Supplementary file

Additional Methodology

Exclusion criteria

Exclusion criteria included American College of Rheumatology (ACR) functional class IV, rheumatic autoimmune disease or a history of/current inflammatory joint disease other than RA, previous use of tocilizumab, another IL-6 acting drug, targeted synthetic disease modifying antirheumatic drug or high potency opioid analgesic, use of nonsteroidal anti-inflammatory drugs within 4 weeks of randomisation (if not at a stable dose or if more than the allowed maximum dose), use of oral corticosteroids >10 mg/day prednisone or equivalent within 6 weeks of randomisation (if not at a stable dose), presence of a serious and/or unstable and/or poorly controlled medical condition and confirmed or suspected COVID-19 or other non-allowed infection. Non-allowed infections included: Herpes zoster or any opportunistic invasive infection (e.g., histoplasmosis, coccidioidomycosis, blastomycosis, pneumocystis, listeriosis, legionellosis, or parasitic infestations) within 6 months of screening; frequent (>3 of the same type of infection per year requiring treatment) chronic or recurrent infections (e.g., urinary tract or upper respiratory tract infections); a positive test for human immunodeficiency virus Subtype 1 or 2, hepatitis C antibody, hepatitis B surface antigen and/or core antibody for immunoglobulin G and/or immunoglobulin M or total immunoglobulin at screening; a serious infection defined as requiring hospitalization or treatment with intravenous antibiotics within 8 weeks prior to randomisation; required treatment with oral antibiotics and/or antifungal drugs within 14 days prior to randomisation; medical evidence of active or latent tuberculosis as indicated by a

positive QuantiFERON®-TB Gold Plus test, chest X-ray, and/or clinical examination or active or latent tuberculosis disease at any time in the past.

Patients were screened for latent tuberculosis infection by the QuantiFERON®-TB Gold Plus test and by chest X-ray. If a patient tested positive for latent tuberculosis infection at screening, the patient failed screening and was not eligible; if the QuantiFERON®-TB Gold Plus test was indeterminate, the patient could be retested once within the screening period. If the retest was negative, the patient was eligible; if the retest was positive, the patient was not eligible. If the retest was again indeterminate, the patient was considered as having latent tuberculosis infection and was not eligible. No further QuantiFERON®-TB Gold Plus testing was performed.

Grading of adverse events

Adverse events (AEs) were graded using Version 5 of the National Cancer Institute–Common Terminology Criteria for Adverse Events (NCI-CTCAE); if no specific guidance was provided by the NCI CTCAE, the investigator used general NCI CTCAE definitions to assess the severity of AEs based on best medical judgment using the 5-point scale: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), Grade 5 (death).

Statistical analyses

Analysis sets

Efficacy endpoints were summarised using the intention-to-treat (ITT) analysis set, which included all randomised patients, and the per-protocol (PP) analysis set, which included all randomised and treated patients who completed the 24-week core period with treatment compliance of ≥80% and with no clinically important protocol deviations.

Additional estimands and models

In addition to the main estimand (treatment policy estimand), supportive estimands were defined. A supportive estimand was defined using the subset of compliant and adherent patients (i.e., the PP analysis set) as the population of interest. In addition, hypothetical return-to-baseline and hypothetical continuing per protocol estimands were defined, for which data impacted by intercurrent events were censored.

A pattern-mixture model was applied to missing and censored data for the hypothetical return-to-baseline estimand, and a multiple imputation procedure was used to impute both missing and censored data for the hypothetical continuing per protocol estimand.

Additional Results

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. In the core period, mean (SD) exposure was 22.3 (5.2) weeks for the MSB11456 group and 22.9 (3.9) weeks) in the EU-approved tocilizumab group; 21.6 (5.2) and 22.2 (4.0) injections per patient, respectively, were administered. Mean (SD) percentage treatment compliance was also similar between treatment groups (MSB11456: 90.0% [21.6]; EU-approved tocilizumab: 92.7% [16.7]), as were the proportions of patients with compliance of ≥80 to ≤100% during the core period (86.8% in the MSB11456 group and 90.7% in the EU-approved tocilizumab group). In the overall period (to week 52), the mean (SD) total duration of exposure to MSB11456 and EU-approved tocilizumab were 45.3 (14.6) weeks and 44.3 (15.4) weeks, respectively.

During the extended period (weeks 24 to 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.

Supplementary Table 1 Categorical efficacy responses at week 52 for patients with moderate-to-severe rheumatoid arthritis randomised to MSB11456 or EU-approved tocilizumab, extended period ITT analysis set

Parameter	**MSB11456 (N=267)**	**EU-approved tocilizumab (N=139)**	**EU-approved tocilizumab/ MSB11456 (N=137)**
DAS28-ESR[a]	n=248	n=126	n=126
Remission	161 (64.9)	83 (65.9)	86 (68.3)
Low	41 (16.5)	24 (19.0)	21 (16.7)
Moderate	39 (15.7)	16 (12.7)	15 (11.9)
High	7 (2.8)	3 (2.4)	4 (3.2)
DAS28-CRP	n=247	n=125	N=125
Responder[b]	70 (28.3)	35 (28.0)	38 (30.4)
CDAI[c]	n=248	n=126	n=126
Remission	87 (35.1)	47 (37.3)	47 (37.3)
Low	113 (45.6)	58 (46.0)	59 (46.8)
Moderate	36 (14.5)	15 (11.9)	14 (11.1)
High	12 (4.8)	6 (4.8)	6 (4.8)
SDAI[d]	n=247	n=125	N=125
Remission	95 (38.5)	47 (37.6)	50 (40.0)
Low	108 (43.7)	57 (45.6)	55 (44.0)
Moderate	34 (13.8)	17 (13.6)	15 (12.0)
High	10 (4.0)	4 (3.2)	5 (4.0)

Data are shown as number (percentage), with percentages calculated based on number of subjects with available data.

[a]DAS28-ESR: remission <2.6; low ≤2.6–<3.2; moderate ≤3.2–≤5.1; high >5.1.

[b]DAS28-CRP responder: TJC28 ≤1 and SJC28 ≤1 and PGA ≤10 mm and CRP ≤10 mg/L.

[c]CDAI: remission ≤2.8; low <2.8–≤10; moderate <10–≤22; high >22.

[d]SDAI: remission ≤3.3; low <3.3–≤11; moderate <11–≤26; high >26.

CDAI, Clinical Disease Activity Index; DAS28-CRP, Disease Activity Score-28 C-reactive protein; DAS28-ESR, Disease Activity Score-28 erythrocyte sedimentation rate; EU, European Union; ITT, intention-to-treat; SDAI, Simplified Disease Activity Index; SJC28, 28 Joint Count for Swelling, TJC28, 28 Joint Count for Tenderness.

Supplementary Table 2 Summary of adverse events in patients with moderate-to-severe rheumatoid arthritis treated with MSB11456 or EU-approved tocilizumab during the overall period,[a] safety analysis set

Adverse event; n (%) [no. of events]	**MSB11456 (N=302)**	**EU-approved tocilizumab (N=163)**
Any TEAE	234 (77.5) [713]	123 (75.5) [385]
Any treatment-related TEAE	106 (35.1) [296]	46 (28.2) [108]
Any SAE	48 (15.9) [55]	33 (20.2) [39]
Any treatment-related SAE	4 (1.3) [4]	3 (1.8) [6]
Any Grade ≥3 TEAE	43 (14.2) [58]	30 (18.4) [41]
Any treatment-related Grade ≥3 TEAE	15 (5.0) [20]	5 (3.1) [12]
Any Grade ≥4 TEAE[b]	3 (1.0) [5]	5 (3.1) [5]
Any treatment-related Grade ≥4 TEAE	2 (0.7) [2]	1 (0.6) [1]
Any AESI	115 (38.1) [192]	58 (35.6) [95]
Any treatment-related AESI	48 (15.9) [89]	22 (13.5) [40]
Any TEAE leading to treatment withdrawal	41 (13.6) [51]	23 (14.1) [31]
Any treatment-related TEAE leading to treatment withdrawal	22 (7.3) [26]	9 (5.5) [16]
Any TEAE leading to treatment interruption	84 (27.8) [140]	39 (23.9) [63]
Any treatment-related TEAE leading to treatment interruption	30 (9.9) [62]	13 (8.0) [23]
Any TEAE leading to discontinuation from the study	27 (8.9) [31]	19 (11.7) [25]
Any treatment-related TEAE leading to discontinuation from the study	13 (4.3) [14]	6 (3.7) [11]
Any TEAE leading to death	0	3 (1.8) [3]
Any treatment-related TEAE leading to death	0	0
Any serious ISR	2 (0.7) [5]	2 (1.2) [4]
Most common TEAEs by System Organ Class[c]		
Investigations	82 (27.2) [148]	49 (30.1) [92]
Infections and infestations	94 (31.1) [135]	47 (28.8) [64]
Blood and lymphatic system disorders	50 (16.6) [138]	32 (19.6) [62]
Metabolism and nutrition disorders	28 (9.3) [33]	17 (10.4) [23]

Adverse event; n (%) [no. of events]	**MSB11456 (N=302)**	**EU-approved tocilizumab (N=163)**
Gastrointestinal disorders	22 (7.3) [25]	20 (12.3) [26]
Musculoskeletal and connective tissue disorders	29 (9.6) [35]	13 (8.0) [15]
Nervous system disorders	29 (9.6) [43]	14 (8.6) [21]
Skin and subcutaneous tissue disorders	21 (7.0) [32]	13 (8.0) [15]
Vascular disorders	19 (6.3) [20]	7 (4.3) [8]
Renal and urinary disorders	6 (2.0) [8]	3 (1.8) [4]
Most common treatment-related TEAEs[d]		
Alanine aminotransferase increased	23 (7.6) [30]	10 (6.1) [14]
Neutropenia	16 (5.3) [35]	7 (4.3) [11]
Leukopenia	14 (4.6) [42]	7 (4.3) [17]
Aspartate aminotransferase increased	10 (3.3) [10]	7 (4.3) [7]
Thrombocytopenia	10 (3.3) [24]	5 (3.1) [5]
Hypercholesterolaemia	8 (2.6) [10]	3 (1.8) [3]

[a]Data for the EU-approved tocilizumab to MASB11456 treatment group are not shown because, unlike the other two treatment groups, this group included only patients who remained on treatment at the end of the core period, which could result in an imbalance in the reported rates of TEAEs.

[b]Grade 4 and 5 TEAEs occurring in the MSB11456 and EU-approved tocilizumab group all occurred during the core period, except one event of COVID-19 during the extended period in a patient in the EU-approved tocilizumab group. Grade 4 TEAEs were neutropenia, hypercholesterolaemia and complete atrioventricular block/cardiogenic shock/myocardial infarction in 1 patient each in the MSB11456 group (i.e., 5 TEAEs in 3 patients), and neutropenia and coronary artery thrombosis in 1 patient each in the EU-approved tocilizumab group (i.e., 2 TEAEs in 2 patients); Grade 5 TEAEs were COVID-19 in 2 patients and acute myocardial infarction in 1 patient from the EU-approved tocilizumab group.

[c]TEAEs by System Organ Class with an event by preferred term occurring in ≥2% of either treatment group

[d]Treatment-related TEAEs occurring in ≥2% of either treatment group

AESI, adverse events of special interest; CI, confidence interval; EU, European Union; ISR, injection site reaction; SAE, serious TEAE; TEAE, treatment-emergent adverse event.

Supplementary Table 3 Summary of adverse events in patients with moderate-to-severe rheumatoid arthritis treated with MSB11456 or EU-approved tocilizumab during the extended period (week 24 to 55); safety analysis set

Adverse event; n (%) [no. of events]	**MSB11456 (N=266)**	**EU-approved tocilizumab (N=136)**	**EU-approved tocilizumab/ MSB11456 (N=139)**
Any TEAE	120 (45.1) [250]	55 (40.4) [111]	57 (41.0) [121]
Any treatment-related TEAE	40 (15.0) [90]	13 (9.6) [29]	19 (13.7) [28]
Any SAE	20 (7.5) [21]	12 (8.8) [16]	10 (7.2) [13]
Any treatment-related SAE	1 (0.4) [1]	1 (0.7) [4]	0
Any Grade ≥3 TEAE	16 (6.0) [19]	10 (7.4) [15]	9 (6.5) [12]
Any treatment-related Grade ≥3 TEAE	5 (1.9) [6]	2 (1.5) [6]	1 (0.7) [1]
Any Grade ≥4 TEAE[a]	0	1 (0.7) [1]	2 (1.4) [3]
Any treatment-related Grade ≥4 TEAE	0	0	0
Any AESI	42 (15.8) [61]	17 (12.5) [26]	21 (15.1) [29]
Any treatment-related AESI	13 (4.9) [24]	4 (2.9) [10]	10 (7.2) [13]
Any TEAE leading to treatment withdrawal	9 (3.4) [12]	4 (2.9) [7]	10 (7.2) [11]
Any treatment-related TEAE leading to treatment withdrawal	5 (1.9) [8]	2 (1.5) [5]	7 (5.0) [8]
Any TEAE leading to treatment interruption	35 (13.2) [49]	13 (9.6) [15]	13 (9.4) [82]
Any treatment-related TEAE leading to treatment interruption	9 (3.4) [16]	2 (1.5) [5]	5 (3.6) [25]
Any TEAE leading to discontinuation from the study	5 (1.9) [5]	5 (3.7) [6]	6 (4.3) [19]
Any treatment-related TEAE leading to discontinuation from the study	1 (0.4) [1]	2 (1.5) [4]	4 (2.9) [10]
Any TEAE leading to death	0	1 (0.7) [1]	1 (0.7) [2]
Any treatment-related TEAE leading to death	0	0	0
Any serious ISR	1 (0.4) [4]	0	1 (0.7) [5]

Adverse event; n (%) [no. of events]	**MSB11456 (N=266)**	**EU-approved tocilizumab (N=136)**	**EU-approved tocilizumab/ MSB11456 (N=139)**
Most common TEAEs by System Organ Class[b]			
Infections and infestations	50 (18.8) [66]	22 (16.2) [27]	19 (13.7) [23]
Investigations	31 (11.7) [46]	17 (12.5) [20]	19 (13.7) [28]
Blood and lymphatic system disorders	20 (7.5) [52]	8 (5.9) [22]	10 (7.2) [17]
Metabolism and nutrition disorders	4 (1.5) [4]	4 (2.9) [7]	5 (3.6) [6]
Most common treatment-related TEAEs[c]			
Alanine aminotransferase increased	9 (3.4) [11]	3 (2.2) [3]	3 (2.2) [3]
Leukopenia	7 (2.6) [19]	3 (2.2) [9]	3 (2.2) [6]
Thrombocytopenia	8 (3.0) [13]	0	0

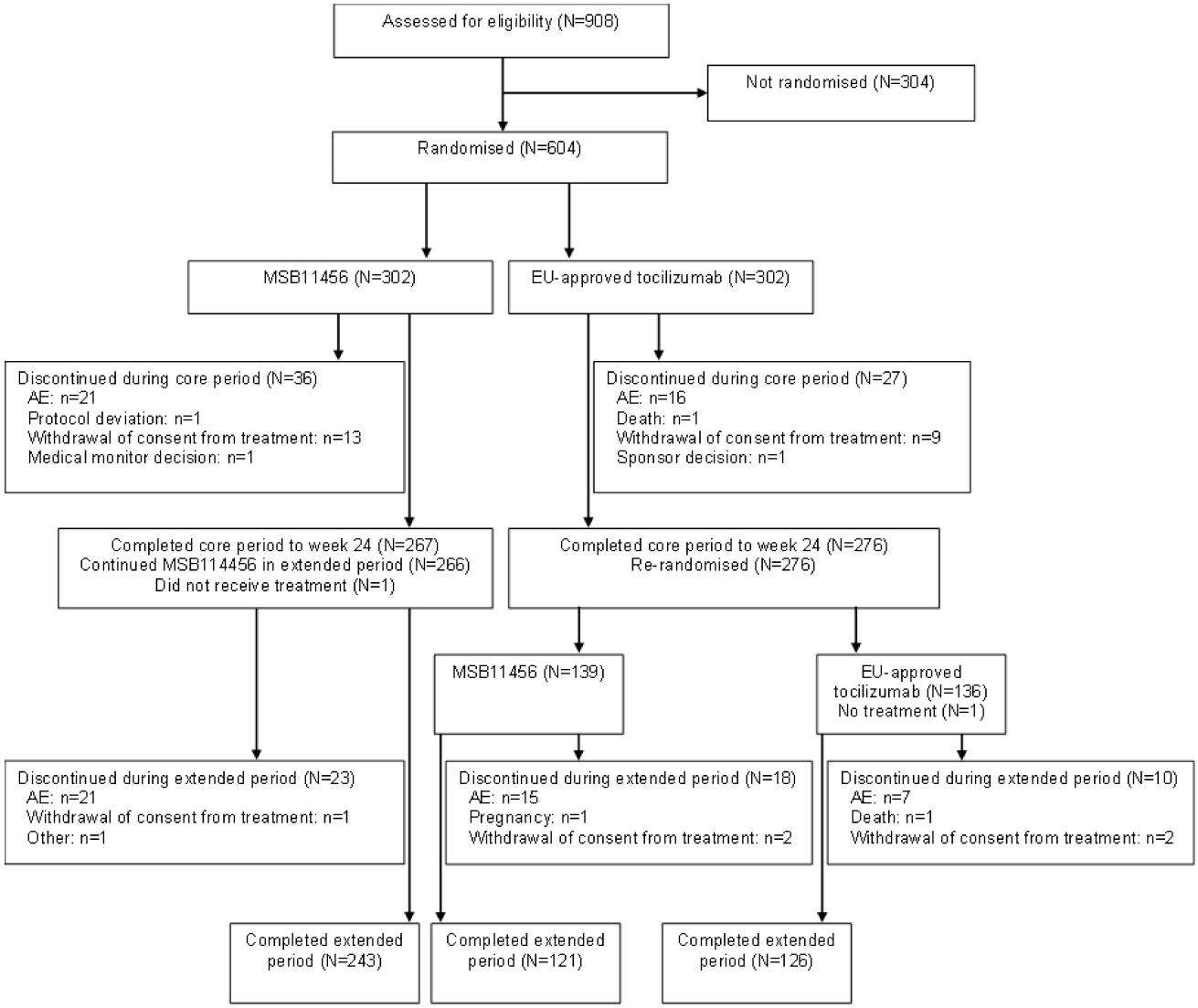
[a]Grade 4 TEAEs were pelvic inflammatory disease and mechanical ileus in 1 patient in the EU-approved tocilizumab to MSB11456 group; Grade 5 TEAEs were COVID-19 in 1 patient from the EU-approved tocilizumab group and myocardial infarction in 1 patient in the EU-approved tocilizumab to MSB11456 group.

[b]TEAEs by System Organ Class with an event by preferred term occurring in ≥2% of either treatment group

[c]Treatment-related TEAEs occurring in ≥2% of either treatment group

AESI, adverse events of special interest; CI, confidence interval; EU, European Union; ISR, injection site reaction; SAE, serious TEAE; TEAE, treatment-emergent adverse event.

Supplementary Figure 1. Patient disposition



Note that patients could discontinue treatment and remain in the study up to the end of the period; patients who completed each period remained in the study but were not necessarily still on treatment.