Clinical trial results:
A Randomised, Double-Blind, Parallel Group, Multicentre Clinical Study to Evaluate the Efficacy, Safety, Pharmacokinetics and Immunogenicity of SB4 Compared to Enbrel® in Subjects with Moderate to Severe Rheumatoid Arthritis despite Methotrexate Therapy

Summary

EudraCT number	2012-005026-30
Trial protocol	HU LT CZ BG PL
Global end of trial date	28 November 2014

Results information

Result version number	v1 (current)
This version publication date	07 February 2019
First version publication date	07 February 2019

Trial information

Trial identification

Sponsor protocol code	SB4-G31-RA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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 862261 3634,
Scientific contact	Quintiles Contact Centre, Quintiles Limited, +1 862261 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	28 November 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 November 2014
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 SB4 to Enbrel® at Week 24, in terms of American College of Rheumatology 20% response criteria (ACR 20) 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) for each study centre.
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 May 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	Colombia: 8
Country: Number of subjects enrolled	Korea, Republic of: 23
Country: Number of subjects enrolled	Mexico: 21
Country: Number of subjects enrolled	Ukraine: 121
Country: Number of subjects enrolled	Poland: 217
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Bulgaria: 50
Country: Number of subjects enrolled	Czech Republic: 92
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Lithuania: 53
Worldwide total number of subjects	596
EEA total number of subjects	423

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)	515
From 65 to 84 years	81
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants who fulfilled the inclusion/exclusion criteria were randomly assigned to 1 of the 2 treatments of this study.

Pre-assignment period milestones

Number of subjects started	777[1]
Number of subjects completed	596

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screening failure: 181

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: the Sponsor used data from 'Enrolled Set', not 'Randomised Set' to fill in 'Pre-assignment period' and 'Enrolled Set' was consisted of all subjects who provided informed consent for this study. Screened(Pre-assignment) subjects: 747, Randomised subjects: 544.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	SB4 (proposed etanercept biosimilar)

Arm description:

Presentation: prefilled syringe
Dose regimen: 50 mg once weekly
Mode of administration: subcutaneous injection

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

Dosage and administration details:

Dose regimen: 50 mg once weekly
Mode of administration: subcutaneous injection

Arm title	Enbrel

Arm description:

Presentation: prefilled syringe
Dose regimen: 50 mg once weekly
Mode of administration: subcutaneous injection

Arm type	Active comparator

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

Dosage and administration details:

Dose regimen: 50 mg once weekly
Mode of administration: subcutaneous injection

Number of subjects in period 1	SB4 (proposed etanercept biosimilar)	Enbrel
Started	299	297
Completed	259	246
Not completed	40	51
Adverse event, serious fatal	2	-
Physician decision	15	10
Consent withdrawn by subject	9	18
Adverse event, non-fatal	11	17
Lost to follow-up	1	3
Protocol deviation	1	-
Lack of efficacy	1	3

Baseline characteristics

Reporting groups	
Reporting group title	SB4 (proposed etanercept biosimilar)
Reporting group description:	
Presentation: prefilled syringe Dose regimen: 50 mg once weekly Mode of administration: subcutaneous injection	
Reporting group title	Enbrel
Reporting group description:	
Presentation: prefilled syringe Dose regimen: 50 mg once weekly Mode of administration: subcutaneous injection	

Reporting group values	SB4 (proposed etanercept biosimilar)	Enbrel	Total
Number of subjects	299	297	596
Age categorical Units: Subjects			
Less than 65 years	253	262	515
65 years or over	46	35	81
Age continuous Units: years			
arithmetic mean	52.1	51.6	
standard deviation	± 11.72	± 11.63	-
Gender categorical Units: Subjects			
Female	249	253	502
Male	50	44	94

End points

End points reporting groups

Reporting group title	SB4 (proposed etanercept biosimilar)
Reporting group description:	
Presentation: prefilled syringe Dose regimen: 50 mg once weekly Mode of administration: subcutaneous injection	
Reporting group title	Enbrel
Reporting group description:	
Presentation: prefilled syringe Dose regimen: 50 mg once weekly Mode of administration: subcutaneous injection	
Subject analysis set title	Per-protocol set 1
Subject analysis set type	Per protocol
Subject analysis set description:	
consists of all FAS subjects who complete the Week 24 visit and have an adherence(through Week 24) within the range 80–120% of both the expected number of IP injections and the expected sum of MTX doses without any major protocol deviations that affect the efficacy assessment.	
Subject analysis set title	Per-protocol set 2
Subject analysis set type	Per protocol
Subject analysis set description:	
consisted of all FAS subjects who completed the Week 52 visit and had an adherence (from baseline to Week 52) within the range 80-120% of both the expected number of IP injections and the expected sum of MTX doses without any major PDs that affected the efficacy assessment.	

Primary: ACR20 Response Rate at Week 24

End point title	ACR20 Response Rate at Week 24
End point description:	
End point type	Primary
End point timeframe:	
At week 24	

End point values	SB4 (proposed etanercept biosimilar)	Enbrel	Per-protocol set 1	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	247	236	483	
Units: number of subjects				
nymber ofsubjects achieving ACR20 response at Week	193	190	383	

Statistical analyses

Statistical analysis title	Equivalence test
Comparison groups	SB4 (proposed etanercept biosimilar) v Enbrel

Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Adjusted
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.15

Secondary: ACR20 Response Rate at Week 52

End point title	ACR20 Response Rate at Week 52
End point description:	
End point type	Secondary
End point timeframe:	
At Seek 52	

End point values	SB4 (proposed etanercept biosimilar)	Enbrel	Per-protocol set 2	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	224	216	440	
Units: number of subejcts achieving ACR20 respo				
Number of subejcts achieving ACR20 response	181	176	357	

Statistical analyses

Statistical analysis title	Equivalence test
Comparison groups	SB4 (proposed etanercept biosimilar) v Enbrel
Number of subjects included in analysis	440
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Adjusted
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.15

Adverse events

Adverse events information

Timeframe for reporting adverse events:

an onset date on or after the date of first dose of IP until the Follow-up Visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	SB4 (proposed etanercept biosimilar)

Reporting group description:

Safety Set: consisted of all subjects who received at least one dose of double-blind IP during the study phase

Reporting group title	Enbrel

Reporting group description:

Safety Set: consisted of all subjects who received at least one dose of double-blind IP during the study phase

Serious adverse events	SB4 (proposed etanercept biosimilar)	Enbrel	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 299 (6.02%)	15 / 297 (5.05%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	2	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ADENOCARCINOMA GASTRIC			
subjects affected / exposed	1 / 299 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
BREAST CANCER			
subjects affected / exposed	1 / 299 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG CANCER METASTATIC			
subjects affected / exposed	1 / 299 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INVASIVE DUCTAL BREAST CARCINOMA			

subjects affected / exposed	0 / 299 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
HYPERTENSIVE CRISIS			
subjects affected / exposed	0 / 299 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
DEVICE FAILURE			
subjects affected / exposed	1 / 299 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
OVARIAN CYST			
subjects affected / exposed	1 / 299 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UTERINE POLYP			
subjects affected / exposed	1 / 299 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VAGINAL PROLAPSE			
subjects affected / exposed	1 / 299 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
FEMORAL NECK FRACTURE			
subjects affected / exposed	0 / 299 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			

subjects affected / exposed	1 / 299 (0.33%)	0 / 297 (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 / 299 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIOPULMONARY FAILURE			
subjects affected / exposed	1 / 299 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
CORONARY ARTERY DISEASE			
subjects affected / exposed	0 / 299 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
SYNCOPE			
subjects affected / exposed	1 / 299 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
NEUTROPENIA			
subjects affected / exposed	0 / 299 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
CHORIORETINOPATHY			
subjects affected / exposed	0 / 299 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ENTEROCOLITIS			

subjects affected / exposed	0 / 299 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRITIS			
subjects affected / exposed	0 / 299 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	0 / 299 (0.00%)	1 / 297 (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 / 299 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLANGITIS			
subjects affected / exposed	1 / 299 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLECYSTITIS			
subjects affected / exposed	1 / 299 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLELITHIASIS			
subjects affected / exposed	1 / 299 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GALLBLADDER PERFORATION			
subjects affected / exposed	1 / 299 (0.33%)	0 / 297 (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			

PSORIASIS			
subjects affected / exposed	1 / 299 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
RHEUMATOID ARTHRITIS			
subjects affected / exposed	1 / 299 (0.33%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
STILL'S DISEASE ADULT ONSET			
subjects affected / exposed	1 / 299 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
LIVER ABSCESS			
subjects affected / exposed	1 / 299 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERITONITIS			
subjects affected / exposed	1 / 299 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
APPENDICITIS			
subjects affected / exposed	0 / 299 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			
subjects affected / exposed	0 / 299 (0.00%)	2 / 297 (0.67%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ERYSIPELAS			
subjects affected / exposed	0 / 299 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

PNEUMONIA			
subjects affected / exposed	0 / 299 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	SB4 (proposed etanercept biosimilar)	Enbrel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 299 (20.07%)	70 / 297 (23.57%)	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	18 / 299 (6.02%)	17 / 297 (5.72%)	
occurrences (all)	25	26	
General disorders and administration site conditions			
INJECTION SITE ERYTHEMA			
subjects affected / exposed	6 / 299 (2.01%)	33 / 297 (11.11%)	
occurrences (all)	16	85	
Infections and infestations			
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	24 / 299 (8.03%)	16 / 297 (5.39%)	
occurrences (all)	28	18	
NASOPHARYNGITIS			
subjects affected / exposed	15 / 299 (5.02%)	16 / 297 (5.39%)	
occurrences (all)	17	17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 December 2012	• Screening period was increased to 6 weeks. • Washout period was removed. • Potential benefits and risks of SB4 were added. • Additional example for subject withdrawal was added. • The number of permitted use of intra-articular injections was limited to 2. • The number of subjects being unblinded during the study was limited. • The DAS28 score calculation equation was changed. • The use of corticosteroid for prevention or treatment of any condition other than RA was allowed. • Questionnaires (subject pain assessment VAS, subject global assessment VAS, physician global assessment VAS, HAQ-DI) were replaced with different versions. • The method to assess the expectedness of an AE was added. • The condition as to when hospitalisation should be considered SAE was clarified. • Analysis sets were clarified. • Administrative changes were implemented, which included changes in the composition of the DSMB and changes in the address and contact information for Sponsor and study staff. • Clarifications and editorial changes were made throughout the protocol, as appropriate.
15 March 2013	• Administrative changes were implemented. • Clarifications and editorial changes were made throughout the protocol, as appropriate. • Duration of morning stiffness was removed from listing of continuous variables for consistency with the study design.
12 March 2014	• Coordinating Investigator for the study was designated. • Editorial changes were made for clarification throughout the protocol, as appropriate

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported