Clinical trial results:
A Randomised, Double-blind, Parallel Group, Multicentre Clinical Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacokinetics and Immunogenicity of SB5 Compared to Humira® in Subjects with Moderate to Severe Rheumatoid Arthritis despite Methotrexate Therapy

Summary

EudraCT number	2013-005013-13
Trial protocol	CZ LT PL BG
Global end of trial date	19 October 2015

Results information

Result version number	v1 (current)
This version publication date	02 November 2016
First version publication date	02 November 2016

Trial information

Trial identification

Sponsor protocol code	SB5-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, Yeonsu-gu, Incheon, Korea, Republic of, 21987
Public contact	Information Desk, Samsung Bioepis Co., Ltd. , +82 324553114, bioepisinfo@samsung.com
Scientific contact	Information Desk, Samsung Bioepis Co., Ltd. , +82 324553114, bioepisinfo@samsung.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	19 October 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 October 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to demonstrate the equivalence of SB5 to Humira® atWeek 24, in terms of 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 May 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 216
Country: Number of subjects enrolled	Bulgaria: 51
Country: Number of subjects enrolled	Czech Republic: 90
Country: Number of subjects enrolled	Lithuania: 35
Country: Number of subjects enrolled	Bosnia and Herzegovina: 65
Country: Number of subjects enrolled	Korea, Republic of: 87
Worldwide total number of subjects	544
EEA total number of subjects	392

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)	475
From 65 to 84 years	69
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	747[1]
Number of subjects completed	544

Pre-assignment subject non-completion reasons

Reason: Number of subjects	subject lost to follow up: 3
Reason: Number of subjects	Consent withdrawn by subject: 33
Reason: Number of subjects	Adverse event, non-fatal: 1
Reason: Number of subjects	Other: 6
Reason: Number of subjects	does not meet Inclusion/Exclusion Criteria: 160

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 'Randomised Set', not 'Enrolled Set' to fill in 'Population of trial subjects' section, thus the total worldwide subject number is same with the overall number of baseline participants.
Screened(Pre-assignment) subjects: 747, Randomised subjects: 544.

Period 1

Period 1 title	Randomised, Double-blind
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	SB5 (Proposed Biosimilar to Adalimumab)

Arm description:

SB5 40 mg every other week via subcutaneous injection SB5 (proposed biosimilar to adalimumab)

Arm type	Experimental
Investigational medicinal product name	SB5 (proposed adalimumab biosimilar)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects self-administered 40 mg of either SB5 or EU-sourced Humira® every other week, via subcutaneous injection, up to Week 50 (a total of 26 administrations of IP) unless they withdrew early from the study.

Arm title	Humira (Adalimumab)

Arm description:

Humira 40 mg every other week via subcutaneous injection to Week 24, then randomised again in a 1:1 ratio to either continue on Humira® 40 mg (Humira®/Humira®) or be transitioned to SB5 40 mg (Humira®/SB5) every other week up to Week 50.

Arm type	Active comparator
Investigational medicinal product name	Humira®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects self-administered 40 mg of either SB5 or EU-sourced Humira® every other week, via subcutaneous injection, up to Week 50 (a total of 26 administrations of IP) unless they withdrew early from the study.

Number of subjects in period 1	SB5 (Proposed Biosimilar to Adalimumab)	Humira (Adalimumab)
Started	271	273
Completed	254	254
Not completed	17	19
Consent withdrawn by subject	11	8
Adverse event, non-fatal	2	9
Other	3	-
Lack of efficacy	1	2

Period 2

Period 2 title	Transition-extension
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	SB5 (Proposed Biosimilar to Adalimumab)

Arm description:

SB5 40 mg every other week via subcutaneous injection SB5 (proposed biosimilar to adalimumab)

Arm type	Experimental
Investigational medicinal product name	SB5 (proposed adalimumab biosimilar)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects self-administered 40 mg of either SB5 or EU-sourced Humira® every other week, via subcutaneous injection, up to Week 50 (a total of 26 administrations of IP) unless they withdrew early from the study.

Arm title	Humira (Adalimumab), Switch to SB5

Arm description:	
From Week 24, SB5 40 mg (Humira®/SB5) every other week up to Week 50.	
Arm type	Experimental
Investigational medicinal product name	SB5 (proposed adalimumab biosimilar)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use
Dosage and administration details:	
Subjects self-administered 40 mg of either SB5 or EU-sourced Humira® every other week, via subcutaneous injection, up to Week 50 (a total of 26 administrations of IP) unless they withdrew early from the study.	
Arm title	Humira (Adalimumab), Continue as Humira
Arm description:	
From Week 24, Humira® 40 mg (Humira®/Humira®) every other week up to Week 50.	
Arm type	Active comparator
Investigational medicinal product name	Humira®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use
Dosage and administration details:	
Subjects self-administered 40 mg of either SB5 or EU-sourced Humira® every other week, via ubcutaneous injection, up to Week 50 (a total of 26 administrations of IP) unless they withdrew early from the study.	

Number of subjects in period 2	SB5 (Proposed Biosimilar to Adalimumab)	Humira (Adalimumab), Switch to SB5	Humira (Adalimumab), Continue as Humira
Started	254	125	129
Completed	248	117	124
Not completed	6	8	5
Consent withdrawn by subject	2	4	1
Adverse event, non-fatal	2	2	3
Other	1	1	-
Lost to follow-up	1	-	-
Lack of efficacy	-	1	1

Baseline characteristics

Reporting groups	
Reporting group title	SB5 (Proposed Biosimilar to Adalimumab)
Reporting group description:	
SB5 40 mg every other week via subcutaneous injection SB5 (proposed biosimilar to adalimumab)	
Reporting group title	Humira (Adalimumab)
Reporting group description:	
Humira 40 mg every other week via subcutaneous injection to Week 24, then randomised again in a 1:1 ratio to either continue on Humira® 40 mg (Humira®/Humira®) or be transitioned to SB5 40 mg (Humira®/SB5) every other week up to Week 50.	

Reporting group values	SB5 (Proposed Biosimilar to Adalimumab)	Humira (Adalimumab)	Total
Number of subjects	271	273	544
Age categorical Units: Subjects			
Adults (18-64 years)	242	233	475
From 65-84 years	29	40	69
Age continuous Units: years			
median	51	55	
standard deviation	± 12.67	± 11.91	-
Gender categorical Units: Subjects			
Female	217	224	441
Male	54	49	103

End points

End points reporting groups

Reporting group title	SB5 (Proposed Biosimilar to Adalimumab)
Reporting group description:	
SB5 40 mg every other week via subcutaneous injection SB5 (proposed biosimilar to adalimumab)	
Reporting group title	Humira (Adalimumab)
Reporting group description:	
Humira 40 mg every other week via subcutaneous injection to Week 24, then randomised again in a 1:1 ratio to either continue on Humira® 40 mg (Humira®/Humira®) or be transitioned to SB5 40 mg (Humira®/SB5) every other week up to Week 50.	
Reporting group title	SB5 (Proposed Biosimilar to Adalimumab)
Reporting group description:	
SB5 40 mg every other week via subcutaneous injection SB5 (proposed biosimilar to adalimumab)	
Reporting group title	Humira (Adalimumab), Switch to SB5
Reporting group description:	
From Week 24, SB5 40 mg (Humira®/SB5) every other week up to Week 50.	
Reporting group title	Humira (Adalimumab), Continue as Humira
Reporting group description:	
From Week 24, Humira® 40 mg (Humira®/Humira®) every other week up to Week 50.	

Primary: American College of Rheumatology 20% Response Criteria (ACR20) response rate in subjects

End point title	American College of Rheumatology 20% Response Criteria (ACR20) response rate in subjects
End point description:	
End point type	Primary
End point timeframe:	
at Week 24	

End point values	SB5 (Proposed Biosimilar to Adalimumab)	Humira (Adalimumab)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239	237		
Units: number	173	171		

Statistical analyses

Statistical analysis title	Equivalence test
Comparison groups	Humira (Adalimumab) v SB5 (Proposed Biosimilar to Adalimumab)

Number of subjects included in analysis	476
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Risk difference (RD)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.15
Variability estimate	Standard error of the mean

Secondary: American College of Rheumatology 20% Response Criteria (ACR20) response rate in subjects

End point title	American College of Rheumatology 20% Response Criteria (ACR20) response rate in subjects
End point description:	
End point type	Secondary
End point timeframe: at Week 52	

End point values	SB5 (Proposed Biosimilar to Adalimumab)	Humira (Adalimumab), Switch to SB5	Humira (Adalimumab), Continue as Humira	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	212	106	111	
Units: number	163	86	79	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
at Week 24	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	SB5 (Proposed Biosimilar to Adalimumab)
Reporting group description:	
SB5 40 mg every other week via subcutaneous injection SB5 (proposed biosimilar to adalimumab)	
Reporting group title	Humira (Adalimumab)
Reporting group description:	
Humira 40 mg every other week via subcutaneous injection to Week 24, then randomised again in a 1:1 ratio to either continue on Humira® 40 mg (Humira®/Humira®) or be transitioned to SB5 40 mg (Humira®/SB5) every other week up to Week 50.	

Serious adverse events	SB5 (Proposed Biosimilar to Adalimumab)	Humira (Adalimumab)	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 268 (3.36%)	16 / 273 (5.86%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Small cell lung cancer			
subjects affected / exposed	1 / 268 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma multiforme			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoma			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to spine			

subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seminoma			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	
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 / 268 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Nervous system disorders			
Lumber radiculopathy			
subjects affected / exposed	1 / 268 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	
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			
Eosinophilia			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal oedema			
subjects affected / exposed	1 / 268 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Femoral hernia, obstructive			
subjects affected / exposed	1 / 268 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 268 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal inflammation			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	1 / 268 (0.37%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Escherichia urinary tract infection			
subjects affected / exposed	1 / 268 (0.37%)	0 / 273 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 268 (0.37%)	0 / 273 (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	0 / 268 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	
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 / 268 (0.00%)	2 / 273 (0.73%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary tract infection			
subjects affected / exposed	0 / 268 (0.00%)	1 / 273 (0.37%)	
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	SB5 (Proposed Biosimilar to Adalimumab)	Humira (Adalimumab)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 268 (13.06%)	44 / 273 (16.12%)	
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 268 (4.10%)	14 / 273 (5.13%)	
occurrences (all)	13	15	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	24 / 268 (8.96%)	30 / 273 (10.99%)	
occurrences (all)	27	34	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported