Clinical trial results:
A Randomised, Double-blind, Parallel Group, Multicentre Clinical Study to Evaluate the Efficacy, Safety, Pharmacokinetics and Immunogenicity of SB2 Compared to Remicade® in Subjects with Moderate to Severe Rheumatoid Arthritis despite Methotrexate Therapy

Summary

EudraCT number	2012-005733-37
Trial protocol	CZ LT BG LV GB
Global end of trial date	25 August 2015

Results information

Result version number	v1 (current)
This version publication date	10 February 2019
First version publication date	10 February 2019

Trial information

Trial identification

Sponsor protocol code	SB2-G31-RA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01936181
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Samsung Bioepis Co., Ltd.
Sponsor organisation address	107, Cheomdan-daero, Incheon, Korea, Republic of,
Public contact	Quintiles Contact Centre, Quintiles Limited, +1 862 261 3634,
Scientific contact	Quintiles Contact Centre, Quintiles Limited, +1 862 261 3634,

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	25 August 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to demonstrate the equivalence of SB2 to Remicade at Week 30, in terms of the American College of Rheumatology 20% response criteria (ACR20) response rate in subjects with moderate to severe rheumatoid arthritis (RA) despite methotrexate (MTX) therapy.

Protection of trial subjects:

The study and clinical study protocols were reviewed and approved by Independent Ethics Committee (IEC) or Institutional Review Board (IRB).
This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (2008) and that are consistent with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines (ICH E6) and applicable local regulatory requirements and laws.
The nature and purpose of the study was fully explained to each subject and written informed consent was obtained at Screening from each subject before any study related procedures were performed. The consent documents for the study was reviewed and approved by the appropriate IEC or IRB prior to use.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 August 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	Poland: 122
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Bulgaria: 61
Country: Number of subjects enrolled	Czech Republic: 63
Country: Number of subjects enrolled	Latvia: 17
Country: Number of subjects enrolled	Lithuania: 39
Country: Number of subjects enrolled	Korea, Republic of: 59
Country: Number of subjects enrolled	Philippines: 16
Country: Number of subjects enrolled	Ukraine: 110
Country: Number of subjects enrolled	Romania: 37
Country: Number of subjects enrolled	Bosnia and Herzegovina: 58
Worldwide total number of subjects	584
EEA total number of subjects	341

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)	499
From 65 to 84 years	85
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 73 study centres were initiated in randomised, double-blind period. Among them, 57 study centres were participated for the transition-extension study period.

Pre-assignment

Screening details:

Participants who fulfilled the inclusion/exclusion criteria were randomly assigned to 1 of the 2 treatments of this study in randomised, double-blind period. At Week 54, subjects receiving Remicade® from the randomised, double-blind period were randomised again in a 1:1 ratio to either continue on Remicade (Remicade/Remicade).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	SB2 (proposed infliximab biosimilar)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	SB2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

3 mg/kg at Week 0, 2, 6 and then every 8 weeks until Week 46 (for the randomised, double-blind period) or Week 70 (for the transition-extension period); from Week 30 the dose level may have been increased step-wise by 1.5 mg/kg, up to a maximum of 7.5 mg/kg, every 8 weeks if the subject's RA symptoms were not well controlled by existing dose. If adequate response was achieved, subjects continued on the selected dose.

Arm title	Remicade

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Infliximab
Investigational medicinal product code	
Other name	Remicade
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

3 mg/kg at Week 0, 2, 6 and then every 8 weeks until Week 46 (for the randomised, double-blind period) or Week 70 (for the transition-extension period); from Week 30 the dose level may have been increased step-wise by 1.5 mg/kg, up to a maximum of 7.5 mg/kg, every 8 weeks if the subject's RA symptoms were not well controlled by existing dose. If adequate response was achieved, subjects continued on the selected dose.

Number of subjects in period 1	SB2 (proposed infliximab biosimilar)	Remicade
Started	291	293
Completed	227	225
Not completed	64	68
Physician decision	4	4
Consent withdrawn by subject	23	26
Adverse event, non-fatal	27	21
Subjects from Eastern Ukraine sites	4	4
Pregnancy	-	1
Lost to follow-up	-	1
Protocol deviation	1	5
Lack of efficacy	5	6

Period 2

Period 2 title	Transition-extension period
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	SB2/SB2

Arm description:

SB2 followed by SB2 from Week 54

Arm type	Experimental
Investigational medicinal product name	SB2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

3 mg/kg at Week 0, 2, 6 and then every 8 weeks until Week 46 (for the randomised, double-blind period) or Week 70 (for the transition-extension period); from Week 30 the dose level may have been increased step-wise by 1.5 mg/kg, up to a maximum of 7.5 mg/kg, every 8 weeks if the subject's RA symptoms were not well controlled by existing dose. If adequate response was achieved, subjects continued on the selected dose.

Arm title	Remicade/SB2

Arm description:

Remicade followed by SB2 from Week 54

Arm type	Experimental

Investigational medicinal product name	Infliximab
Investigational medicinal product code	
Other name	Remicade
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

3 mg/kg at Week 0, 2, 6 and then every 8 weeks until Week 46 (for the randomised, double-blind period) or Week 70 (for the transition-extension period); from Week 30 the dose level may have been increased step-wise by 1.5 mg/kg, up to a maximum of 7.5 mg/kg, every 8 weeks if the subject's RA symptoms were not well controlled by existing dose. If adequate response was achieved, subjects continued on the selected dose.

Investigational medicinal product name	SB2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

3 mg/kg at Week 0, 2, 6 and then every 8 weeks until Week 46 (for the randomised, double-blind period) or Week 70 (for the transition-extension period); from Week 30 the dose level may have been increased step-wise by 1.5 mg/kg, up to a maximum of 7.5 mg/kg, every 8 weeks if the subject's RA symptoms were not well controlled by existing dose. If adequate response was achieved, subjects continued on the selected dose.

Arm title	Remicade/Remicade

Arm description:

Remicade followed by Remicade from Week 54

Arm type	Active comparator
Investigational medicinal product name	Infliximab
Investigational medicinal product code	
Other name	Remicade
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

3 mg/kg at Week 0, 2, 6 and then every 8 weeks until Week 46 (for the randomised, double-blind period) or Week 70 (for the transition-extension period); from Week 30 the dose level may have been increased step-wise by 1.5 mg/kg, up to a maximum of 7.5 mg/kg, every 8 weeks if the subject's RA symptoms were not well controlled by existing dose. If adequate response was achieved, subjects continued on the selected dose.

Number of subjects in period 2[1]	SB2/SB2	Remicade/SB2	Remicade/Remicade
Started	201	94	101
Completed	186	88	96
Not completed	15	6	5
Physician decision	2	-	1
Consent withdrawn by subject	7	2	1
Adverse event, non-fatal	3	3	1
Lost to follow-up	3	1	2

Notes:

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

Justification: 227 subjects in SB2 treatment group and 225 subjects in the Remicade treatment group completed Week 54 of treatment. Among them, 201 subjects from the SB2 treatment group and 195 subjects from the Remicade®
treatment group were enrolled and re-randomised to the transition-extension period at Week 54.

Baseline characteristics

Reporting groups	
Reporting group title	SB2 (proposed infliximab biosimilar)
Reporting group description: -	
Reporting group title	Remicade
Reporting group description: -	

Reporting group values	SB2 (proposed infliximab biosimilar)	Remicade	Total
Number of subjects	291	293	584
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	51.6	52.6	
standard deviation	± 11.92	± 11.74	-
Gender categorical Units: Subjects			
Female	232	236	468
Male	59	57	116

End points

End points reporting groups	
Reporting group title	SB2 (proposed infliximab biosimilar)
Reporting group description: -	
Reporting group title	Remicade
Reporting group description: -	
Reporting group title	SB2/SB2
Reporting group description: SB2 followed by SB2 from Week 54	
Reporting group title	Remicade/SB2
Reporting group description: Remicade followed by SB2 from Week 54	
Reporting group title	Remicade/Remicade
Reporting group description: Remicade followed by Remicade from Week 54	

Primary: American College of Rheumatology 20% Response Criteria (ACR20)	
End point title	American College of Rheumatology 20% Response Criteria (ACR20)
End point description: Proportion of participants achieving clinical response according to the ACR20 criteria at Week 30	
End point type	Primary
End point timeframe: Week 30	

End point values	SB2 (proposed infliximab biosimilar)	Remicade		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231[1]	247[2]		
Units: percentage	148	163		

Notes:

[1] - Per-protocol Set 1

[2] - Per-protoco Set 1

Statistical analyses

Statistical analysis title	ACR20 Criteria at Week 30
Comparison groups	SB2 (proposed infliximab biosimilar) v Remicade
Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	equivalence[3]
Parameter estimate	Difference in proportion
Point estimate	-1.88

Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.26
upper limit	6.51

Notes:

[3] - - Equivalence margin: [-15%, 15%]

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Screening to Week 78	
Adverse event reporting additional description:	
Remicade group includes subjects who were treated with SB2 in the transition-extension period.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	SB2 (overall study period)
Reporting group description: -	
Reporting group title	Remicade (overall study period)
Reporting group description:	
- Remicade group includes subjects who are treated with SB2 in the transition-extension period.	

Serious adverse events	SB2 (overall study period)	Remicade (overall study period)	
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 290 (12.41%)	38 / 293 (12.97%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign Lung Neoplasm			
subjects affected / exposed	1 / 290 (0.34%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain Neoplasm			
subjects affected / exposed	1 / 290 (0.34%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast Cancer			
subjects affected / exposed	1 / 290 (0.34%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate Cancer			

subjects affected / exposed	1 / 290 (0.34%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal Cell Carcinoma			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign Salivary Gland Neoplasm			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lip And/Or Oral Cavity Cancer			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Device Damage			
subjects affected / exposed	1 / 290 (0.34%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic Reaction			
subjects affected / exposed	2 / 290 (0.69%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	2 / 290 (0.69%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic Shock			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Drug Hypersensitivity			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign Prostatic Hyperplasia			
subjects affected / exposed	1 / 290 (0.34%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometriosis			
subjects affected / exposed	1 / 290 (0.34%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian Cyst Torsion			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Major Depression			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic Disorder			

subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Lower Limb Fracture			
subjects affected / exposed	1 / 290 (0.34%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar Vertebral Fracture			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprosthetic Fracture			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib Fracture			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic Vertebral Fracture			
subjects affected / exposed	0 / 290 (0.00%)	2 / 293 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia Fracture			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina Unstable			
subjects affected / exposed	1 / 290 (0.34%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial Fibrillation			
subjects affected / exposed	1 / 290 (0.34%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Infarction			
subjects affected / exposed	1 / 290 (0.34%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Pectoris			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left Ventricular Failure			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericarditis			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Sciatica			
subjects affected / exposed	1 / 290 (0.34%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebrobasilar Insufficiency			
subjects affected / exposed	1 / 290 (0.34%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy Peripheral			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Thrombocytosis			
subjects affected / exposed	1 / 290 (0.34%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diverticulum			
subjects affected / exposed	1 / 290 (0.34%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus Paralytic			
subjects affected / exposed	1 / 290 (0.34%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Irritable Bowel Syndrome			
subjects affected / exposed	1 / 290 (0.34%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall haemorrhage			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal Perforation			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer haemorrhage			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary Gland Calculus			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Bile Duct Stone			
subjects affected / exposed	1 / 290 (0.34%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis Acute			
subjects affected / exposed	1 / 290 (0.34%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rheumatoid Arthritis			
subjects affected / exposed	4 / 290 (1.38%)	4 / 293 (1.37%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot Deformity			
subjects affected / exposed	1 / 290 (0.34%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral Disc Protrusion			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint Swelling			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Osteoarthritis			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovitis			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 290 (1.03%)	2 / 293 (0.68%)	
occurrences causally related to treatment / all	3 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 290 (0.34%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 290 (0.34%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium Difficile Colitis			
subjects affected / exposed	1 / 290 (0.34%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Bacterial			
subjects affected / exposed	1 / 290 (0.34%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomembranous Colitis			
subjects affected / exposed	1 / 290 (0.34%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			

subjects affected / exposed	1 / 290 (0.34%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft Tissue Infection			
subjects affected / exposed	1 / 290 (0.34%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculous Pleurisy			
subjects affected / exposed	1 / 290 (0.34%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	1 / 290 (0.34%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 290 (0.34%)	0 / 293 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis Bacterial			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic Foot Infection			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			

subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma Infection			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound Infection			
subjects affected / exposed	0 / 290 (0.00%)	1 / 293 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	SB2 (overall study period)	Remicade (overall study period)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	108 / 290 (37.24%)	104 / 293 (35.49%)	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	27 / 290 (9.31%)	14 / 293 (4.78%)	
occurrences (all)	32	15	
Aspartate Aminotransferase Increased			
subjects affected / exposed	16 / 290 (5.52%)	15 / 293 (5.12%)	
occurrences (all)	18	15	
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 290 (5.52%)	15 / 293 (5.12%)	
occurrences (all)	30	16	
Musculoskeletal and connective tissue disorders			

Rheumatoid Arthritis			
subjects affected / exposed	20 / 290 (6.90%)	12 / 293 (4.10%)	
occurrences (all)	26	16	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	26 / 290 (8.97%)	25 / 293 (8.53%)	
occurrences (all)	34	34	
Latent Tuberculosis			
subjects affected / exposed	24 / 290 (8.28%)	27 / 293 (9.22%)	
occurrences (all)	31	33	
Upper Respiratory Tract Infection			
subjects affected / exposed	13 / 290 (4.48%)	18 / 293 (6.14%)	
occurrences (all)	32	31	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 March 2013	• The PK population was clarified as the first 50% of the enrolled subjects. • The end of study was defined. • An assumption for sample size calculation was revised. • Details on IP preparation were added. • Blood volume to be collected and sample handling process for PK assessment was changed based on final decision of required blood volume and sample handling procedures. • Interim analyses for DSMB review were added. • Other administrative changes
28 June 2013	• The period of contraception after the last dose of IP was increased from 2 months to 6 months based on SmPC of Remicade® and MTX. • The sentence "If adequate response is achieved, subjects should be continued on the selected dose" was added in accordance with the SmPC of Remicade®. • The clinical chemistry parameters were updated. • Other administrative changes
22 August 2013	• The observation period for acute infusion-related reaction was added based on the SmPC of Remicade®. • The follow up action for IP discontinuation criteria was changed according to the SmPC of Remicade®.
11 April 2014	* Not submitted to the Philippines and the United Kingdom • The transition-extension period of SB2-G31-RA study was added to evaluate the safety and tolerability in subjects who transitioned to SB2 from Remicade® compared to subjects who maintained Remicade®. • Other administrative changes

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29042358

http://www.ncbi.nlm.nih.gov/pubmed/28957563

http://www.ncbi.nlm.nih.gov/pubmed/26318384