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ORIGINAL RESEARCH

Comparison of the efficacy and safety of a proposed biosimilar MSB11456 with tocilizumab reference product in subjects with moderate-to-severe rheumatoid arthritis: results of a randomised double-blind study

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ABSTRACT

Objective To evaluate the efficacy, immunogenicity and safety of the proposed biosimilar MSB11456 versus European Union (EU)-approved tocilizumab reference product in patients with rheumatoid arthritis (RA) in a multicentre, randomised, double-blind, multinational, parallel-group study (NCT04512001).

Methods Adult patients with moderate-to-severe active RA and inadequate clinical response to ≥1 disease-modifying antirheumatic drug (synthetic or biologic) receiving methotrexate were randomised to receive 24 weekly subcutaneous 162 mg injections of either MSB11456 or EU-approved tocilizumab. Equivalence between treatments was considered if the 95% CI (European Medicines Agency)/90% CI (US Food and Drug Administration) for the difference in mean change from baseline to week 24 in Disease Activity Score-28 Joint Count with erythrocyte sedimentation rate (DAS28-ESR) between treatments was entirely within prespecified equivalence intervals (−0.6 to 0.6 and −0.6 to 0.5, respectively). At week 24, patients were rerandomised to continued treatment or MSB11456. Secondary efficacy endpoints to week 52, and safety and immunogenicity to week 55 were also evaluated.

Results At week 24, the least squares mean difference in the change from baseline in DAS28-ESR between treatments was 0.01 (95% CI −0.19 to 0.22) in the 604 randomised patients. Similarity between treatments was shown for all other efficacy, safety and immunogenicity endpoints, including in patients who switched from EU-approved tocilizumab to MSB114466.

Conclusions Therapeutic equivalence was demonstrated for efficacy endpoints, and safety and immunogenicity analyses support the similarity of the two treatments. The results of this study strengthen the evidence that the proposed biosimilar MSB11456 and EU-approved tocilizumab exert similar clinical effects.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Biologics are established treatments for rheumatoid arthritis (RA), but their cost can be an impediment to use, leading to possible limited access; biosimilars provide the opportunity to improve access to treatment and can be cost saving.

⇒ Tocilizumab is a recombinant humanised monoclonal immunoglobulin G1 antibody approved for the treatment of adult patients with moderate-to-severe active RA.

WHAT THIS STUDY ADDS

⇒ Therapeutic equivalence of the proposed biosimilar MSB11456 to European Union-approved tocilizumab was demonstrated in adult patients with moderate-to-severe RA, supporting that these treatments have similar clinical behaviour.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The proposed tocilizumab biosimilar MSB11456 has the potential to expand access to interleukin-6 inhibitors for patients with moderate-to-severe RA.

INTRODUCTION

Interleukin-6 (IL-6) is a pleiotropic proinflammatory cytokine produced by a variety of cell types that is involved in diverse physiological processes such as B-cell and T-cell activation, induction of antibody secretion, induction of hepatic acute phase protein synthesis and stimulation of haematopoiesis. IL-6 has been implicated in the pathogenesis of diseases, including inflammatory and cardiovascular diseases and osteoporosis.[1 2] In rheumatoid arthritis (RA), many of the immune responses are mediated by IL-6, which is present both in

blood and in synovial joints. IL-6 has a pivotal role in the joint inflammatory process, in osteoclast-mediated bone resorption, in pannus development and in the systemic manifestations of RA.[2]

The biological disease-modifying antirheumatic drug (bDMARD) tocilizumab is a recombinant humanised monoclonal IgG_1 antibody that binds to both soluble (sIL-6R) and membrane (mIL-6R)-bound human IL-6 receptors, inhibiting sIL-6R- and mIL-6R-mediated signalling. Tocilizumab is approved for the treatment of adult patients with moderate-to-severe active RA and is marketed as RoActemra in the European Union (EU) and Actemra in the USA.[3 4] Tocilizumab can be used alone or with methotrexate or other conventional synthetic DMARDs (csDMARDs) in adults with RA who are intolerant to or have failed to respond to, other antirheumatic medications. In the EU, tocilizumab is also indicated in adult patients with severe, active and progressive RA who previously have not been treated with methotrexate. Other tocilizumab indications include treatment of giant cell arteritis, polyarticular and systemic juvenile idiopathic arthritis, cytokine release syndrome and selected patients with COVID-19 in the EU and USA, as well as systemic sclerosis-associated interstitial lung disease in the USA.

Although biologics are established treatments for RA, their cost can be an impediment to use, leading to limitations and inequities in treatment access.[5 6] Biologics are genetically engineered from living cells, and therefore, cannot be identical to one another.[7] Indeed because they are often large, complex proteins containing amino acids and numerous glycan structures, with natural variation along with heterogeneity in product processes, identical batches of any individual biological drug cannot be developed. Variations in the nature and extent of post-translational modifications, particularly glycosylation, as well as differences in product aggregation and host cell-related impurities all contribute to this heterogeneity.[7]

Biosimilars, which are biologics that are structurally highly similar and functionally equivalent to the approved reference product,[7–11] provide the opportunity to improve access to treatment.[6–8] Biosimilars can be cost saving if priced appropriately, their use is reinforced by payors and health authorities[6] and they are accepted by patients. Regulatory agencies provide clear guidance regarding the evidence needed to establish similarity between a biosimilar and the reference biologic.[8–11] A biosimilar must demonstrate no clinically meaningful differences from its reference product in terms of structure, purity, pharmacokinetics (PK), pharmacodynamics (PD), safety, immunogenicity and efficacy, with evidence obtained from clinical studies.[8–11]

MSB11456 is a proposed biosimilar to tocilizumab that would be used for the same indications as those for the currently available products in local markets. It has demonstrated PK, PD, safety and immunogenic similarity to the US-licensed and EU-approved tocilizumab in studies in healthy subjects.[12 13] The aim of this clinical study (NCT04512001) was to evaluate the efficacy, immunogenicity and safety of MSB11456 compared with the EU-approved tocilizumab in patients with moderate-to-severe active RA who had experienced an inadequate clinical response to at least one DMARD (either synthetic or biologic) and were receiving a stable dose of methotrexate. Additional aims were to evaluate the long-term efficacy of MSB11456 and the effects on efficacy, safety and immunogenicity of a single treatment transition from EU-approved tocilizumab to MSB11456. Applicable guidelines from the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) were followed.[8–11]

METHODS

Study design and treatments

This was a multicentre, randomised, double-blind, multinational, parallel-group study to compare the efficacy, safety and immunogenicity of MSB11456 and EU-approved tocilizumab in patients with moderate-to-severe active RA who had an inadequate response to one or more previous DMARD(s) (either synthetic or biologic). In this study, moderate-to-severe active RA was defined by a Swollen Joint Count (SJC) ≥6 (66 joint count) and Tender Joint Count (TJC)≥6 (68 joint count) at screening and randomisation, C reactive protein (CRP)≥10 mg/L and/or erythrocyte sedimentation rate (ESR) ≥28 mm/hour at screening and radiographic evidence within the past 6 months of ≥1 joint with a definite erosion attributable to RA at screening. The study included a screening period of up to 28 days, a double-blind 24-week core treatment period (day 1–week 24), an additional 28-week double-blind extended treatment period during which patients in the EU-approved tocilizumab group were rerandomised to either MSB11456 or continued EU-approved tocilizumab, with the last dose of study drug at week 51 (weeks 24–52), and a 12-week safety evaluation period following the last administered dose (weeks 51–63) (online supplemental figure 1).

Patients were randomised (1:1; randomisation block size: 4) using a central interactive response technology system to receive 24 weekly subcutaneous 162 mg injections of either MSB11456 or EU-approved tocilizumab into the lower abdomen starting on day 1. Injection kits were blinded before delivery to investigational sites, with the patients, investigators and sponsor being blinded to the allocated treatment. Randomisation was stratified by previous exposure to biological treatment for RA (yes/no). All patients continued their stable dose of methotrexate (which was 10–25 mg/week, and their stable dose of oral corticosteroids (≤10 mg/day) if being administered at baseline) and received a stable dose of folic acid (≥5 mg/week folate total dose). At week 24, after all efficacy and safety assessments were performed, patients remaining on study treatment entered the double-blind extended period; those originally in the MSB11456 group were rerandomised to continue treatment with

MSB11456. Patients originally in the EU-approved tocilizumab group were rerandomised in a 1:1 ratio to continue their weekly treatment with EU-approved tocilizumab or transition to MSB11456 starting at week 24.

Patients

Eligible patients were aged ≥18 years, had a body weight of <100 kg at screening and a diagnosis of RA based on the American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR)[14] Classification 2010 criteria, with a disease duration of ≥6 months prior to screening and moderate-to-severe disease activity. The vast majority of patients had high disease activity at baseline, according to multiple measures of disease activity (Disease Activity Score-28 Joint Count (DAS28)-ESR: 93.5% of patients; Clinical Disease Activity Index (CDAI): 93.5% of patients; Simplified Disease Activity Index (SDAI): 88.2% of patients).

All patients had been treated with methotrexate for ≥12 consecutive weeks immediately prior to randomisation and were receiving a stable dose of methotrexate of 10–25 mg/week, starting 8 weeks prior to screening and had a previous inadequate clinical response to one or more csDMARD(s) or biologics. Previous csDMARDs, other than methotrexate, were required to have been discontinued at least 8 weeks previously and leflunomide or biologics were required to have been discontinued at least 12 weeks previously. Patients who had received more than two previous biologics for RA were not eligible. The number of patients with previous exposure to one or two biological treatments was capped at 10% of the total study population. All patients were non-pregnant and, if of childbearing potential, took precautions against pregnancy. Additional inclusion and exclusion criteria are summarised in online supplemental file.

Patients provided informed written consent for participation in the trial.

Assessments

Efficacy assessments were performed according to ACR/EULAR recommendations for reporting disease activity in clinical studies of patients with RA.[15] Joint count assessments were conducted by trained independent assessors who were blinded to the medical history and treatment of the patients. Patient-reported outcomes (Health Assessment Questionnaire Disability Index, Patient's Assessment of Arthritis Pain (Pain), Patient's Global Assessment of Disease Activity (PtGA)) and the Physician's Global Assessment of Disease Activity (PGA)) were assessed immediately after body temperature measurement and before any other assessments at all relevant visits. Pain, PtGA and PGA were recorded using a Visual Analogue Scale (0–100 mm).

Immunogenicity was determined using a multitiered approach. In the first tier, all samples were assessed and categorised as 'negative' or 'potential positive' using a screening assay. Samples testing putative positive in the screening assay then underwent a more stringent confirmatory assay designed to minimise falsepositives in the second tier. Both the screening and confirmatory assays were ligand-binding immunoassays. Finally, all confirmed positive samples were characterised by antidrug antibody (ADA) titres and tested in a neutralising antibody (NAb) assay to determine whether ADAs against the drug were neutralising the biological activity of the drug. ADAs and ADA titres were detected using a validated electrochemiluminescence bridging assay including an acid dissociation step, which resulted in a highly sensitive and drug tolerant ADA assay. NAbs were determined with a validated cell-based assay.

Safety, including adverse events (AEs), serious AEs (SAEs), AEs of special interest (AESIs; serious infections (those requiring intravenous antibiotics), hypersensitivity occurring during or within 24 hours of an injection (excluding injection site reactions, ISR) deemed to be related to treatment and anaphylaxis, AEs leading to interruption or permanent discontinuation of study drug or study withdrawal), laboratory findings and vital signs, and immunogenicity assessments were performed throughout the study. AEs were reported using Medical Dictionary for Regulatory Activities V.23.1 and graded using V.5 of the National Cancer Institute–Common Terminology Criteria for Adverse Events (see online supplemental file). The relationship of AEs to treatment was also reported.

Endpoints

The primary endpoint was the change from baseline in DAS28-ESR at week 24. The key secondary endpoint was 20% improvement in ACR core set measures (ACR20) at week 24. Change from baseline in DAS28-ESR at week 12 was defined as the early efficacy endpoint. Additional endpoints included 50%/70% improvement in ACR core set measures (ACR50/70), change from baseline in DAS28-CRP, categorical DAS28-ESR and DAS28-CRP responses, SDAI and CDAI at additional time points up to week 52 and change in DAS28-ESR and ACR20 over the 52-week period. Safety and immunogenicity data were collected and analysed to week 55.

Study estimands

Therapeutic equivalence was determined using one main estimand, which evaluated the treatment effect for all randomised patients regardless of adherence to treatment or to protocol. Treatment interruption and treatment discontinuation, intake of prohibited medication, methotrexate dose modification and COVID-19 vaccination were considered as potential intercurrent events and were accounted for by the treatment policy strategy for the main estimand. Supportive estimands were also defined, answering different clinical questions and for which possible hypothetical strategies were used for the intercurrent events (a description of the supportive estimands used is included in online supplemental file).

Table 1 Baseline patient characteristics of patients with moderate-to-severe rheumatoid arthritis randomised to MSB11456 or EU-approved tocilizumab—core period ITT analysis set

Parameter	MSB11456 (N=302)	EU-approved tocilizumab (N=302)	Total (N=604)
Age, years	51.2±12.7	53.2±11.3	52.2±12.1
Female	250 (82.8)	248 (82.1)	498 (82.5)
White	302 (100)	302 (100)	604 (100)
Not Hispanic/Latino	300 (99.3)	300 (99.3)	600 (99.3)
Weight, kg	73.6±14.1	71.8±13.5	72.7±13.8
BMI, kg/m^2	26.9±4.7	26.2±4.6	26.6±4.7
Functional classification			
Class I	25 (8.3)	17 (5.6)	42 (7.0)
Class II	231 (76.5)	246 (81.5)	477 (79.0)
Class III	46 (15.2)	39 (12.9)	85 (14.1)
Previous use of biologics	28 (9.3)	26 (8.6)	54 (8.9)
Time since symptom onset, months	110.5±88.2	110.5±88.5	110.5±88.3
Time since first RA diagnosis, months	95.2±79.9	90.9±83.5	93.1±81.7
DAS28-ESR*	6.28±0.79	6.26±0.80	6.27±0.79
Remission	0	0	0
Low	1 (0.3)	0	1 (0.2)
Moderate	16 (5.3)	22 (7.3)	38 (6.3)
High	285 (94.4)	280 (92.7)	565 (93.5)
DAS28-CRP	5.44±0.90	5.42±0.90	5.43±0.88
CDAI†			
Remission	0	0	0
Low	1 (0.3)	1 (0.3)	2 (0.3)
Moderate	16 (5.3)	21 (7.0)	37 (6.1)
High	285 (94.4)	280 (92.7)	565 (93.5)
SDAI‡			
Remission	0	0	0
Low	1 (0.3)	1 (0.3)	2 (0.3)
Moderate	33 (10.9)	36 (11.9)	69 (11.4)
High	268 (88.7)	265 (87.7)	533 (88.2)

Data are shown as mean±SD for continuous parameters or number (percentage) for categorical parameters.
*DAS28-ESR: remission <2.6; low ≤2.6 to <3.2; moderate ≤3.2 to ≤5.1; high >5.1.
†CDAI: remission ≤2.8; low <2.8 to ≤10; moderate <10 to ≤22; high >22.
‡SDAI: remission ≤3.3; low <3.3 to ≤11; moderate <11 to ≤26; high >26.
BMI, body mass index; CDAI, Clinical Disease Activity Index; DAS28-CRP, Disease Activity Score-28 C reactive protein; ESR, erythrocyte sedimentation rate; EU, European Union; ITT, intention to treat; RA, rheumatoid arthritis; SDAI, Simplified Disease Activity Index.

Statistical analyses

A sample size of 542 randomised patients (271 patients per arm) was chosen to provide approximately 460 evaluable patients (230 per arm) at week 24, assuming a 15% drop-out rate. This would provide 90% power to demonstrate equivalence between treatments for the primary endpoint, assuming no difference between the two treatment groups and a common SD of 1.76 for the following success criteria: for the EMA, 95% CIs within the equivalence margin (−0.6 to 0.6) and for the FDA, 90% CIs within the equivalence margin (−0.6 to 0.5). This sample size would also provide more than 80% power to demonstrate that the 95% CI for the difference between treatments in the key secondary endpoint (ACR20 response rate at week 24) would be included in the equivalence interval (−15% to 15%), assuming no difference between the two treatment groups and a common ACR20 response rate of 60% at week 24.

Safety and immunogenicity analyses were performed in the Safety Analysis Set (SAS), which included all patients who received at least one dose of study drug. Efficacy endpoints were summarised using the intention-to-treat

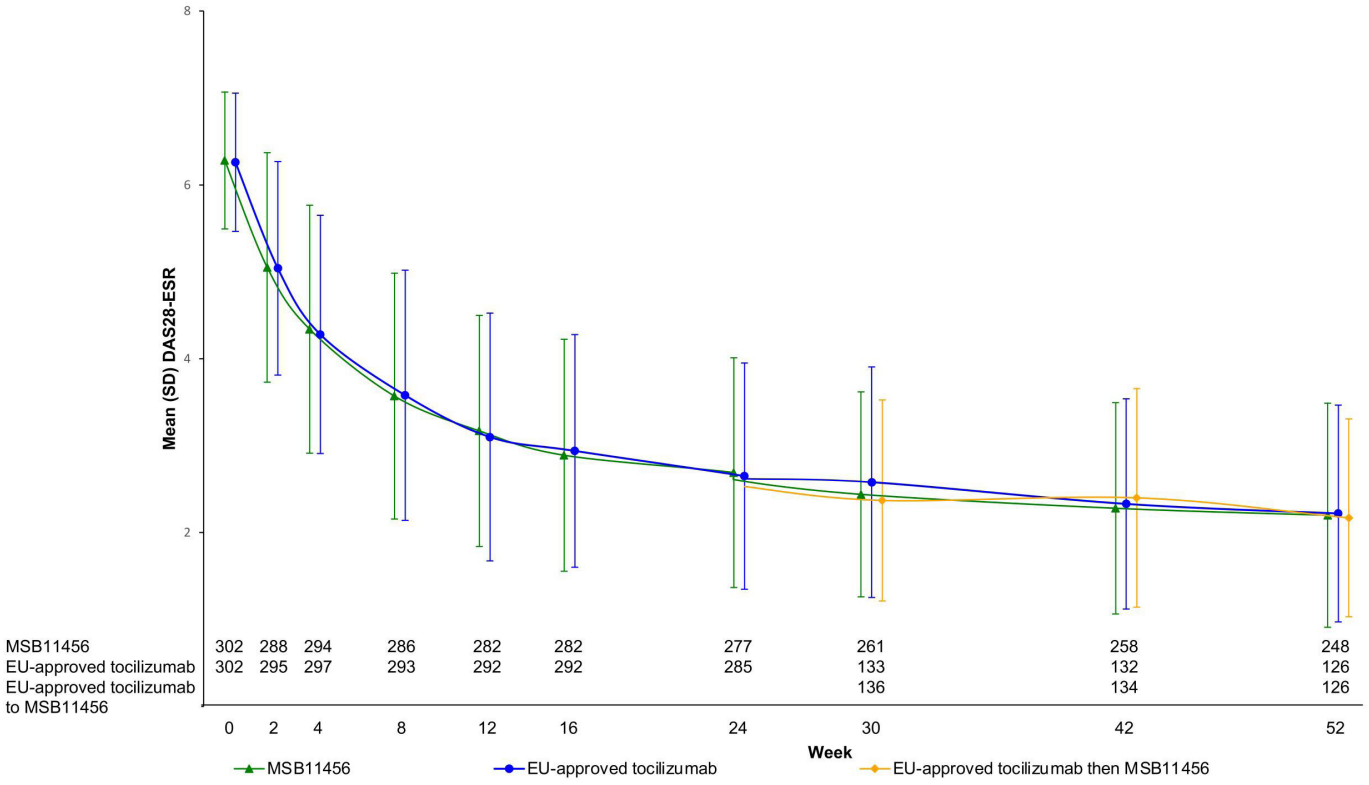


Figure 1 Change from baseline over 52 weeks in DAS28-ESR in patients with moderate-to-severe rheumatoid arthritis initially randomised to MSB11456 or EU-approved tocilizumab and in those rerandomised from EU-approved tocilizumab to MSB11456 at week 24, ITT analysis set. DAS28-ESR, Disease Activity Score-28 Joint erythrocyte sedimentation rate; EU, European Union; ITT, intention to treat.

(ITT) analysis set. The definitions for the analysis sets are included in online supplemental file.

Analysis of the change from baseline at week 24 in DAS28-ESR used an analysis of covariance with treatment group and previous exposure to biological treatment for RA (yes/no) as fixed effects and baseline DAS28-ESR as a covariate. The difference between treatments was estimated by the least squares (LS) mean difference between MSB11456 and EU-approved tocilizumab, with both the 95% CI and 90% CI presented. For the FDA, MSB11456 was considered equivalent to EU-approved tocilizumab if the 90% CI for the difference in mean change from baseline to week 24 in DAS28-ESR between treatments was entirely within the equivalence interval of −0.6 to 0.5; for the EMA, MSB11456 was considered equivalent to EU-approved tocilizumab if the 95% CI for the difference in mean change from baseline to week 24 in DAS28-ESR between treatments was entirely within the equivalence interval of −0.6 to 0.6. For the main estimand, a multiple imputation procedure was used for missing DAS28-ESR scores at week 24. A tipping point analysis was conducted as sensitivity analysis to assess the robustness of results.

Similar analyses, using week 12 data, were performed for the early efficacy endpoint.

The difference in ACR20 response rate at week 24 was compared using a 95% stratified Newcombe CI to adjust for previous exposure to biological treatment for RA (yes/no) and assessed against an equivalence margin of −15% to 15%. Mantel-Haenszel weights were used to combine the stratum components. For the main estimand, missing ACR20 response data were imputed using the last observation carried forward method; patients who had just a baseline assessment had their postbaseline assessments imputed as non-responders. Sensitivity analyses included a tipping point analysis and a multiple imputation approach to impute missing data.

The primary and key secondary endpoints were also analysed in the following subgroups: previous exposure to biological treatment for RA (yes/no), COVID-19 vaccination status at week 24 (vaccinated/unvaccinated prior to week 24), ADA status (positive (at least one confirmatory positive post-dose result)/negative) and NAb status (positive (at least one positive postdose result)/negative).

The number and percentage of patients within each DAS28-ESR, DAS28-CRP, CDAI and SDAI disease activity/categorical response were summarised by treatment group and visit. Categorical disease activity for DAS28-ESR, CDAI and SDAI was categorised as remission/low/moderate/high, and categorical response for DAS28-CRP was categorised as yes/no by the EULAR Boolean response criterion. No imputation of missing data was performed for these analyses.

ADA and NAb incidence over time, as well as ADA titre over time, were summarised descriptively by visit (and overall for incidence) and treatment arm, with the number of patients with a valid immunogenicity

Table 2 Efficacy endpoints for patients with moderate-to-severe RA randomised to MSB11456 or EU-approved tocilizumab—main estimand analyses

Parameter	MSB11456 (N=302)	EU-approved tocilizumab (N=302)	Difference MSB11456—EU-approved tocilizumab (N=604)
LS mean (SE) change from baseline to week 24 in DAS28-ESR	−3.53 (0.11)	−3.54 (0.11)	
LS mean difference (90% CI) (95% CI)*			0.01 (−0.16 to 0.18) (−0.19 to 0.22)
ACR20 response rate at week 24, n (%)	244 (80.8)	256 (84.8)	
Difference (95% CI)†			−3.94 (−9.97 to 2.11)
LS mean (SE) change from baseline to week 12 in DAS28-ESR	−3.13 (0.10)	−3.12 (0.10)	
LS mean difference (95% CI)			−0.01 (−0.21 to 0.19)
LS mean (SE) change from baseline to week 24 in DAS28-CRP	−2.78 (0.07)	−2.83 (0.07)	
LS mean difference (95% CI)			0.05 (−0.12 to 0.22)
ACR50 response rate at week 24, n (%)	183 (60.6)	188 (62.3)	
Difference (95% CI)			−1.59 (−9.29 to 6.15)
ACR70 response rate at week 24, n (%)	118 (39.1)	116 (38.4)	
Difference (95% CI)			0.73 (−7.01 to 8.45)

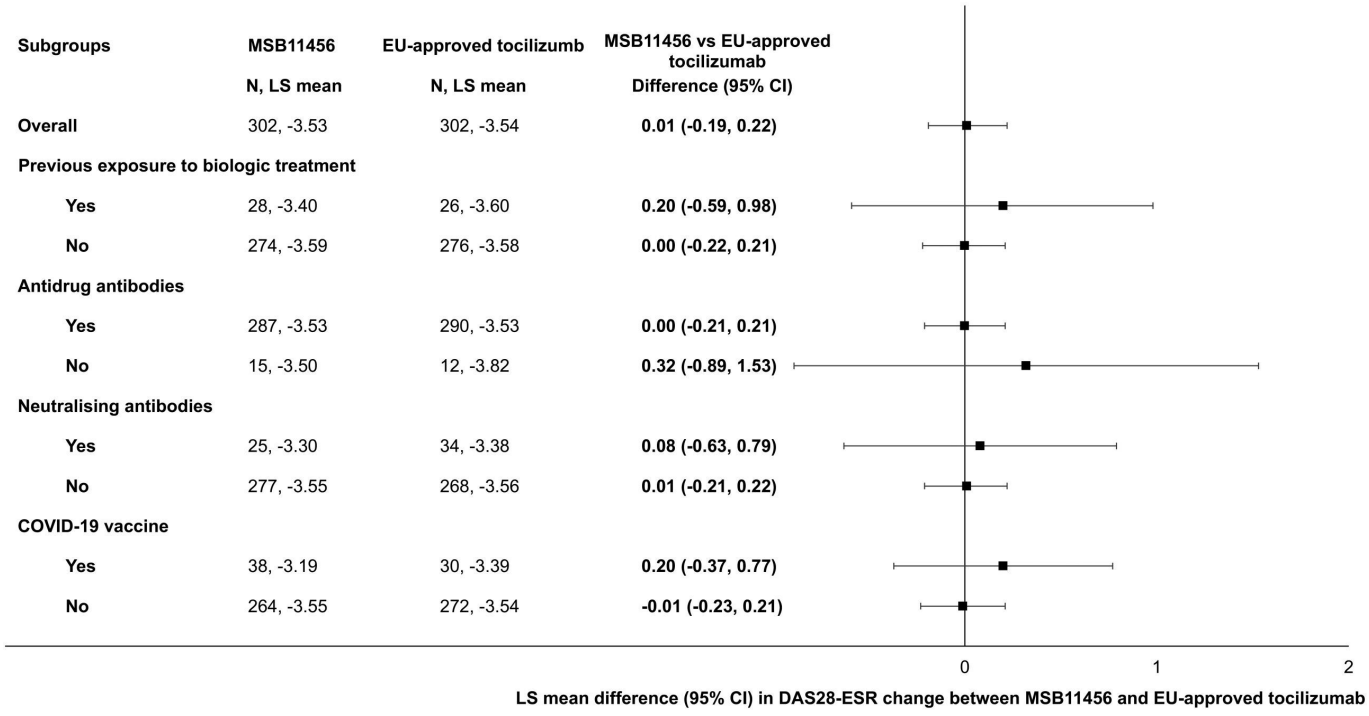
*Change from baseline to week 24 in DAS28-ESR was analysed using analysis of covariance with treatment group and previous exposure to biological treatment for RA (yes/no) as fixed effects and baseline DAS28-ESR as a covariate. For the FDA: MSB11456 was considered equivalent to EU-approved tocilizumab if the 90% CI was included in the equivalence interval of (−0.6 to 0.5). For the EMA: MSB11456 was considered equivalent to EU-approved tocilizumab if the 95% CI was included in the equivalence interval of (−0.6 to 0.6).
†The stratified difference in ACR20 response rate at week 24 was analysed using a 95% stratified Newcombe CI adjusting for the stratification factor previous exposure to biological treatment for RA; the equivalence margin was (−15%, 15%).
ACR20/50/70, 20%/50%/70% improvement in American College of Rheumatology core set measures; DAS28-CRP, Disease Activity Score-28 C reactive protein; EMA, European Medicines Agency; ESR, erythrocyte sedimentation rate; EU, European Union; FDA, Food and Drug Administration; LS, least squares; RA, rheumatoid arthritis.

assessment at each visit as the denominator for that visit. A treatment-induced ADA positive status was defined as any positive postdose sample in the ADA confirmatory assay when the predose sample was negative, and as an at least 1.808-fold increase (the minimum significant ratio) in titres from a positive predose sample. The ADA titre value was defined as the reciprocal of total sample dilution factor, including the assay minimum required dilution. Serum samples were analysed using validated bioanalytical methods.

AEs (events and number and percentage of patients) were summarised for the following categories: overall and by system organ class: treatment-emergent AE (TEAE), SAE, grade ≥3 TEAE, grade ≥4 TEAE, TEAE of special interest, TEAE leading to treatment withdrawal, treatment interruption, discontinuation from the study or death, serious ISR and treatment-related TEAE, SAE, grade ≥3 TEAE, grade ≥4 TEAE, TEAE of special interest and TEAE leading to treatment withdrawal, treatment interruption, discontinuation from the study or death. Summary statistics for observed values and changes from baseline over time were provided for continuous laboratory variables (haematology, coagulation, biochemistry and urinalysis) and vital signs (systolic and diastolic blood pressure, pulse rate, temperature and respiratory rate). ISRs were summarised by treatment group and overall.

RESULTS

The study was conducted between 3 August 2020 and 6 June 2022. Of the 908 patients screened, a total of 604 patients were randomised to treatment with MSB11456 (N=302) or EU-approved tocilizumab (N=302) from 81 investigative sites in Europe (Bulgaria, the Czech Republic, Georgia, Hungary, Moldova, Poland, Russia, Serbia and Slovakia). Similar proportions of patients in the MSB11456 and EU-approved tocilizumab groups discontinued treatment prior to week 24 (36 (11.9%) and 27 (8.9%), respectively; online supplemental figure 1). At baseline, patient demographics and characteristics, including disease characteristics, were well balanced across treatment groups (table 1). Overall, the study population was aged 19–79 years, was 82.5% female and had a body mass index of 16.3–43.5 kg/m^2 (weight of 40–118 kg; body weight was >100 kg in one patient, which was considered a protocol violation). Prior to study entry,



LS means and CIs were from an analysis of covariance model based on change from baseline in DAS28-ESR with fixed effects for study drug and previous exposure to biologic treatment for rheumatoid arthritis [yes/no] and baseline DAS28-ESR as a covariate.
CI, confidence interval; DAS28-ESR, Disease Activity Score-28 erythrocyte sedimentation rate; EU, European Union; ITT, intention-to-treat; LS, least squares

Figure 2 Change from baseline to week 24 in DAS28-ESR for subgroups of patients with moderate-to-severe rheumatoid arthritis randomised to MSB11456 or EU-approved tocilizumab, core period ITT analysis set.

biological therapy had been used by 28 patients in the MSB11456 group (9.3%) and 26 patients in the EU-approved tocilizumab group (8.6%).

Similar proportions of patients in the MSB11456 and EU-approved tocilizumab groups were rerandomised in the extended period (267/302 (88.4%) and 276/302 (91.4%), respectively); two patients (one in the MSB11456 group and one in the EU-approved tocilizumab group) were rerandomised but did not receive further treatment after rerandomisation. These patients were included in the extended period ITT analysis set but not the extended period SAS. The extended period ITT analysis set included 267 patients on MSB11456 throughout the entire study period, 137 patients on EU-approved tocilizumab throughout the entire study period and 139 patients who were initially allocated to EU-approved tocilizumab and were rerandomised to MSB11456 for the extended period.

Efficacy

Analysis of DAS28-ESR changes throughout the 52-week efficacy assessment revealed similar decreases, seen as early as week 2, with both treatments (figure 1). For the primary endpoint, clinically relevant similar LS mean decreases in DAS28-ESR from baseline were evident at week 24 with both MSB11456 and EU-approved tocilizumab (table 2). At week 24, the LS mean difference in the change in DAS28-ESR between treatments was 0.01 (95% CI −0.19, 0.22; 90% CI −0.16, 0.18) for the main estimand analysis (table 2). As these CIs were fully included within the respective predefined equivalence intervals, therapeutic equivalence of MSB11456 and EU-approved tocilizumab was demonstrated. Similar results were obtained in the sensitivity analyses and for the supportive estimand analyses (data not shown). Subgroup analyses revealed that irrespective of previous exposure to biologics, ADA status, NAb status and COVID-19 vaccination status, the efficacy of MSB11456 and EU-approved tocilizumab were maintained, as was the similarity of efficacy between the treatments (figure 2).

ACR20 response rates were >80% at week 24 for both MSB11456 and EU-approved tocilizumab, with equivalence between the two treatments demonstrated for this key secondary endpoint (table 2) for the main estimand and for the sensitivity analysis and supportive estimand analyses. Consistent results were obtained in subgroup analyses (data not shown).

The secondary early efficacy endpoint, change in DAS28-ESR from baseline to week 12, also supported the therapeutic equivalence of MSB11456 and EU-approved tocilizumab based on the main estimand analysis, as well as the supportive estimand analyses (table 2).

Furthermore, changes in DAS28-CRP at week 24 (table 2), and categorical responses for the DAS28-ESR, DAS28-CRP, CDAI and SDAI at week 24 analyses (table 3) all support the efficacy and therapeutic similarity of MSB11456 and EU-approved tocilizumab.

Decreases from baseline in DAS28 ESR at week 24 were sustained throughout the extended period in all

Table 3 Categorical efficacy responses at week 24 for patients with moderate-to-severe rheumatoid arthritis randomised to MSB11456 or EU-approved tocilizumab, core period ITT analysis set

Parameter	MSB11456 (N=302)	EU-approved tocilizumab (N=302)
DAS28-ESR*	n=277	n=285
Remission	139 (50.2)	149 (52.3)
Low	43 (15.5)	42 (14.7)
Moderate	83 (30.0)	82 (28.8)
High	12 (4.3)	12 (4.2)
DAS28-CRP	n=276	n=285
Responder†	46 (16.7)	55 (19.3)
CDAI‡	n=278	n=286
Remission	53 (19.1)	62 (21.7)
Low	119 (42.8)	115 (40.2)
Moderate	84 (30.2)	90 (31.5)
High	22 (7.9)	19 (6.6)
SDAI§	n=276	n=285
Remission	62 (22.5)	68 (23.9)
Low	112 (40.6)	113 (39.6)
Moderate	85 (30.8)	92 (32.3)
High	17 (6.2)	12 (4.2)

Data are shown as number (percentage), with percentages calculated based on number of subjects with available data.
*DAS28-ESR: remission <2.6; low ≤2.6 to <3.2; moderate ≤3.2 to ≤5.1; high >5.1.
†DAS28-CRP responder: TJC28 ≤1 and SJC28 ≤1 and PGA ≤10 mm and CRP ≤10 mg/L.
‡CDAI: remission ≤2.8; low <2.8 to ≤10; moderate <10 to ≤22; high >22.
§SDAI: remission ≤3.3; low <3.3 to ≤11; moderate <11 to ≤26; high >26.
CDAI, Clinical Disease Activity Index; DAS28-CRP, Disease Activity Score-28 C reactive protein; ESR, erythrocyte sedimentation rate; EU, European Union; ITT, intention to treat; PGA, Physician's Global Assessment; SDAI, Simplified Disease Activity Index; SJC28, 28 Joint Count for Swelling; TJC28, 28 Joint Count for Tenderness.

Table 4 Change from baseline to week 52 in DAS28 efficacy endpoints in patients with moderate-to-severe rheumatoid arthritis after rerandomisation to MSB11456 or EU-approved tocilizumab—extended period

Parameter	MSB11456 (N=302)	EU-approved tocilizumab (N=163)	EU-approved tocilizumab/ MSB11456 (N=139)
LS mean (SE) change from baseline to week 52 in DAS28-ESR	−4.00 (0.09)	−3.80 (0.12)	−4.05 (0.12)
LS mean (SE) change from baseline to week 52 in DAS28-CRP	−3.14 (0.08)	−3.06 (0.10)	−3.21 (0.10)

Data from a mixed-effect repeated measures model assuming an unstructured covariance matrix with treatment, visit, treatment by visit interaction, previous exposure to biological treatment for rheumatoid arthritis (Y/N) included as factors and baseline DAS28-ESR/DAS28-CRP from the core period as a covariate.
DAS28-CRP, Disease Activity Score-28 C reactive protein; ESR, erythrocyte sedimentation rate; EU, European Union; LS, least squares.

treatment groups and were similar in the MSB11456, EU-approved tocilizumab and EU-approved tocilizumab to MSB11456 groups. Analyses of other efficacy measures supported the findings of the DAS28-ESR analyses (table 4 and online supplemental table 1).

Immunogenicity

The incidence of patients who were overall ADA positive in the 24-week core period (ie, having at least one positive ADA result after dosing) was similar between the MSB11456 and EU-approved tocilizumab groups (figure 3). Treatment-induced ADA positivity was reported in 95.0% and 92.4% of the MSB11456 and EU-approved tocilizumab treatment groups, respectively, and there were no clinically meaningful between-treatment differences at the week 24 time point (73.4% and 62.9% of patients, respectively). For both treatments, the incidence of patients with a positive ADA result was greatest at week 2 (87.1% and 88.7% of patients, respectively). Median (≤120.0) and geometric mean (≤138.4) ADA titres were low, with no clinically meaningful differences

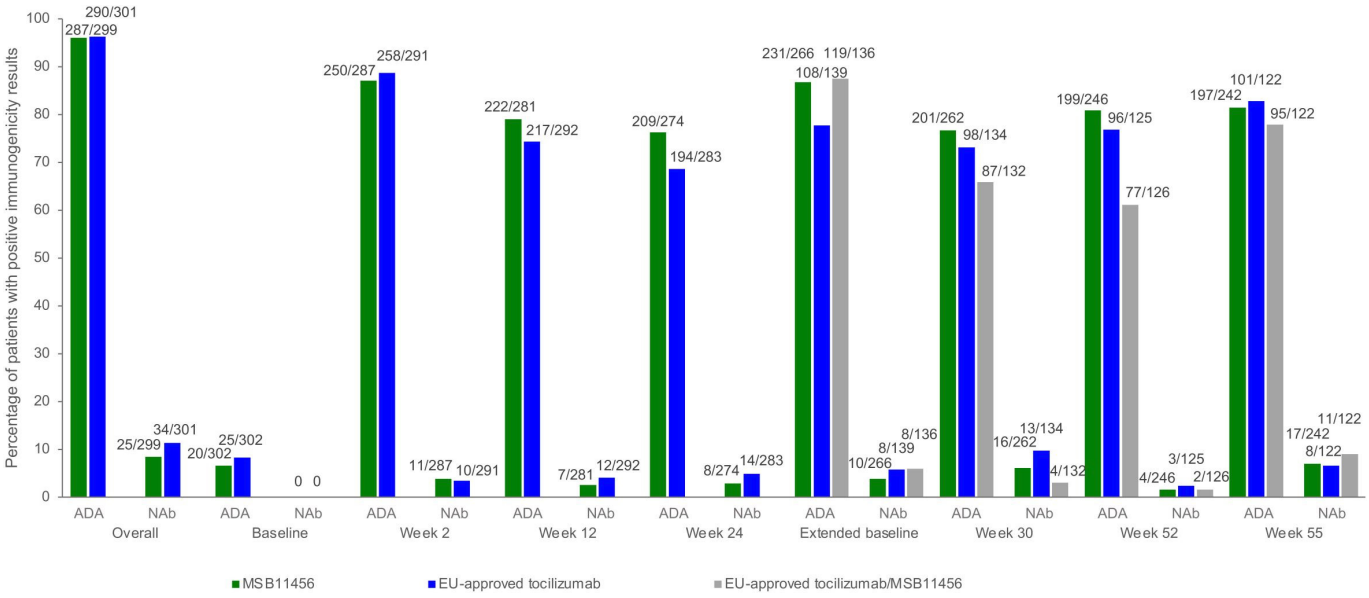


Figure 3 Immunogenicity findings over 55 weeks in patients with moderate-to-severe rheumatoid arthritis treated with MSB11456, EU-approved tocilizumab or EU-approved tocilizumab to MSB11456, safety analysis set. ADA, antidrug antibody; EU, European Union; n/N, number of patients with positive status/number of patients with a valid ADA/Nab result; NAb, neutralising antibody.

between treatment groups at each postbaseline sample collection. The overall incidence of Nabs against tocilizumab was low and similar between the MSB11456 and EU-approved tocilizumab groups (8.4% and 11.3% of patients, respectively; figure 3).

When ADA incidence over the overall (55-week) period was considered, 98.7% of MSB11456 and 98.1% of EU-approved tocilizumab recipients had a positive ADA reported, with the incidence at week 55 being 81.4% and 87.7%, respectively. The overall incidence of Nabs against tocilizumab up to week 55 was 19.1% in both treatment groups. Switching from EU-approved tocilizumab to MSB11456 at week 24 appeared to have no clinically meaningful effect on immunogenicity findings (figure 3).

In the 18 patients with treatment-related hypersensitivity during the 55-week safety and immunogenicity analysis period, median ADA titres were low at each visit (≤300 in those with available data), with no clinically meaningful differences in titres between the MSB11456, EU-approved tocilizumab and EU-approved tocilizumab to MSB11456 groups.

Exposure and compliance

Both mean total duration of exposure to tocilizumab (including the 7 days after the last dose for the core period) and mean number of injections administered per patient were similar between the MSB11456 and EU-approved tocilizumab groups in the core period and overall period, as were the proportions of patients with compliance of ≥80 to ≤100% during the core period. Additional details are summarised in online supplemental file. During the extended period (weeks 24–52), the mean treatment duration, the mean number of injections administered per patient, the mean percentage treatment compliance, and the proportion of patients with compliance of ≥80 to ≤100% were similar between the three treatment groups.

Safety

TEAEs and SAEs occurred with similar frequency in patients treated with MSB11456 and EU-approved tocilizumab in the 24-week core period (table 5). The majority of TEAEs in both treatment groups were classified by the investigator as grade 1 or grade 2 in severity, with no differences observed between treatment groups with respect to severity. The most common TEAEs were as expected for patients with RA treated with tocilizumab and for a study conducted during the COVID-19 pandemic, being increased alanine aminotransferase (9.3% vs 11.6%), COVID-19 (6.0% vs 5.6%), neutropenia (6.0% vs 5.0%), leucopenia (5.6% vs 4.6%) and increased aspartate aminotransferase (4.6% vs 5.3%) in patients treated with MSB11456 and EU-approved tocilizumab. In both groups, the most common treatment-related SAE was COVID-19, with no other SAE reported in more than one patient, except for spinal stenosis (two patients treated with MSB11456). There were no discernible patterns in terms of the nature, frequency or other characteristics of SAEs or treatment-related TEAEs that would suggest a difference between treatment groups. TEAEs of positive mycobacterium tuberculosis complex test were the most common TEAEs leading to permanent discontinuation of treatment or patient withdrawal from the study. A similar proportion of patients in the MSB11456 and EU-approved tocilizumab groups experienced at least one AESI (29.1% and 26.8% of patients, respectively), the majority being TEAEs leading to treatment interruption. The most frequently reported infection AESI was COVID-19

Table 5 Summary of adverse events in patients with moderate-to-severe rheumatoid arthritis treated with MSB11456 or EU-approved tocilizumab during the core period; safety analysis set

Adverse event; n (%) (no of events)	MSB11456 (N=302)	EU-approved tocilizumab (N=302)	Total (N=604)
Any TEAE	199 (65.9) (463)	190 (62.9) (480)	389 (64.4) (943)
Any treatment-related TEAE	92 (30.5) (206)	72 (23.8) (149)	164 (27.2) (355)
Any SAE	28 (9.3) (34)	30 (9.9) (32)	58 (9.6) (66)
Any treatment-related SAE	3 (1.0) (3)	3 (1.0) (3)	6 (1.0) (6)
Any Grade ≥3 TEAE	28 (9.3) (39)	33 (10.9) (40)	61 (10.1) (79)
Any treatment-related grade ≥3 TEAE	11 (3.6) (14)	9 (3.0) (14)	20 (3.3) (28)
Any grade ≥4 TEAE*	3 (1.0) (5)	4 (1.3) (4)	7 (1.2) (9)
Any treatment-related grade ≥4 TEAE	2 (0.7) (2)	1 (0.3) (1)	3 (0.5) (3)
Any AESI	88 (29.1) (131)	81 (26.8) (120)	169 (28.0) (251)
Any treatment-related AESI	38 (12.6) (65)	35 (11.6) (55)	73 (12.1) (120)
Any TEAE leading to treatment withdrawal	32 (10.6) (39)	24 (7.9) (29)	56 (9.3) (68)
Any treatment-related TEAE leading to treatment withdrawal	17 (5.6) (18)	9 (3.0) (13)	26 (4.3) (31)
Any TEAE leading to treatment interruption	62 (20.5) (91)	62 (20.5) (91)	124 (20.5) (182)
Any treatment-related TEAE leading to treatment interruption	24 (7.9) (46)	26 (8.6) (42)	50 (8.3) (88)
Any TEAE leading to discontinuation from the study	22 (7.3) (26)	17 (5.6) (20)	39 (6.5) (46)
Any treatment-related TEAE leading to discontinuation from the study	12 (4.0) (13)	5 (1.7) (7)	17 (2.8) (20)
Any TEAE leading to death	0	2 (0.7) (2)	2 (0.3) (2)
Any treatment-related TEAE leading to death	0	0	0
Any serious ISR	1 (0.3) (1)	2 (0.7) (4)	3 (0.5) (5)
Most common TEAEs by system organ class†			
Investigations	65 (21.5) (102)	78 (25.8) (146)	143 (23.7) (248)
Infections and infestations	56 (18.5) (69)	54 (17.9) (60)	110 (18.2) (129)
Blood and lymphatic system disorders	42 (13.9) (86)	38 (12.6) (68)	80 (13.2) (154)
Metabolism and nutrition disorders	25 (8.3) (29)	20 (6.6) (25)	45 (7.5) (54)
Nervous system disorders	24 (7.9) (36)	19 (6.3) (27)	45 (7.5) (54)
Gastrointestinal disorders	15 (5.0) (17)	19 (6.3) (25)	34 (5.6) (42)
Vascular disorders	14 (4.6) (15)	11 (3.6) (13)	25 (4.1) (28)
Most common treatment-related TEAEs‡			
Alanine aminotransferase increased	16 (5.3) (19)	20 (6.6) (28)	36 (6.0) (47)
Neutropenia	15 (5.0) (26)	9 (3.0) (18)	24 (4.0) (44)
Leucopenia	12 (4.0) (23)	8 (2.6) (14)	20 (3.3) (37)
Aspartate aminotransferase increased	5 (1.7) (5)	11 (3.6) (11)	16 (2.6) (16)
Hypercholesterolaemia	8 (2.6) (9)	2 (0.7) (2)	10 (1.7) (11)

Continued

Table 5 Continued

Adverse event; n (%) (no of events)	MSB11456 (N=302)	EU-approved tocilizumab (N=302)	Total (N=604)

*Grade 4 TEAEs were neutropenia, hypercholesterolaemia and complete atrioventricular block/cardiogenic shock/myocardial infarction in one patient each in the MSB11456 group (ie, five TEAEs in three patients), and neutropenia and coronary artery thrombosis in one patient each in the EU-approved tocilizumab group (ie, two TEAEs in two patients); grade 5 TEAEs were COVID-19 and acute myocardial infarction in one patient each from the EU-approved tocilizumab group.
†TEAEs by system organ class with an event by preferred term occurring in ≥2% of either treatment group.
‡Treatment-related TEAEs occurring in ≥2% of either treatment group.
AESI, adverse events of special interest; EU, European Union; ISR, injection site reaction; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

(6.0 vs 5.6% of patients), followed by upper respiratory tract infection (1.7% vs 2.0% of patients); other types of infection AESI occurred in ≤0.5% of patients, except for latent tuberculosis (0.7% of patients overall). Hypersensitivity reactions, reported in 11 patients (3.6%) in the MSB11456 group and 16 subjects (5.2%) in the EU-approved tocilizumab group, were pruritus, dermatitis, rash, dermatitis contact, rash pruritic, dermatitis allergic, erythema, rash erythematous, contrast media allergy, drug hypersensitivity, allergic rhinitis, mouth ulceration, swelling face and flushing.

ISRs, most commonly erythema and pruritus, occurred in 7.9% of patients overall during the 24-week core period, and were reported in 11.3% of patients in the MSB11456 group and 4.6% of the EU-approved tocilizumab group. All ISRs were grade 1 or 2 in severity. A total of 20 patients with a negative baseline mycobacterium tuberculosis complex test result had a positive test result at 24 weeks (MSB11456 11/302, 3.6% of patients and EU-approved tocilizumab 9/302, 3.0% of patients), all of whom discontinued treatment due to the positive test results (mycobacterium tuberculosis complex test positive, seven in each group; latent tuberculosis, two in each group; mycobacterium tuberculosis complex test, one in the MSB11456 group; and false positive tuberculosis test, one in the MSB11456 group).

During the overall period (to week 55), there were no notable differences in the proportions of patients in the MSB11456 and EU-approved tocilizumab groups who experienced at least one event per TEAE category, and the frequency distribution of events per TEAE category was similar, although slightly higher due to the longer exposure, to that in the core period. No treatment-related deaths or anaphylactic reactions occurred during the overall study period, and SAEs and TEAEs leading to treatment or study withdrawal or treatment interruption were reported in similar proportions of patients and were similar in a nature in the MSB11456 and EU-approved tocilizumab groups (online supplemental table 2). ADA or NAb positivity did not appear to affect the safety of either treatment.

Following the transition from EU-approved tocilizumab to MSB11456 at week 24, the proportions of patients with at least one event per TEAE category and the severity of those events up to week 55 did not differ notably from those in the groups continuing MSB11456 or EU-approved tocilizumab (online supplemental table 3).

Laboratory findings and vital signs during the 24-week core period and the overall period were similar between MSB11456 and EU-approved tocilizumab. Similarly, there were no clinically meaningful differences between treatment groups in the extended period (after treatment switch).

DISCUSSION

The results of this randomised, double-blind trial demonstrate that, as expected for tocilizumab, efficacy was shown as early as week 2, increased through the first 12–16 weeks of treatment and was sustained to week 24 and week 52, thereafter. The efficacy profile of MSB11456 was therapeutically equivalent to that of EU-approved tocilizumab when subcutaneously administered weekly for 24 weeks at a dose of 162 mg to patients with moderate-to-severe active RA receiving concomitant methotrexate. Therapeutic equivalence between MSB11456 and EU-approved tocilizumab was demonstrated for the primary endpoint (change from baseline in DAS28-ESR at week 24), for the key secondary efficacy endpoint (ACR20 response at week 24) and for the early efficacy endpoint (change from baseline in DAS28-ESR at week 12). Multiple other efficacy endpoints commonly used to assess the efficacy of therapeutics in patients with RA[15] also supported the therapeutic similarity of MSB11456 and EU-approved tocilizumab and similar efficacy was observed between MSB11456 and EU-approved tocilizumab at each assessment time point. The study also showed that it is possible to switch from EU-approved tocilizumab to MSB11456 without any clinically relevant effect on efficacy, immunogenicity or safety parameters.

The DAS28 is a sensitive and specific tool to measure disease activity and response to treatment in RA.[16 17] Continuous endpoints such as the DAS28 combine both a measure of improvement and achievement of a specific disease activity state. Although both DAS28-ESR and DAS28-CRP were used as efficacy endpoints in this study, DAS28-ESR was selected as the primary endpoint over DAS28-CRP as IL-6 stimulates CRP synthesis in the liver. Tocilizumab, which directly affects CRP concentrations, can cause a rapid drop in CRP levels due to this

direct effect on CRP rather than its therapeutic effect.[18] The DAS28-CRP has also been shown to lack sensitivity for detecting inflammation in some patients.[18] Notably, no considerable differences were observed between DAS28-CRP and DAS28-ESR responses, especially not in favour of DAS28-CRP over DAS28-ESR. The timing of the primary efficacy analysis at week 24 was based on the availability of historical data from the originator's tocilizumab phase III clinical studies at the time of protocol development,[19–22] on which the assumptions for the equivalence margin and sample size were based. ACR20 was selected as the key secondary endpoint because ACR response rate is a widely used measure for assessing improvement in RA in clinical studies and includes more components to measure disease activity than the DAS28.[23] It is a dichotomous composite endpoint indicating the proportion of patients with at least 20% (50%/70%) improvement from baseline in the number of TJC and SJCs and in three or more out of the five ACR core set measures. ACR20 is also recommended by the FDA as a preferred measure for testing the efficacy of new drugs for RA, with respect to the signs and symptoms of disease.[23] In addition to the week 24 assessment, change from baseline in DAS28-ESR at week 12 was defined as the early efficacy endpoint to allow comparison of responses at a steeper part of the therapeutic response curve. The other supporting efficacy endpoints used to compare MSB11456 and EU-approved tocilizumab included validated, well-accepted composite endpoints as measures of clinical response (ACR50/70), as well as disease state (SDAI and CDAI).[15] Indeed, the DAS28, CDAI and SDAI are three of the six RA disease activity measures recommended and endorsed by the ACR to facilitate clinical decision-making in practice and are based on accurate reflections of disease activity, sensitivity to change, good discrimination between low, moderate and high disease activity states, incorporation of remission criteria and feasibility to perform in clinical settings,[24] supporting their selection as endpoints for this study.

Patients with previous biological treatment for RA are typically a harder population to treat than those who are biological naïve,[25 26] although tocilizumab has demonstrated efficacy irrespective of biological treatment history.[27] To ensure population homogeneity, which is crucial for biosimilar studies, we capped the proportion of patients who previously received one or two biologics for RA at 10% of the total study population, and excluded patients with prior use of more than two biologics for RA. That the study was conducted in central and eastern European countries, where access to biologics is still limited, may have assisted inclusion of sufficient numbers of patients who were bDMARD-naïve. However, when subgroups with and without previous exposure to biological treatment for RA were considered separately, no meaningful differences in efficacy between MSB11456 and EU-approved tocilizumab were observed in either subgroup, with efficacy shown irrespective of previous biological use. Similarly, because body weight is known to have an impact on the efficacy of tocilizumab (body weight >100 kg results in lower treatment effect[28 29]), body weight >100 kg was an exclusion criterion of the study.

Tocilizumab is generally considered a highly effective treatment with high clinical response rates.[1] In one study, the primary endpoint, mean change in DAS28-ESR at week 24, was −3.3 with tocilizumab, a significantly larger reduction than was seen with adalimumab.[30]

In this study, more than 98% of patients had at least one positive ADA result during the 55-week overall period, with a similarly high overall incidence in both the MSB11456 and EU-approved tocilizumab groups. While median ADA titres were low in all treatment groups, the incidence of ADA positivity was higher than that reported in trials of tocilizumab monotherapy conducted in patients with RA.[31 32] This higher incidence may, in part, be related to the ADA assay used in this study that has higher sensitive and drug tolerance than previously used assays.[31 33] Importantly, the incidence of NAb was low and similar in both groups, and the efficacy of both treatments did not appear to be affected by a positive ADA or NAb status. All treatments had similar efficacy irrespective of ADA/NAb status.

The safety profile of MSB11456 was similar to that of EU-approved tocilizumab overall treatment periods (the core, extended and overall periods), with safety measures such as SAEs, TEAEs leading to treatment or study discontinuation, AESIs including hypersensitivity reactions—the most commonly reported TEAEs—and other relevant measures of clinical safety showing no noteworthy imbalances between the treatment groups, including when ADA status was considered. It should be noted that the most commonly reported SAEs were related to COVID-19. Due to the ongoing COVID-19 pandemic, all cases of COVID-19, irrespective of severity, were considered to be medically important and were recorded as SAEs. These results further support the similarity between MSB11456 and EU-approved tocilizumab and build on evidence supporting the PK, PD, safety and immunogenic similarity of MSB11456 to the US-licensed and EU-approved tocilizumab in healthy subjects.[12]

To ensure population homogeneity, which is important to maximise sensitivity to detect potential differences between the proposed biosimilar product and the reference product, the participants in our study were all Caucasian, from Eastern Europe, with long-standing RA, a bodyweight <100 kg and, as noted above, were predominantly biological naïve. These population characteristics could also be considered a limitation of the study as they do not allow generalisability of our findings.

CONCLUSIONS

The primary objective of this study, to demonstrate equivalent efficacy at 24 weeks of the proposed biosimilar MSB11456 and EU-approved tocilizumab both administered subcutaneously in patients with moderate-to-severe active RA, was met. Notably, therapeutic equivalence

was demonstrated for the primary and key secondary endpoints, and results from multiple well-accepted efficacy measures and safety and immunogenicity analyses support the similarity of the two treatments. The results of the extension phase show that patients receiving EU-approved tocilizumab can be switched to MSB11456 without clinically relevant effects on efficacy, immunogenicity or safety. Thus, this study adds to the increasing body of evidence that the clinical effects of the proposed biosimilar MSB11456 are similar to those of the EU-approved tocilizumab.

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