



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 | | | | |
| Number of subjects 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 | |
| GASTROESOPHAGEAL 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 | <ul style="list-style-type: none">• 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 | <ul style="list-style-type: none">• 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 | <ul style="list-style-type: none">• 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