



Clinical trial results:

A multicenter, randomized, double-blind, phase III trial to evaluate the safety, immunogenicity, and efficacy of MSB11022 compared with Humira® in patients with moderately to severely active rheumatoid arthritis

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2016-002852-26 |
| Trial protocol | CZ GB HU DE LT BG |
| Global end of trial date | 27 August 2018 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 |
| This version publication date | 13 July 2019 |
| First version publication date | 13 July 2019 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | MS200588-0004 |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03052322 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Fresenius Kabi SwissBioSim GmbH |
| Sponsor organisation address | Route de Crassier 23 – Bâtiment A3, Eysins, Switzerland, 1262 |
| Public contact | Andrea Rossi, Fresenius Kabi SwissBioSim GmbH, +41 79 3054454, andrea.rossi@fresenius-kabi.com |
| Scientific contact | Andrea Rossi, Fresenius Kabi SwissBioSim GmbH, +41 79 3054454, andrea.rossi@fresenius-kabi.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 | 27 August 2018 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 August 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study is to evaluate the safety profile of MSB11022- modified buffer and stabilizer compared to Humira® in subjects with moderately to severely active Rheumatoid Arthritis (RA).

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 31 January 2017 |
| 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 | Bulgaria: 61 |
| Country: Number of subjects enrolled | Czech Republic: 52 |
| Country: Number of subjects enrolled | Germany: 15 |
| Country: Number of subjects enrolled | Hungary: 23 |
| Country: Number of subjects enrolled | Poland: 135 |
| Country: Number of subjects enrolled | United Kingdom: 2 |
| Worldwide total number of subjects | 288 |
| EEA total number of subjects | 288 |

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) | 241 |
| From 65 to 84 years | 47 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were randomized in 1:1 ratio to receive either MSB11022 or EU-Humira for 48 weeks.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|----------|
| Arm title | MSB11022 |
|------------------|----------|

Arm description:

Subjects received MSB11022 subcutaneously at dose of 40 milligram (mg) every other week from Day 1 up to Week 48.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | MSB11022 |
| Investigational medicinal product code | MSB11022 |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects received MSB11022 subcutaneously at dose of 40 milligram (mg) every other week from Day 1 up to Week 48.

| | |
|------------------|-----------|
| Arm title | EU-Humira |
|------------------|-----------|

Arm description:

Subjects received EU-Humira subcutaneously at dose of 40 mg every other week from Day 1 up to Week 48.

| | |
|--|------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | EU-Humira |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects received EU-Humira subcutaneously at dose of 40 mg every other week from Day 1 up to Week 48.

| Number of subjects in period 1 | MSB11022 | EU-Humira |
|---------------------------------------|----------|-----------|
| Started | 143 | 145 |
| Completed | 122 | 113 |
| Not completed | 21 | 32 |
| Consent withdrawn by subject | 10 | 9 |
| Adverse events | 6 | 13 |
| Other un-specified | 1 | 2 |
| Death | - | 2 |
| Lost to follow-up | 2 | 4 |
| Lack of efficacy | 1 | 2 |
| Protocol deviation | 1 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | MSB11022 |
|-----------------------|----------|

Reporting group description:

Subjects received MSB11022 subcutaneously at dose of 40 milligram (mg) every other week from Day 1 up to Week 48.

| | |
|-----------------------|-----------|
| Reporting group title | EU-Humira |
|-----------------------|-----------|

Reporting group description:

Subjects received EU-Humira subcutaneously at dose of 40 mg every other week from Day 1 up to Week 48.

| Reporting group values | MSB11022 | EU-Humira | Total |
|------------------------|----------|-----------|-------|
| Number of subjects | 143 | 145 | 288 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|--------|--------|-----|
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | 53.9 | 54.0 | |
| standard deviation | ± 11.9 | ± 11.0 | - |
| Sex: Female, Male | | | |
| Units: Subjects | | | |
| Female | 108 | 119 | 227 |
| Male | 35 | 26 | 61 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 2 | 2 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 |
| White | 142 | 143 | 285 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 1 | 0 | 1 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 3 | 1 | 4 |
| Not Hispanic or Latino | 140 | 144 | 284 |
| Unknown or Not Reported | 0 | 0 | 0 |

End points

End points reporting groups

| | |
|---|-----------|
| Reporting group title | MSB11022 |
| Reporting group description: Subjects received MSB11022 subcutaneously at dose of 40 milligram (mg) every other week from Day 1 up to Week 48. | |
| Reporting group title | EU-Humira |
| Reporting group description: Subjects received EU-Humira subcutaneously at dose of 40 mg every other week from Day 1 up to Week 48. | |

Primary: Percentage of Subjects with Treatment-emergent Adverse Events of Special Interest (AESI)

| | |
|--|---|
| End point title | Percentage of Subjects with Treatment-emergent Adverse Events of Special Interest (AESI) ^[1] |
| End point description: Adverse event (AE) was defined as any untoward medical occurrence in subjects, which does not necessarily have causal relationship with treatment. Term TEAE is defined as AEs starting/worsening after first intake of the study drug. Hypersensitivity was the pre-defined TEAE of special Interest for this study. The percentage of subjects with treatment emergent AESIs (hypersensitivity) were reported. The Safety Analysis Set included all randomized subjects who received at least one dose of study treatment. | |
| End point type | Primary |
| End point timeframe: Up to Week 52 | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was planned to be reported for this endpoint.

| End point values | MSB11022 | EU-Humira | | |
|----------------------------------|------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 143 | 145 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 4.2 (1.6 to 8.9) | 5.5 (2.4 to 10.6) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved American College of Rheumatology 20 Response (ACR20) at Week 12

| | |
|--|---|
| End point title | Percentage of Subjects Who Achieved American College of Rheumatology 20 Response (ACR20) at Week 12 |
| End point description: ACR 20 Response: ≥ 20 percent improvement in swollen joint count (66 joints) & tender joint count (68 joints) & ≥ 20 percent improvement in 3 of following 5 assessments: patient's assessment of pain using Visual Analog Scale (VAS) ; 0-10 millimeter [mm], 0=no pain & 10=worst possible pain), patient's global assessment of disease activity by using VAS (scale ranges from 0 to 100 mm, [0 mm=no pain & | |

100 mm=worst possible pain]), physician's global assessment of disease activity using VAS, subjects's assessment of physical function measured by Health Assessment Questionnaire-Disability Index (HAQ-DI, defined as a 20-question instrument assessing 8 functional areas). Derived HAQ-DI ranges from 0= no difficulty & 3= inability to perform task) & acute-phase marker. Intent-To-Treat Analysis Set included all subjects randomly allocated to treatment, based on intent to treat "as randomized" principle. Here "Number of subjects analyzed" signifies those who were evaluable for this endpoint.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 12 | |

| End point values | MSB11022 | EU-Humira | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 142 | 141 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | 79.6 (72.0 to 85.9) | 80.9 (73.4 to 86.9) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Positive Anti-Drug Antibodies (ADAs) Status to Adalimumab

| | |
|-----------------|---|
| End point title | Percentage of Subjects with Positive Anti-Drug Antibodies (ADAs) Status to Adalimumab |
|-----------------|---|

End point description:

Percentage of subjects with positive anti-Drug antibodies (ADAs) status to Adalimumab were reported. The Safety Analysis Set included all randomized subjects who received at least one dose of study treatment. Here "n" signifies those subjects who were evaluable for this endpoint at specified time points.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 2, 4, 12, 24, 36 and 52 | |

| End point values | MSB11022 | EU-Humira | | |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 143 | 145 | | |
| Units: Percentage of Subjects | | | | |
| number (not applicable) | | | | |
| Baseline (n= 142, 144) | 7.7 | 4.2 | | |
| Week 2 (n= 143, 145) | 20.3 | 15.2 | | |
| Week 4 (n= 141, 141) | 29.8 | 21.3 | | |
| Week 12 (n= 142, 140) | 54.2 | 48.6 | | |
| Week 24 (n= 139, 133) | 71.9 | 61.7 | | |
| Week 36 (n= 124, 121) | 66.9 | 65.3 | | |
| Week 52 (n= 120, 119) | 60.8 | 62.2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-Drug Antibodies (ADAs) Titer Levels for Adalimumab

| | |
|-----------------|---|
| End point title | Anti-Drug Antibodies (ADAs) Titer Levels for Adalimumab |
|-----------------|---|

End point description:

Titer was defined as the degree to which the antibody-serum sample could be diluted and still contained detectable amounts of antibody. Anti-Drug Antibodies (ADAs) Titer levels for adalimumab were reported. Data was collected using validated bioanalytical method. The Safety Analysis Set included all randomized subjects who received at least one dose of study treatment. Here "number of subject analyzed" signifies those who were evaluable for this endpoint and "n" signifies those subjects who were evaluable for this endpoint at specified time points.

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|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 2, 4, 12, 24, 36 and 52

| End point values | MSB11022 | EU-Humira | | |
|-------------------------------|-------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 115 | 104 | | |
| Units: Titer | | | | |
| median (full range (min-max)) | | | | |
| Baseline (n= 11, 6) | 4.0 (1 to 512) | 1.5 (1 to 8) | | |
| Week 2 (n= 29, 22) | 4.0 (1 to 32768) | 12.0 (1 to 1024) | | |
| Week 4 (n= 42, 30) | 6.0 (1 to 16384) | 6.0 (1 to 512) | | |
| Week 12 (n= 77, 68) | 16.0 (1 to 4096) | 16.0 (1 to 16384) | | |
| Week 24 (n= 100, 82) | 16.0 (1 to 32768) | 24.0 (1 to 131072) | | |
| Week 36 (n= 83, 79) | 16.0 (1 to 32768) | 16.0 (1 to 131072) | | |
| Week 52 (n= 73, 74) | 16.0 (1 to 16384) | 12.0 (1 to 32768) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Confirmed Neutralizing Antibodies (NAb) Status to Adalimumab

| | |
|-----------------|---|
| End point title | Percentage of Subjects with Confirmed Neutralizing Antibodies |
|-----------------|---|

End point description:

Percentage of subjects with confirmed neutralizing antibodies status to Adalimumab were reported. The Safety Analysis Set included all randomized subjects who received at least one dose of study treatment. Here "Number of subjects analyzed" signifies those subjects who were evaluable for this endpoint and "n" signifies those subjects who were evaluable for this endpoint at specified time points.

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|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 2, 4, 12, 24, 36 and 52

| End point values | MSB11022 | EU-Humira | | |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 115 | 104 | | |
| Units: Percentage of Subjects | | | | |
| number (not applicable) | | | | |
| Baseline (n= 11, 6) | 45.5 | 50.0 | | |
| Week 2 (n= 29, 22) | 31.0 | 40.9 | | |
| Week 4 (n= 42, 30) | 33.3 | 30.0 | | |
| Week 12 (n= 77, 68) | 33.8 | 38.2 | | |
| Week 24 (n= 100, 82) | 27.0 | 29.3 | | |
| Week 36 (n= 83, 79) | 24.1 | 29.1 | | |
| Week 52 (n= 73, 74) | 32.9 | 39.2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved American College of Rheumatology 20 (ACR20) Response at Week 2, 4, 8, 24 and 52

| | |
|-----------------|---|
| End point title | Percentage of Subjects Who Achieved American College of Rheumatology 20 (ACR20) Response at Week 2, 4, 8, 24 and 52 |
|-----------------|---|

End point description:

ACR 20 Response: defined as greater than or equal to (\geq) 20 percent improvement in swollen joint count (66 joints) and tender joint count (68 joints) and \geq 20 percent improvement in 3 of following 5 assessments: patient's assessment of pain using Visual Analog Scale (VAS ; 0-10 millimeter [mm], 0 mm=no pain and 10 mm=worst possible pain), patient's global assessment of disease activity by using VAS (scale ranges from 0 mm to 100 mm, [0 mm=no pain to 100 mm=worst possible pain]), physician's global assessment of disease activity using VAS, subjects's assessment of physical function measured by Health Assessment Questionnaire-Disability Index (HAQ-DI, defined as a 20-question instrument assessing 8 functional areas). derived HAQ-DI ranges from 0, indicating no difficulty, to 3, indicating inability to perform a task in that area) and acute-phase marker (CRP). ITT Analysis Set was used. Here "n" signifies those subjects who were evaluable for this endpoint at specified time points.

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|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 2, 4, 8, 24 and 52

| End point values | MSB11022 | EU-Humira | | |
|----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 143 | 145 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| Week 2 (n= 143, 145) | 30.0 (22.55 to 38.32) | 29.7 (22.36 to 37.80) | | |
| Week 4 (n= 142, 144) | 52.1 (43.58 to 60.56) | 52.8 (44.29 to 61.15) | | |
| Week 8 (n= 142, 144) | 71.1 (62.93 to 78.42) | 72.9 (64.89 to 79.98) | | |
| Week 24 (n= 139, 133) | 88.5 (81.98 to 93.28) | 83.3 (75.86 to 89.25) | | |
| Week 52 (n= 122, 119) | 81.8 (73.78 to 88.24) | 86.4 (78.92 to 92.05) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved American College of Rheumatology 50 (ACR50) Response at Week 2, 4, 8, 12, 24 and 52

| | |
|-----------------|---|
| End point title | Percentage of Subjects Who Achieved American College of Rheumatology 50 (ACR50) Response at Week 2, 4, 8, 12, 24 and 52 |
|-----------------|---|

End point description:

ACR 50 Response is defined as greater than or equal to (\geq) 50 percent improvement in swollen joint count (66 joints) and tender joint count (68 joints) and \geq 50 percent improvement in 3 of following 5 assessments: patient's assessment of pain using Visual Analog Scale (VAS ; 0-10 millimeter [mm], 0 mm=no pain and 10 mm=worst possible pain), patient's global assessment of disease activity by using VAS (scale ranges from 0 mm to 100 mm, [0 mm=no pain to 100 mm=worst possible pain]), physician's global assessment of disease activity using VAS, subjects's assessment of physical function measured by Health Assessment Questionnaire-Disability Index (HAQ-DI, defined as a 20-question instrument assessing 8 functional areas). derived HAQ-DI ranges from 0, indicating no difficulty, to 3, indicating inability to perform a task in that area) and acute-phase marker (CRP). ITT Analysis Set was used. Here "n" signifies those subjects who were evaluable for this endpoint at specified time points.

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|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 2, 4, 8, 12, 24 and 52

| End point values | MSB11022 | EU-Humira | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 143 | 145 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| Week 2 (n= 143, 145) | 6.4 (2.9 to 11.9) | 6.2 (2.9 to 11.5) | | |
| Week 4 (n= 142, 144) | 17.6 (11.7 to 24.9) | 19.4 (13.3 to 26.9) | | |
| Week 8 (n= 142, 144) | 40.8 (32.7 to 49.4) | 34.7 (26.9 to 43.1) | | |

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|-----------------------|---------------------|---------------------|--|--|
| Week 12 (n= 142, 141) | 54.2 (45.7 to 62.6) | 51.1 (42.5 to 59.6) | | |
| Week 24 (n= 139, 133) | 65.5 (56.9 to 73.3) | 60.6 (51.7 to 68.9) | | |
| Week 52 (n= 122, 119) | 64.5 (55.3 to 72.9) | 66.1 (56.8 to 74.6) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved American College of Rheumatology 70 (ACR70) Response at Week 2, 4, 8, 12, 24 and 52

| | |
|-----------------|---|
| End point title | Percentage of Subjects Who Achieved American College of Rheumatology 70 (ACR70) Response at Week 2, 4, 8, 12, 24 and 52 |
|-----------------|---|

End point description:

ACR 70 Response is defined as greater than or equal to (\geq) 70 percent improvement in swollen joint count (66 joints) and tender joint count (68 joints) and \geq 70 percent improvement in 3 of following 5 assessments: patient's assessment of pain using Visual Analog Scale (VAS ; 0-10 millimeter [mm], 0 mm=no pain and 10 mm=worst possible pain), patient's global assessment of disease activity by using VAS (scale ranges from 0 mm to 100 mm, [0 mm=no pain to 100 mm=worst possible pain]), physician's global assessment of disease activity using VAS, subjects's assessment of physical function measured by Health Assessment Questionnaire-Disability Index (HAQ-DI, defined as a 20-question instrument assessing 8 functional areas). derived HAQ-DI ranges from 0, indicating no difficulty, to 3, indicating inability to perform a task in that area) and acute-phase marker (CRP). ITT Analysis Set was used. Here "n" signifies those subjects who were evaluable for this endpoint at specified time points.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 2, 4, 8, 12, 24 and 52

| End point values | MSB11022 | EU-Humira | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 143 | 145 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| Week 2 (n= 143, 145) | 0.7 (0.0 to 3.9) | 0.7 (0.0 to 3.8) | | |
| Week 4 (n= 142, 144) | 4.9 (2.00 to 9.9) | 2.8 (0.8 to 6.9) | | |
| Week 8 (n= 142, 144) | 14.8 (9.4 to 21.7) | 12.5 (7.6 to 19.0) | | |
| Week 12 (n= 142, 141) | 26.8 (19.7 to 34.8) | 19.9 (13.6 to 27.4) | | |
| Week 24 (n= 139, 133) | 33.8 (26.0 to 42.3) | 35.6 (27.5 to 44.4) | | |
| Week 52 (n= 122, 119) | 39.7 (30.9 to 48.9) | 42.4 (33.3 to 51.8) | | |

Statistical analyses

Secondary: Change from Baseline in Disease Activity Score Based on a 28 Joint Count- Erythrocyte Sedimentation Rate (DAS28-ESR) Score at Week 2, 4, 8, 12, 24 and 52

| | |
|-----------------|---|
| End point title | Change from Baseline in Disease Activity Score Based on a 28 Joint Count- Erythrocyte Sedimentation Rate (DAS28-ESR) Score at Week 2, 4, 8, 12, 24 and 52 |
|-----------------|---|

End point description:

DAS calculated on 28 joints is composite score derived from 4 measures: number of swollen joints, number of tender joints, ESR, Patient's Global Assessment of Disease Activity on VAS. Overall DAS28 was derived using following formulas from DAS28: $DAS28 = 0.56 \times \sqrt{TJC28} + 0.28 \times \sqrt{SJC28} + 0.014 \times GH + 0.70 \times \ln(ESR)$. Where: TJC28 = 28 joint count for tenderness, SJC28 = 28 joint count for swelling, $\ln(ESR)$ = natural log of ESR, GH = general health component of DAS (ie, Patient's Global Assessment of Disease Activity, assessed using scale of 1-100 where 100 is maximal activity; For analyses, GH divided by 10 & converted to a 0.5 scale, i.e., 0, 0.5, 1, 1.5. DAS28-ESR of >5.1 implies active disease, <3.2 low disease activity, & <2.6 remission. Change of 1.2 (twice measurement error) = significant change of disease activity state. Overall score ranges from 0-10 where higher score means more severe disease. ITT Analysis Set used. Here "n" = subjects evaluable for this endpoint at specified time points.

| | |
|----------------------|---------------------------------------|
| End point type | Secondary |
| End point timeframe: | Baseline, Week 2, 4, 8, 12, 24 and 52 |

| End point values | MSB11022 | EU-Humira | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 143 | 145 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change at Week 2 (n= 140, 145) | -0.9 (± 0.9) | -0.7 (± 0.9) | | |
| Change at Week 4 (n= 141, 144) | -1.4 (± 1.1) | -1.2 (± 1.0) | | |
| Change at Week 8 (n= 142, 144) | -1.9 (± 0.9) | -1.7 (± 1.1) | | |
| Change at Week 12 (n= 142, 141) | -2.4 (± 1.1) | -2.1 (± 1.2) | | |
| Change at Week 24 (n= 138, 132) | -2.7 (± 1.0) | -2.3 (± 1.2) | | |
| Change at Week 52 (n= 121, 118) | -2.8 (± 1.1) | -2.5 (± 1.1) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Disease Activity Score Based on 28-joints Count- Erythrocyte Sedimentation Rate (DAS28-ESR) low Disease Activity and Remission at Week 2, 4, 8, 12, 24, and 52

| | |
|-----------------|--|
| End point title | Percentage of Subjects with Disease Activity Score Based on 28-joints Count- Erythrocyte Sedimentation Rate (DAS28-ESR) low Disease Activity and Remission at Week 2, 4, 8, 12, 24, and 52 |
|-----------------|--|

End point description:

Disease Activity Score calculated on 28 joints is composite score derived from 4 measures: number of swollen joints (out of 28), -number of tender joints (out of 28), -Erythrocyte sedimentation rate (ESR), - Patient's Global Assessment of Disease Activity on visual analog scale (VAS). Overall disease activity

score DAS28 was derived using following formulas from DAS28:

$DAS28 = 0.56 \times \sqrt{(TJC28)} + 0.28 \times \sqrt{(SJC28)} + 0.014 \times GH + 0.70 \times \ln(ESR)$. Where: -TJC28 = 28 joint count for tenderness, -SJC28 = 28 joint count for swelling, -ln(ESR) = natural logarithm of ESR, -GH = general health component of DAS (ie, Patient's Global Assessment of Disease Activity, assessed using scale of 1 to 100 where 100 is maximal activity; For analyses, GH was divided by 10 and converted to a 0.5 scale, i.e., 0, 0.5, 1, 1.5. DAS28-ESR of >5.1 implies active disease, <3.2 low disease activity, and <2.6 remission. ITT Analysis Set used. Here "n" = subjects who were evaluable for this endpoint at

| | |
|------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 2, 4, 8, 12, 24, and 52 | |

| End point values | MSB11022 | EU-Humira | | |
|---|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 143 | 145 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| Low Disease Activity: Week 2 (n= 143, 145) | 10.0 (5.6 to 16.2) | 8.3 (4.4 to 14.0) | | |
| Low Disease Activity: Week 4 (n= 142, 144) | 20.6 (14.2 to 28.2) | 16.0 (10.4 to 23.0) | | |
| Low Disease Activity: Week 8 (n= 142, 144) | 33.1 (25.4 to 41.5) | 33.3 (25.7 to 41.7) | | |
| Low Disease Activity: Week 12 (n= 142, 141) | 46.5 (38.1 to 55.0) | 42.6 (34.3 to 51.2) | | |
| Low Disease Activity: Week 24 (n= 139, 133) | 55.1 (46.4 to 63.5) | 53.8 (44.9 to 62.5) | | |
| Low Disease Activity: Week 52 (n= 122, 119) | 57.0 (47.7 to 65.9) | 56.8 (47.3 to 65.9) | | |
| Remission: Week 2 (n= 143, 145) | 3.6 (1.2 to 8.1) | 2.1 (0.4 to 5.9) | | |
| Remission: Week 4 (n= 142, 144) | 7.8 (3.9 to 13.5) | 6.9 (3.4 to 12.4) | | |
| Remission: Week 8 (n= 142, 144) | 18.3 (12.3 to 25.7) | 16.0 (10.4 to 23.0) | | |
| Remission: Week 12 (n= 142, 141) | 29.6 (22.2 to 37.8) | 24.1 (17.3 to 32.0) | | |
| Remission: Week 24 (n= 139, 133) | 31.2 (23.6 to 39.6) | 34.1 (26.1 to 42.8) | | |
| Remission: Week 52 (n= 122, 119) | 40.5 (31.7 to 49.8) | 36.4 (27.8 to 45.8) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Simplified Disease Activity Index (SDAI) Total Score at Week 2, 4, 8, 12, 24, and 52

| | |
|-----------------|--|
| End point title | Change from Baseline in Simplified Disease Activity Index (SDAI) Total Score at Week 2, 4, 8, 12, 24, and 52 |
|-----------------|--|

End point description:

SDAI is numerical sum of 5 parameters: tender & swollen joint count, Patient's & Physician's Global Assessment of Disease Activity (VAS) & level of C-reactive protein (CRP) (mg/dL), normal <1 mg/dL. SDAI was calculated based on following formula: $SDAI = 28 \text{ joint count for swelling (SJC28)} + 28 \text{ joint for tenderness (TJC28)} + GH + PGA + CRP$ Where: GH = general health component of DAS (i.e. Patient's

Global Assessment of Disease Activity, assessed using scale of 1 to 100, here 100 is maximal activity. GH was divided by 10 & converted to 0.5 scale (0, 0.5, 1, 1.5). -PGA = Physician's Global Assessment of Disease Activity assessed using scale of 1 to 100 where 100 is maximal activity. For analyses, PGA was divided by 10 & converted to 0.5 scale (0, 0.5, 1, 1.5). where [0-0.25]=0, [0.25-0.75]=0.5, [0.76-1.25]=1. Total score range was 0-86 & lower score indicates less disease activity. ITT Analysis Set used. Here "n" signifies subjects who were evaluable for this endpoint at specified time points.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 2, 4, 8, 12, 24, and 52 | |

| End point values | MSB11022 | EU-Humira | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 143 | 145 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change at Week 2 (n= 139, 145) | -11.5 (± 10.6) | -9.1 (± 10.0) | | |
| Change at Week 4 (n= 140, 140) | -18.0 (± 11.3) | -16.0 (± 10.9) | | |
| Change at Week 8 (n= 141, 144) | -24.0 (± 10.6) | -21.4 (± 11.0) | | |
| Change at Week 12 (n= 140, 141) | -27.9 (± 10.8) | -24.7 (± 10.9) | | |
| Change at Week 24 (n= 136, 131) | -31.4 (± 11.2) | -27.8 (± 10.6) | | |
| Change at Week 52 (n= 118, 118) | -31.5 (± 11.6) | -29.1 (± 10.8) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinical Disease Activity Index (CDAI) Total Score at Week 2, 4, 8, 12, 24 and 52

| | |
|-----------------|---|
| End point title | Change From Baseline in Clinical Disease Activity Index (CDAI) Total Score at Week 2, 4, 8, 12, 24 and 52 |
|-----------------|---|

End point description:

Clinical Disease Activity Index (CDAI) is a composite index (without acute-phase reactant) for assessing disease activity. CDAI was calculated based on following formula: CDAI = 28 joint count for swelling (SJC28) + 28 joint count for tenderness (TJC28) + GH + PGA. Where, -GH = general health component of DAS (i.e., Patient's Global Assessment of Disease Activity, assessed using a scale of 1 to 100 where 100 is maximal activity; GH was divided by 10 & converted to a 0.5 scale, i.e., 0, 0.5, 1, 1.5 etc. where [0-0.25] = 0, [0.25-0.75] = 0.5, [0.76-1.25] = 1, etc.). -PGA = Physician's Global Assessment of Disease Activity assessed using a scale of 1 to 100 where 100 is maximal activity. PGA was divided by 10 & converted to a 0.5 scale, ie, 0, 0.5, 1, 1.5 etc. where [0-0.25] = 0, [0.25-0.75] = 0.5, [0.76-1.25] = 1. CDAI ranges from 0 to 76. Lower score indicates less disease activity. ITT Analysis Set used. Here "n"= subjects who were evaluable for this endpoint at specified time points.

| | |
|---------------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 2, 4, 8, 12, 24 and 52 | |

| End point values | MSB11022 | EU-Humira | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 143 | 145 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change at Week 2 (n= 139, 145) | -10.8 (± 10.3) | -8.5 (± 9.9) | | |
| Change at Week 4 (n= 141, 144) | -17.4 (± 11.2) | -15.2 (± 10.7) | | |
| Change at Week 8 (n= 141, 144) | -23.5 (± 10.6) | -20.6 (± 10.9) | | |
| Change at Week 12 (n= 141, 141) | -27.4 (± 10.5) | -24.1 (± 10.7) | | |
| Change at Week 24 (n= 138, 132) | -30.8 (± 10.9) | -27.1 (± 10.7) | | |
| Change at Week 52 (n= 120, 118) | -31.1 (± 11.2) | -28.5 (± 10.6) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Boolean Remission at Week 2, 4, 8, 12, 24 and 52

| | |
|-----------------|--|
| End point title | Percentage of Subjects With American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Boolean Remission at Week 2, 4, 8, 12, 24 and 52 |
|-----------------|--|

End point description:

According to Boolean-based definition of remission of ACR/EULAR, a Subjects must satisfy all of the following: tender joint count ≤ 1, swollen joint count ≤ 1, CRP ≤ 1 mg/dL, and Patient's Global Assessment of Disease Activity ≤ 1 (0 to 10 VAS). Physician's Global Assessment of Disease Activity (PGA) was assessed on a 10 mm VAS ranging from 0 (very well) to 10 (very poor), where higher scores indicate worse health condition. Here "n" signifies those subjects who were evaluable for this endpoint at specified time points.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 2, 4, 8, 12, 24 and 52

| End point values | MSB11022 | EU-Humira | | |
|----------------------------------|---------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 143 | 145 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| Week 2 (n= 143, 145) | 0.7 (0.0 to 3.9) | 0.0 (0.0 to 2.5) | | |
| Week 4 (n= 142, 144) | 0.7 (0.0 to 3.9) | 1.4 (0.8 to 5.1) | | |
| Week 8 (n= 142, 144) | 3.5 (1.2 to 8.0) | 4.2 (1.5 to 8.9) | | |
| Week 12 (n= 142, 141) | 5.7 (2.5 to 10.9) | 12.1 (7.2 to 18.6) | | |
| Week 24 (n= 139, 133) | 11.7 (6.8 to 18.3) | 8.4 (4.3 to 14.5) | | |
| Week 52 (n= 122, 119) | 21.0 (14.1 to 29.4) | 13.6 (7.9 to 21.1) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Treatment Emergent Adverse Events (TEAEs), Serious TEAEs and TEAEs Leading to Death

| | |
|-----------------|---|
| End point title | Percentage of Subjects With Treatment Emergent Adverse Events (TEAEs), Serious TEAEs and TEAEs Leading to Death |
|-----------------|---|

End point description:

Adverse event(AE) was defined as any untoward medical occurrence in participants which does not necessarily have causal relationship with treatment. A serious adverse event(SAE) was AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial/prolonged inpatient hospitalization; congenital anomaly/birth defect or was otherwise considered medically important. Term TEAE is defined as AEs starting/worsening after first intake of the study drug. All abnormal physical examinations occurring during the study have been reported as Adverse events. TEAEs included both Serious TEAEs and non-serious TEAEs. The Safety Analysis Set included all randomized subjects who received at least one dose of study treatment.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to Week 69

| End point values | MSB11022 | EU-Humira | | |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 143 | 145 | | |
| Units: Percentage of Subjects | | | | |
| number (not applicable) | | | | |
| TEAEs | 58.0 | 64.1 | | |
| Serious TEAEs | 5.6 | 9.7 | | |
| TEAEs Leading to Death | 0 | 0.7 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Clinically Meaningful Differences in Vital Signs

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Clinically Meaningful Differences in Vital Signs |
|-----------------|--|

End point description:

Vital signs including body temperature, respiratory rate, and heart rate (after 5-minute rest) were measured. Percentage of subjects with clinically meaningful abnormalities in vital signs were reported. Clinical meaningful was determined by the investigator. The Safety Analysis Set included all randomized subjects who received at least one dose of study treatment.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to Week 52 | |

| End point values | MSB11022 | EU-Humira | | |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 143 | 145 | | |
| Units: Percentage of Subjects | | | | |
| number (not applicable) | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Clinically Meaningful Differences in Laboratory values

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Clinically Meaningful Differences in Laboratory values |
|-----------------|--|

End point description:

Laboratory parameters including hematology, urinalysis, and biochemistry analysis were analyzed. The Safety Analysis Set included all randomized subjects who received at least one dose of study treatment.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to Week 52

| End point values | MSB11022 | EU-Humira | | |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 143 | 145 | | |
| Units: Percentage of Subjects | | | | |
| number (not applicable) | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Clinically Significant Abnormal Values for 12-lead Electrocardiogram (ECG) at Week 12, 24, and 52

| | |
|-----------------|---|
| End point title | Percentage of Subjects With Clinically Significant Abnormal Values for 12-lead Electrocardiogram (ECG) at Week 12, 24, and 52 |
|-----------------|---|

End point description:

Percentage of subjects with clinically significant abnormal values for 12-lead electrocardiogram (ECG) at

week 12, 24, and 52 were reported. Here "n" signifies those subjects who were evaluable for this endpoint at specified time points.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 12, 24, and 52 | |

| End point values | MSB11022 | EU-Humira | | |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 143 | 145 | | |
| Units: Percentage of Subjects | | | | |
| number (not applicable) | | | | |
| Week 12 (n= 142, 141) | 0 | 0 | | |
| Week 24 (n= 139, 133) | 0 | 1.5 | | |
| Week 52 (n= 122, 119) | 0 | 0.8 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Anti-Nuclear Antibody (ANA) and Anti double-stranded Deoxyribonucleic acid (Anti-dsDNA) at Baseline, Week 24 and 52

| | |
|-----------------|---|
| End point title | Percentage of Subjects With Anti-Nuclear Antibody (ANA) and Anti double-stranded Deoxyribonucleic acid (Anti-dsDNA) at Baseline, Week 24 and 52 |
|-----------------|---|

End point description:

For ANA, positivity is defined as any subject with ANA titer greater than (>) 1:160 and negativity is defined as ANA titer less than (<) 1:160. For anti-ds DNA, positivity is defined as any subject with adsDNA > 15 units per milliliter (U/mL), intermediate category is defined as value between 10 U/mL to 15 U/mL and negativity is defined as adsDNA < 10 U/mL. Percentage of subjects with anti-nuclear antibody (ANA) and anti double-stranded deoxyribonucleic acid (Anti-dsDNA) at baseline, week 24 and 52 were reported. Here "n" signifies those subjects who were evaluable for this endpoint at specified time points.

| | |
|--------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 24 and 52 | |

| End point values | MSB11022 | EU-Humira | | |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 143 | 145 | | |
| Units: Percentage of Subjects | | | | |
| number (not applicable) | | | | |
| Baseline: ANA: Negative (n= 143, 145) | 97.2 | 95.1 | | |
| Baseline: ANA: Positive (n= 143, 145) | 2.8 | 4.9 | | |
| Week 24: ANA: Negative (n= 138, 131) | 92.0 | 91.6 | | |
| Week 24: ANA: Positive (n= 138, 131) | 8.0 | 8.4 | | |
| Week 52: ANA: Negative (n= 118, 111) | 78.8 | 84.7 | | |

| | | | | |
|--|------|------|--|--|
| Week 52: ANA: Positive (n= 118, 111) | 21.2 | 15.3 | | |
| Baseline: Anti-dsDNA: Negative (n= 141, 141) | 97.9 | 98.6 | | |
| Baseline: Anti-dsDNA: Intermediate (n= 141, 141) | 1.4 | 0.7 | | |
| Baseline: Anti-dsDNA: Positive (n= 141, 141) | 0.7 | 0.7 | | |
| Week 24: Anti-dsDNA: Negative (n= 138, 132) | 95.7 | 96.2 | | |
| Week 24: Anti-dsDNA: Intermediate (n= 138, 132) | 2.2 | 3.0 | | |
| Week 24: Anti-dsDNA: Positive (n= 138, 132) | 2.2 | 0.8 | | |
| Week 52: Anti-dsDNA: Negative (n= 121, 118) | 95.0 | 97.5 | | |
| Week 52: Anti-dsDNA: Intermediate (n= 121, 118) | 0.8 | 1.7 | | |
| Week 52: Anti-dsDNA: Positive (n= 121, 118) | 4.1 | 0.8 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Health assessment questionnaire disability index (HAQ-DI) Total Score at Baseline, Weeks 12, 24 and 52

| | |
|-----------------|---|
| End point title | Health assessment questionnaire disability index (HAQ-DI) Total Score at Baseline, Weeks 12, 24 and 52 |
|-----------------|---|

End point description:

The HAQ-DI is a participant-reported questionnaire that is commonly used in RA to measure disease associated disability (assessment of physical function). It consists of several questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities. HAQ-DI scores range from 0 to 3. The disability section of the questionnaire scores the participant's self-perception on the degree of difficulty (0 = without any difficulty, 1 = with some difficulty, 2 = with much difficulty, and 3 = unable to do). ITT analysis set was used. Here "n" signifies those subjects who were evaluable for this endpoint at specified time points.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Weeks 12, 24 and 52

| End point values | MSB11022 | EU-Humira | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 143 | 145 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n= 143, 145) | 1.6 (± 0.6) | 1.6 (± 0.6) | | |
| Week 12 (n= 142, 141) | 1.1 (± 0.6) | 1.1 (± 0.6) | | |
| Week 24 (n= 139, 132) | 1.0 (± 0.6) | 1.0 (± 0.6) | | |
| Week 52 (n= 121, 118) | 0.9 (± 0.7) | 0.9 (± 0.6) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Short-Form Health Survey- 36 Items (SF-36) at Baseline, Week 12, 24 and 52

| | |
|-----------------|--|
| End point title | Short-Form Health Survey- 36 Items (SF-36) at Baseline, Week 12, 24 and 52 |
|-----------------|--|

End point description:

SF-36: Validated 36-item, patient-reported indication of overall health status not specific to any age, disease/Treatment group. SF-36 questionnaire contains 36 questions pertaining to eight subscales of health status. 8 subscales summarized as relating to either physical health/mental health. Physical component summary (PCS): based primarily on physical functioning, role-physical, bodily pain & general health scales & mental component summary(MCS): vitality, social functioning, role-emotional & mental health scales. Score from mental health, role emotional, social functioning & vitality domains averaged to calculate MCS.Total score range for MCS: 0-100(100=highest level of mental functioning). Score from physical function, role physical, bodily pain & general health domains averaged to calculate PCS. Total score range for PCS: 0-100(100=highest level of physical functioning). ITT analysis set used. Here "n" signifies those subjects who evaluable for this endpoint at specified time.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 12, 24 and 52

| End point values | MSB11022 | EU-Humira | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 143 | 145 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| PCS: Baseline (n= 134, 134) | 30.3 (± 7.6) | 30.6 (± 7.8) | | |
| PCS: Week 12 (n= 142, 141) | 39.0 (± 7.9) | 38.6 (± 8.6) | | |
| PCS: Week 24 (n= 139, 132) | 40.5 (± 8.8) | 40.9 (± 9.1) | | |
| PCS: Week 52 (n= 121, 118) | 41.8 (± 9.5) | 41.6 (± 9.3) | | |
| MCS: Baseline (n= 134, 134) | 40.9 (± 13.2) | 43.4 (± 11.7) | | |
| MCS: Week 12 (n= 142, 141) | 47.4 (± 11.3) | 48.2 (± 11.3) | | |
| MCS: Week 24 (n= 139, 132) | 49.8 (± 10.8) | 48.8 (± 10.9) | | |
| MCS: Week 52 (n= 121, 118) | 48.0 (± 10.4) | 49.3 (± 11.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Euro-Quality of Life - 5 dimension-5 levels (EQ-5D-5L) Utility Index

Score at Baseline, Week 12, 24 and 52

| | |
|-----------------|--|
| End point title | Euro-Quality of Life - 5 dimension-5 levels (EQ-5D-5L) Utility Index Score at Baseline, Week 12, 24 and 52 |
|-----------------|--|

End point description:

EQ-5D-5L: standardized, participant-rated questionnaire to assess health-related quality of life. EQ-5D-5L includes 2 components: EQ-5D-5L health state profile & EQ-5D-5L VAS. EQ-5D-5L descriptive system provides a profile of participant's health state 5 dimensions: mobility, self-care, usual activities, pain/discomfort & anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems & extreme problems) that reflect increasing levels of difficulty. Participant was asked to indicate his/her current health state by selecting most appropriate level in each of 5 dimensions. Responses to 5 dimension scores were combined & converted into single preference-weighted health utility index score 0(0.0- worst health state) to 1(1.0- better health state) representing general health status of individual based on UK scoring algorithm. ITT analysis set used. Here "n"= subjects who were evaluable for this endpoint at specified time point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 12, 24 and 52

| End point values | MSB11022 | EU-Humira | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 143 | 145 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n= 134, 133) | 0.6 (± 0.2) | 0.6 (± 0.2) | | |
| Week 12 (n= 142, 140) | 0.8 (± 0.1) | 0.8 (± 0.1) | | |
| Week 24 (n= 139, 132) | 0.8 (± 0.1) | 0.8 (± 0.1) | | |
| Week 52 (n= 121, 118) | 0.8 (± 0.22) | 0.8 (± 0.1) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Euro-Quality of Life - 5 dimension-5 levels (EQ-5D-5L) Visual Analogue Scale (VAS) Score at Baseline, Week 12, 24 and 52

| | |
|-----------------|--|
| End point title | Euro-Quality of Life - 5 dimension-5 levels (EQ-5D-5L) Visual Analogue Scale (VAS) Score at Baseline, Week 12, 24 and 52 |
|-----------------|--|

End point description:

EQ-5D-5L: Standardized, participant-rated questionnaire to assess health-related quality of life. EQ-5D-5L includes 2 components: EQ-5D-5L health state profile & EQ-5D-5L VAS. EQ-5D-5L descriptive system provides a profile of participant's health state 5 dimensions: mobility, self-care, usual activities, pain/discomfort & anxiety/depression. Each dimension has 5 responses (no problems, slight problems, moderate problems, severe problems & extreme problems) that reflect increasing levels of difficulty. Responses to 5 dimension scores combined & converted into single preference-weighted health utility index score 0(worst health) to 1 (better health). EQ-VAS: Self-rated health status using a vertical VAS. EQ-VAS records participant's perceptions of their own current overall health in range from 0(worst imaginable health)-100(best imaginable health). ITT analysis set used. Here "n" signifies subjects evaluable for this endpoint at specified time point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 12, 24 and 52

| End point values | MSB11022 | EU-Humira | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 143 | 145 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n= 134, 133) | 42.4 (± 18.5) | 45.4 (± 20.4) | | |
| Week 12 (n= 142, 140) | 64.6 (± 19.6) | 63.2 (± 20.9) | | |
| Week 24 (n= 139, 132) | 66.2 (± 22.2) | 65.6 (± 24.3) | | |
| Week 52 (n= 121, 118) | 68.8 (± 21.7) | 69.0 (± 22.7) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline (Week 4) in Injection Site Pain as Assessed by Visual Analogue Scale (VAS) at Week 6 and 8

| | |
|-----------------|--|
| End point title | Mean Change From Baseline (Week 4) in Injection Site Pain as Assessed by Visual Analogue Scale (VAS) at Week 6 and 8 |
|-----------------|--|

End point description:

The participant's reported perception of pain was measured on a VAS where the slash drawn by the participant represents pain of increasing intensity. VAS score ranges from 0-10 millimeter [mm], where; 0 mm=no pain and 10 mm=worst possible pain. The first 2 injections was administered by qualified personnel. The next three doses of Investigational Medicinal Products (IMPs) (3-5) will be self-administered by the participant and injection site pain was assessed. Pain was recorded immediately after, 15 minutes after, and 1 hour after the injections received by the participants. The Safety Analysis Set included all randomized subjects who received at least one dose of study treatment. Here "n" signifies those subjects who were evaluable for this endpoint at specified time points.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Immediately, 15 minutes and 1 hour post-injection on Baseline (Week 4), Week 6 and 8

| End point values | MSB11022 | EU-Humira | | |
|--|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 143 | 145 | | |
| Units: Millimeter (mm) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4: Immediately post-injection (n= 140, 143) | 3.0 (± 8.4) | 6.4 (± 14.3) | | |
| Week 4: 15 min post-injection (n= 140, 143) | 0.6 (± 2.5) | 1.7 (± 7.6) | | |
| Week 4: 1 hour post-injection (n= 140, 143) | 0.1 (± 0.6) | 0.8 (± 5.6) | | |
| Change:Week6:Immediately post-injection(n=140,143) | -1.4 (± 5.1) | -1.3 (± 10.2) | | |
| Change:Week 6:15 min post-injection (n= 140, 143) | -0.2 (± 2.7) | 0.4 (± 3.3) | | |

| | | | | |
|--|--------------|---------------|--|--|
| Change: Week 6:1 hour post-injection (n= 140, 143) | 0.0 (± 0.7) | 0.0 (± 2.7) | | |
| Change:Week8:Immediately post- injection(n=140,139) | -1.7 (± 6.5) | -2.3 (± 10.4) | | |
| Change:Week 8:15 min post-injection (n= 140, 139) | -0.3 (± 2.3) | -0.7 (± 4.1) | | |
| Change:Week 8: 1 hour post-injection (n= 140, 139) | -0.1 (± 0.6) | -0.7 (± 5.4) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 69

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
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| Dictionary version | 21.0 |
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Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | EU-Humira |
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Reporting group description:

Participants received EU-Humira subcutaneously at dose of 40 mg every other week from Day 1 up to Week 48.

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|-----------------------|----------|
| Reporting group title | MSB11022 |
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Reporting group description:

Participants received MSB11022 subcutaneously at dose of 40 milligram (mg) every other week from Day 1 up to Week 48.

| Serious adverse events | EU-Humira | MSB11022 | |
|---|-------------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 15 / 145 (10.34%) | 8 / 143 (5.59%) | |
| number of deaths (all causes) | 2 | 0 | |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| Mycobacterium tuberculosis complex test positive | | | |
| subjects affected / exposed | 1 / 145 (0.69%) | 1 / 143 (0.70%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Arteriosclerosis coronary artery | | | |
| subjects affected / exposed | 1 / 145 (0.69%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 145 (0.69%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial ischaemia | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 145 (0.69%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Nervous system disorders | | | |
| Transient global amnesia | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 1 / 143 (0.70%) | |
| 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 | | | |
| Death | | | |
| subjects affected / exposed | 1 / 145 (0.69%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 1 / 143 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 145 (0.69%) | 0 / 143 (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 | | | |
| Rheumatoid lung | | | |
| subjects affected / exposed | 1 / 145 (0.69%) | 0 / 143 (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 | | | |
| Dermatitis | | | |
| subjects affected / exposed | 1 / 145 (0.69%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Osteoarthritis | | | |
| subjects affected / exposed | 2 / 145 (1.38%) | 1 / 143 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 2 / 145 (1.38%) | 1 / 143 (0.70%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cervical spinal stenosis | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 1 / 143 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Synovial cyst | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 1 / 143 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 145 (0.69%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 145 (0.69%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 1 / 145 (0.69%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tracheobronchitis | | | |
| subjects affected / exposed | 1 / 145 (0.69%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthritis bacterial | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 145 (0.00%) | 1 / 143 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| Device dislocation | | | |
| subjects affected / exposed | 0 / 145 (0.00%) | 1 / 143 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | EU-Humira | MSB11022 | |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 34 / 145 (23.45%) | 15 / 143 (10.49%) | |
| General disorders and administration site conditions | | | |
| Injection site erythema | | | |
| subjects affected / exposed | 12 / 145 (8.28%) | 4 / 143 (2.80%) | |
| occurrences (all) | 93 | 4 | |
| Injection site pain | | | |
| subjects affected / exposed | 10 / 145 (6.90%) | 2 / 143 (1.40%) | |
| occurrences (all) | 25 | 2 | |
| Injection site pruritus | | | |
| subjects affected / exposed | 8 / 145 (5.52%) | 1 / 143 (0.70%) | |
| occurrences (all) | 55 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Erythema | | | |
| subjects affected / exposed | 8 / 145 (5.52%) | 2 / 143 (1.40%) | |
| occurrences (all) | 38 | 20 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 13 / 145 (8.97%) | 6 / 143 (4.20%) | |
| occurrences (all) | 14 | 6 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|--------------|--|
| 11 July 2017 | - Administrative and editorial changes were undertaken to correct typographical errors that do not impact the design or execution of the study |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported