	In addition to the changes made in the Protocol Amendment Version 1.1, the following changes were made in the Protocol Amendment Version 1.1.2. This protocol amendment was implemented only in Japan. • The exclusion criterion No. 7 (Section 4.3) was revised as follows (underlined below) according to the Investigators' opinions that remission is indicated for a patient with a history of cancer who remained cancer-free for 5 years. Patients with active or prior history of malignancies within 5 years prior to Screening (except for successfully treated non-metastatic basal or squamous cell carcinoma of the skin and carcinoma in situ of the cervix). • The following phrase (underlined) was deleted from the description of the pregnancy test in Section 9.6 to be consistent with the actual logistic arrangement. Pregnancy test for females of childbearing potential will be performed at Screening, 24 weeks (or ED) and 52 weeks (or ED) at each clinical site and analyzed in central laboratory. • The following change ("approximately") was made to the target number of patients enrolled in Stage A (Section 10.1.1) because the competitive patient recruitment across 14 countries made it difficult to end recruitment precisely at the target. Approximately 500 patients will be randomized for this study in consideration of the dropouts and deviations. • This amendment concerned the changes of washout period of auranofin and hydroxychloroquine (annexure 15 of the protocol), from 5 months and 8 months, respectively, to 4 weeks for both, based on reconsideration of their maximum half-lives.

26 May 2016	Protocol Amendment Version 2.0 was implemented only in Japan. In this amendment, the study objective was changed to include an additional objective for assessing the sustainability of efficacy of Enbrel and YLB113 after crossing over the treatments. For this purpose, Stage C was added, which, however, was not to be conducted in Japan. Sections across the protocol were amended in line with this change in the objective. Please refers to underlined sentences reported in the Protocol Amendment and full CSR in the following sections: • Study objectives in synopsis and in Section 2.1 • Study population in synopsis • Number of patients in synopsis • Study duration and treatment period in synopsis • Inclusion criteria in synopsis and in Section 4.2. • Exclusion criteria in synopsis and in Section 4.3. • Re-consenting procedure was newly added to the synopsis • Footnote of Table 2 for Stage B or Stage C • Section 3.2.1. • Section 3.2.3. Stage C • Section 6.1.2. • Section 6.3.3. Stage C • Section 7.2.2. • Section 7.2.3. • Refer Section 7.2.5: 'Continuation of Stage B or Stage C treatment' for visits beyond Week 36 for the description of the assessments. • Section 10.1.3. The following changes were also made to the protocol: • The target number of participating sites (Synopsis, Section 4.4.2) was changed to 140 based on the forecasted accruals at the time. • A sentence was deleted in Section 6.4.1 to be consistent with the inclusion criteria. • A phrase was added to Section 4.5.1 to further define study-completed patients, and the phrase in italic was deleted • A phrase was added to Section 6.4.2 to allow study drug continuation beyond 52 weeks up to the follow-up visit for patients participating in an extension study, if conducted.
01 July 2016	Protocol Amendment Version 2.1 was implemented in all regions, except that Stage C was not to be conducted in Japan. In this amendment, the following changes were made to the Protocol Amendment Version 2.0. • The target enrolled patient number in Sections 4.4.1 and in 10.1.1 were changed as follows (underlined) since the competitive recruitment made it unlikely that the target number in each region would be as planned. Planned number of enrolled patients: 500 (250 in each arm) Randomization, YLB113:Enbrel = 1:1. The number of enrolled patients in Japan, EU and India is expected to be 500 with a competitive recruitment aiming to recruit approximately half the patients in Japan and half in Europe and India. • The following underlined sentence was added to Section 6.1.1, since the drastically different screening failure rates between the regions prevented stopping screening in order to ensure enrollment of 500 patients, forcing the Sponsor to deny randomization for some screened and eligible patients to ensure that the total numbers specified in the protocol (500 randomized) was not exceeded by 10%. • The treatment assignment will occur at the time of randomization, after all the required screening procedures have been completed and all required data have been submitted to the IWRS system. Patients who qualify for study randomization will receive a unique randomization number by IWRS (see IWRS manual). After completion of required numbers (500 randomized), some patients who qualify in screening may not be randomized.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported