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ORIGINAL RESEARCH

A Comparison of the Immunogenicity of Intravenous BAT1806, a Tocilizumab Biosimilar, and Its Reference Product

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ABSTRACT

***Introduction*:** Biosimilars need to demonstrate similarity in terms of quality, pharmacokinetics (PK), efficacy, safety, and immunogenicity. Here, we report the outcome of a comprehensive evaluation of the immunogenicity of the biosimilar BAT1806 compared with the tocilizumab reference product (TCZ).

***Methods*:** We conducted a post hoc analysis of study BAT1806-001-CR, a comparative PK study in healthy male volunteers ($n=129$), and BAT1806-002-CR, a phase III, 52-week trial in patients with rheumatoid arthritis ($n=621$). Anti-drug antibodies (ADA), ADA titers, and neutralizing ADA were measured, and their impact on PK, safety, and efficacy parameters were assessed.

***Results*:** In BAT1806-001-CR, treatment-induced ADA were observed in 37.8% of participants for the BAT1806 group, 28.6% for the EU-sourced TCZ group, and 31.0% for the US-sourced TCZ group, without an impact on PK and safety. In BAT1806-002-CR after 52 weeks, 28.2% of participants in the BAT1806 group developed treatment-induced ADA, compared with 24.0% in the TCZ group and 19.7% of participants who initiated TCZ and switched to BAT1806 at week 24. ADA-positive participants reported lower geometric

Prior Publication: This study is a post hoc analysis of data from the BAT1806-002-CR and BAT1806-001-CR studies listed below: Leng X, Leszczyński P, Jeka S, et al. Comparing tocilizumab biosimilar BAT1806/BIIB800 with reference tocilizumab in patients with moderate-to-severe rheumatoid arthritis with an inadequate response to methotrexate: a phase 3, randomized, multicentre, double-blind, active-controlled clinical trial. Lancet Rheumatol. 2024;6(1):e40-e50. Zhang H, Wang H, Wei H, et al. A phase I clinical study comparing the tolerance, immunogenicity, and pharmacokinetics of proposed biosimilar BAT1806 and reference tocilizumab in healthy Chinese men. Front Pharmacol. 2020;11:609522.

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mean serum tocilizumab trough concentrations than ADA-negative participants in all treatment groups. ADA-positive participants achieved similar efficacy outcomes to ADA-negative participants in all treatment groups. ADA were not associated with an incremental risk of treatment-emergent adverse events or hypersensitivity in any of the treatment groups.

Conclusions: The results of these post hoc analyses did not indicate any clinically relevant differences in the immunogenicity profile of intravenously administered BAT1806 compared with TCZ.

Trial registration: ClinicalTrials.gov identifiers, NCT03606876, NCT03830203.

Keywords: Antibodies; Arthritis; Rheumatoid; Biosimilar pharmaceuticals

Key Summary Points

Why carry out this study?

It is a regulatory requirement to assess the immunogenic potential of a biosimilar compared with its reference product in clinical studies, using valid bioanalytical methods.

This study aimed to provide an integrated comparison of the immunogenicity of intravenously administered BAT1806 and the tocilizumab reference product (TCZ) based on a post hoc analysis of data from two clinical studies.

What was learned from the study?

The combined results from two randomized clinical studies, one in patients with rheumatoid arthritis (RA) receiving concomitant methotrexate and one in healthy volunteers, demonstrated similar humoral anti-tocilizumab antibody response profiles for BAT1806 administered intravenously compared with TCZ.

Patients with RA who were anti-drug antibody-positive had lower geometric mean serum tocilizumab trough concentrations in a phase III study (BAT1806-002-CR), but these were comparable between treatment groups and had no impact on efficacy or safety.

INTRODUCTION

BAT1806 (also referred to as BIIB800) is a tocilizumab biosimilar that has received regulatory approval in the United States (US), the European Union (EU), and China for the intravenous formulation. Tocilizumab is an interleukin-6 receptor (IL-6R)-targeted, recombinant, humanized, monoclonal immunoglobulin G1 antibody. Overexpression of IL-6 is associated with the pathogenesis of multiple inflammatory diseases, including rheumatoid arthritis (RA), hence, IL-6 is an important therapeutic target for RA [1]. Tocilizumab, marketed as RoActemra in the EU and Actemra in the US and other countries, was the first anti-IL-6R monoclonal antibody developed for the treatment of rheumatoid arthritis (RA). Tocilizumab specifically binds to both soluble and membrane-bound IL-6Rs and inhibits downstream IL-6 signaling.

All biologics, including biosimilars, may promote unwanted immune responses, which can range from the transient appearance of anti-drug antibodies (ADA) without any clinical significance, to severe life-threatening conditions such as anaphylaxis [2]. Given the potential for ADA/neutralizing ADA (NAb) to influence overall clinical benefit versus risk, it is a regulatory requirement to assess the immunogenic potential of a biosimilar compared with its reference product in clinical studies, using valid bioanalytical methods that have adequate sensitivity and drug tolerance [2–5]. Immunogenicity should always be evaluated in relation to relevant clinical parameters, including pharmacokinetic (PK)/drug exposure, pharmacodynamics (PD)/affinity for drug-receptor site, efficacy, and immune-mediated adverse events (AEs) [2, 6, 7].

Two clinical studies were conducted to evaluate the PK, efficacy, safety, and immunogenicity of BAT1806 in comparison with the tocilizumab reference product (TCZ) and have been reported previously (Table 1) [8–10]. These studies reported ADA and NAb incidences as well as the impact of ADA on primary efficacy endpoints and PK parameters. The objective of the current study was to provide an integrated comparison of the immunogenicity of intravenously

administered BAT1806 and TCZ based on a post hoc analysis of data of clinical studies investigating BAT1806. To complement the data obtained from clinical studies, and given their potential impact on immunogenicity, data from analytical studies on high molecular weight (HMW) variants are also discussed.

METHODS

Description of Bioanalytical Methods

Assay for Detection of Anti-tocilizumab Antibodies

Both the phase I and the phase III studies utilized an electrochemiluminescence (ECL) assay bridging format with labeled BAT1806. Serum samples were pre-treated in an acid dissociation step to ensure suitably sensitive detection of ADA in the presence of on-board drug levels.

The ADA assay was validated in accordance with global regulatory recommendations [2, 3, 11]. Per current recommendations, a single ADA assay using BAT1806 as the antigen was applied for detection of ADA in samples collected from participants treated with either BAT1806 or TCZ sourced from the EU (TCZ EU) or sourced from the US (TCZ US) [12]. Use of a single ADA assay was justified by the demonstration of antigenic equivalence, i.e., equivalent reactivity of anti-BAT1806-positive control antibody with TCZ EU and TCZ US (Supplementary Fig. S1a, b). In addition, it was shown that exchanging BAT1806 and TCZ as capture and detection agents did not result in differences in detecting various concentrations of positive control ADA.

Screening assay sensitivity was 7 ng positive control antibody/ml in the absence of TCZ and tolerant to 200 µg TCZ/ml for the detection of ≥ 10 ng (BAT1806-002-CR study) or ≥ 16 ng (BAT1806-001-CR study) positive control antibody/ml. While concentrations of the target protein, IL-6R, of up to 600 ng/ml did not interfere with detection of the positive control signal, false-positive signals were detected in the screening assay used for the BAT1806-002-CR study when the IL-6R concentration was higher than 150 ng/ml; however, the impact of soluble IL-6R interference was not determined for the confirmatory assay.

ADA positivity was based on the confirmatory ADA assay demonstrating inhibition in the presence of excess TCZ (5 µg BAT1806 per ml). Confirmed ADA-positive samples were further characterized for the magnitude of the signal (titer) in the ADA assay format. In the BAT1806-002-CR study, ADA titer was defined as the highest sample dilution yielding a signal greater than or equal to the assay cut point (0.1% false-positive rate) multiplied by the minimum required dilution ([MRD] = 20). In the BAT1806-001-CR study, ADA titers were presented as interpolated values between the highest dilution that was above the titration cut point and the adjacent dilution below the titration cut point, multiplied by the MRD of 10.

Cut points were calculated by statistical analysis [13] of signals for 54 individual sera from treatment-naive healthy donors for the BAT1806-001-CR study and using pre-treatment samples from 51 patients with RA, the study population for the BAT1806-002-CR study. The cut points were based on false-positive detection rates of 5%, 1%, and 0.1% for the screening, confirmatory and titration tiers, respectively.

NAb Assay to Characterize the Neutralizing Potential of Anti-BAT1806 and Anti-TCZ Antibodies

A competitive ligand-binding ECL assay was used to measure capacity of NAb to inhibit the binding of labeled BAT1806 to recombinant human IL-6R coated on microtiter plates. The NAb assay sensitivity was 138 ng positive control antibody/ml and drug tolerance was 25 µg drug/ml for detection of 500 ng positive control antibody/ml using a cut point corresponding to a 1% false-positive rate. The assay demonstrated that sIL-6R up to 100 ng/ml did not interfere with detecting the positive control antibody at a concentration of 100 ng/ml or higher. Adequate sensitivity and drug tolerance of the NAb assay were confirmed by the high concordance of the ADA and NAb assay results:

Table 1 Clinical studies contributing data for the relative immunogenicity assessment of BAT1806

	Study	
	BAT1806-002-CR (phase III)[a]	**BAT1806-001-CR (phase I)**[b]
Study NCT	NCT03830203	NCT03606876
BAT1806 dose (IV)	8 mg/kg body weight	4 mg/kg body weight
Population	Patients with RA and MTX-IR	Healthy volunteers
Design	Randomized 2:1:1, BAT1806, TCZ EU, TCZ EU switch to BAT1806	Randomized 1:1:1, BAT1806, TCZ EU, TCZ US
Duration	52 weeks (TP1: 24 weeks; TP2: 24 weeks, SFU: 4 weeks)	57 days
Participants randomized/treated	621/621	138/129
Variables		
Immunogenicity[c]		
ADA (including NAb)	✓	✓
ADA titer	✓	✓
NAb	✓	✓
Serum tocilizumab concentration/PK parameters		
Serum tocilizumab concentration [μg/ml]	✓	✓
Serum tocilizumab PK parameters:	N/A	✓
C_{max} [μg/ml]		
AUC_{0-t} [μg*h/ml]		
AUC_{0-inf} [μg*h/ml]		
Efficacy		
ACR20, ACR50, ACR70	✓	N/A
DAS28-ESR	✓	N/A
Safety		
AE (including related AEs)	✓	✓

ACR American College of Rheumatology, *ACR20/50/70* ACR 20/50/70% response, *ADA* anti-drug antibody, *AE* adverse event, AUC_{0-inf} area under the concentration–time curve from time zero to infinity, AUC_{0-t} area under the concentration–time curve from time zero to time *t*, C_{max} maximum concentration, *DAS28* Disease Activity Score-28, *ESR* erythrocyte sedimentation rate, *EU* European Union, *DAS28-ESR* DAS28 for rheumatoid arthritis with ESR, *IV* intravenous, *MTX-IR*, inadequate response to methotrexate, *MTX* methotrexate, *N/A* not applicable, *NAb* neutralizing antibody, *NCT* national clinical trial, *PK* pharmacokinetic, *SFU* safety follow-up, *TCZ* reference tocilizumab, *TP* treatment period, *US* United States

[a]All participants were required to continue a stable MTX dose (10–25 mg/week) by the same route of administration throughout the study. BAT1806 or TCZ EU were administered every 4 weeks across treatment periods. The primary objective of the study was to demonstrate equivalent efficacy of BAT1806 and TCZ EU. Secondary objectives were to: (1) compare BAT1806 and TCZ EU efficacy over time based on secondary efficacy endpoints; (2) evaluate safety and tolerability of BAT1806 compared with TCZ over the study period; (3) evaluate the immunogenicity profile of BAT1806 compared with TCZ EU in terms of ADA/NAb induction; (4) evaluate the steady-state PK of BAT1806 compared with TCZ EU; (5) assess safety and immunogenicity following treatment switch from TCZ EU to BAT1806

[b]Healthy male Chinese participants received a single dose of either BAT1806, TCZ EU, or TCZ US. The primary objective of the study was to establish pairwise biosimilarity between BAT1806 versus TCZ EU or TCZ US, and TCZ US versus TCZ EU. The secondary objective was to evaluate the clinical safety, tolerability and immunogenicity of BAT1806, TCZ US, and TCZ EU

[c]A participant was considered ADA/NAb-positive if they had at least one ADA/NAb-positive sample during the period (excluding baseline/week 0) up to and including the end of the treatment period

95% of confirmed ADA-positive samples from BAT1806-002-CR were also NAb-positive.

Assay for Quantitation of BAT1806 and TCZ (EU and US) in Human Serum

In both studies, serum concentrations of BAT1806 and TCZ were quantified using a ligand-binding enzyme-linked immunosorbent assay where BAT1806 or TCZ in human serum were bound to recombinant human IL-6R coated on 96-well microtiter plate wells, followed by detection of bound drug using a horseradish peroxidase-conjugated anti-tocilizumab non-paratope-specific, anti-idiotype monoclonal antibody (Bio-Rad Cat. No. HCA257). The validated assay range was 0.2–10.0 µg/ml.

Assessment of Clinical Immunogenicity

The immunogenicity analyses described here were based on post hoc analyses of participant-level data for the Safety Analysis populations in the BAT1806-002-CR and BAT1806-001-CR studies.

The BAT1806-001-CR study [10] evaluated comparative PK following a single intravenous (IV) administration of 4 mg/kg of BAT1806, TCZ EU, and TCZ US to 129 healthy Chinese male volunteers in a randomized, double-blind, 3-arm, parallel-group design. The primary objective of the study was to establish a pairwise PK biosimilarity between BAT1806 versus TCZ EU, BAT1806 versus TCZ US and TCZ EU versus TCZ US. Participants were randomized in a 1:1:1 ratio and followed up for 57 days. BAT1806-002-CR [8, 9] was a 52-week, randomized, double-blind, parallel-group study to compare the efficacy and safety of BAT1806 to TCZ EU in 621 patients with RA with an inadequate response to methotrexate (MTX). The primary objective of this study was to demonstrate the equivalent efficacy of BAT1806 and TCZ EU in participants with RA inadequately controlled by MTX. This study comprised three periods: Treatment Period 1 (TP1) (weeks 0–24); Treatment Period 2 (TP2) (weeks 24–48); and a 4-week safety follow-up period. Eligible patients were randomized in a 2:1:1 ratio to one of three treatment groups BAT1806 (TP1)/BAT1806 (TP2), TCZ (TP1)/TCZ (TP2) or TCZ (TP1) followed by BAT1806 (TP2) each to receive intravenously administered tocilizumab every 4 weeks at a dose of 8 mg/kg. Prior treatment with more than two biological disease-modifying anti-rheumatic drugs (DMARDs), or an IL-6 inhibitor or any targeted synthetic DMARD was not permitted. The patients with RA treated in the BAT1806-002-CR study received concomitant MTX (stable dose level of 10–25 mg MTX/week). Participants were expected to remain on their stable dose of MTX throughout the study.

Key characteristics of each study, as well as the variables used in the immunogenicity analyses, are presented in Table 1. ADA evaluable participants were defined as those who had an ADA result at baseline (either ADA-positive or ADA-negative) and had at least one post-treatment result. A participant was considered ADA/NAb-positive if they had at least one ADA/NAb-positive sample during the period (excluding baseline/week 0) up to and including the end of the treatment period. ADA responses were defined as follows: 'Pre-existing ADA' (antibodies reactive with the biologic drug that were present in participants before study treatment) and 'Treatment-induced ADA' (ADA developed de novo [seroconversion] following biologic drug administration [i.e., formation of ADA any time after the initial drug administration in a participant without pre-existing ADA]) [14]. Treatment-induced ADA were further subcategorized as either 'Transient' or 'Persistent'. in line with recommendations from Shankar et al. [14] (Supplementary Material 1). No data imputation for missing ADA data was applied and data were presented 'as observed'. To determine the relative impact on efficacy, American College of Rheumatology (ACR) 20, ACR50 and ACR70 response rates, as well as Disease Activity Score-28 for rheumatoid arthritis with erythrocyte sedimentation rate (DAS28-ESR) were evaluated. Efficacy outcomes were analyzed on the full analysis set, which included all randomized participants. Safety was evaluated with respect to (i) treatment-related serious AEs by ADA

status, and (ii) AEs corresponding to Preferred Terms within the broad Standardised Medical Dictionary for Regulatory Authorities query (SMQ) of 'hypersensitivity' by ADA status [15]. The safety analyses were performed on the safety analysis set, which included all randomized participants who received any treatment with the study drug.

Statistical Analysis

ACR20/50/70 responses and DAS28-ESR were descriptively analyzed in the full analysis set and for predefined subgroups (ADA/NAb status [in TP1 and TP2 separately and combined], region [Central Europe/Asia Pacific]), and treatment period. In BAT1806-002-CR, TP1 and TP1 and TP2 (combined), neither missing values nor intercurrent events were considered in the descriptive analysis.

The estimated response probability/change in DAS28-ESR scores from baseline for each treatment group with the 90% respective 95% confidence intervals for the between-treatment-group difference was calculated.

Product Quality

The analytical and biological characteristics of BAT1806 were assessed using comprehensive analytical techniques and in vitro assays to determine similarity with TCZ EU, TCZ US, and China sourced tocilizumab. The results of these analyses are presented elsewhere [16]. HMW content was determined by size exclusion-high-performance liquid chromatography (HPLC). The degradation trends of BAT1806 and TCZ for HMW-variant content were also compared under accelerated conditions (products stored at 25°C for 12 weeks).

Ethical Approval

BAT1806-002-CR was conducted in accordance with the Declaration of Helsinki and/or all relevant local regulations, in compliance with the International Council for Harmonisation Good Clinical Practice guidelines and according to the appropriate regulatory requirements in the countries where the study was conducted. BAT1806-001-CR was approved by The First Bethune Hospital of Jilin University, Changchun, Jilin, China. The patients/participants provided their written informed consent to participate in this study. Patient consent was not applicable for this comparison article.

RESULTS

In both studies, the treatment groups were balanced in terms of baseline characteristics, including age and weight [10]. The treatment groups in the BAT1806-002-CR study were also balanced in terms of baseline disease activity, ethnicity, gender, and prior targeted synthetic DMARD and biologic DMARD exposure [8]. ADA-positive and ADA-negative subgroups were comparable in terms of baseline characteristics (data not shown).

ADA/NAb Response Dynamics

The BAT1806-001-CR Study

In the single IV dose study in healthy volunteers, BAT1806-001-CR, there were 45 ADA-evaluable participants for BAT1806, 42 for TCZ EU, and 42 for TCZ US. The incidence of treatment-induced ADA was 37.8% for the BAT1806 group compared with 28.6% for the TCZ EU group and 31.0% for the TCZ US group (Supplemental Table S1). Treatment-induced ADA were detectable as early as day 15, with ADA prevalence increasing through days 43 and 57.

The geometric mean maximal ADA titer was 77.4 for BAT1806 compared with 40.1 for TCZ EU and 42.6 for TCZ US. ADA titer distributions substantially overlapped (Fig. 1). Of the ADA-positive participants, 84.2% in the BAT1806 group, 83.3% in the TCZ EU group, and 100% in the TCZ US group were also NAb-positive.

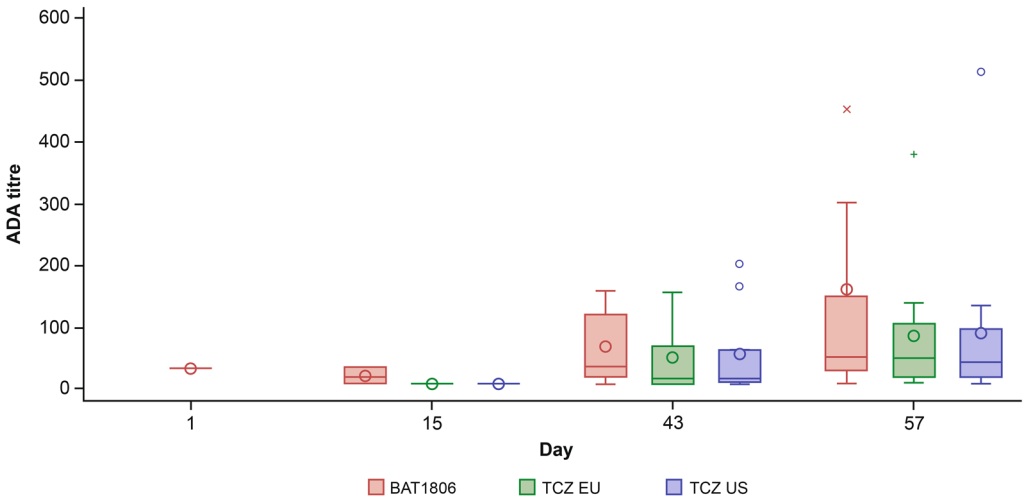

Fig. 1 Box and whiskers plot for ADA titer over time in BAT1806-001-CR. Individual symbols indicate outliers. *Lines within boxes* = median. *Boxes* = IQR. *Bottom whisker* = 25th percentile *IQR. *Top whisker* = 75th percentile *IQR. Note: One outlier with an ADA titer of 1140 that occurred in the BAT1806 group is not presented in this plot. The safety analysis set contained all participants who received study drug and were analyzed according to treatment received. *ADA* anti-drug antibody, *IQR* interquartile range, *PK* pharmacokinetic, *TCZ EU* European Union-approved tocilizumab, *TCZ US* United States-approved tocilizumab

The BAT1806-002-CR Study

During the 52-week treatment period in the BAT1806-002-CR study, ADA and NAb prevalence, and ADA titer profiles were similar for the BAT1806, TCZ EU – TCZ EU and TCZ EU – BAT1806 groups (Table 2). The incidence of treatment-emergent ADA during the complete 52-week period in the BAT1806-002-CR study was 28.2% (88 of 312 participants) for the BAT1806 group compared with 24.0% (40 of 167 participants) for the TCZ EU – TCZ EU group and 19.7% (28 of 142 participants) for the TCZ EU – BAT1806 group. In participants with treatment-induced ADA, these were categorized as transient at 54.5%, 67.9%, and 55.0% for the BAT1806, TCZ EU – TCZ EU, and TCZ EU – BAT1806 groups, respectively. The majority (94.7 to 100%) of ADA-positive participants were also positive in the NAb assay.

ADA prevalence at baseline was 1.3% (four of 312 participants) for BAT1806 versus 1.6% (five of 309 participants) for the TCZ EU combined group. This approximates the expected false-positive rate of 1% for the applied assay cut point. Supplementary Table **S2** shows the ADA status of participants in TP1 compared with their ADA status at weeks 28, 36, 48, and 52 in TP2. Among participants in the BAT1806 and TCZ EU – BAT1806 groups, < 5% seroconverted after re-randomization at week 24. Over half of the participants who were ADA-positive in TP1 became ADA-negative in TP2.

For all treatment groups, geometric mean ADA titer values ranged from 20 to 30 throughout the 52-week study period. The results in the BAT1806 group were slightly skewed by one participant who developed an ADA titer of 1280 at week 24 that was higher than the maximal titer detected in all other participants (160). This participant was ADA- and NAb-positive at baseline and all subsequent visits and was also rheumatoid factor-positive at baseline. Of note, despite these relatively higher ADA titers, this participant still had an ACR20 response from week 24 and an ACR50 response from week 44.

Table 2 Summary of ADA and NAb results across TP1 and TP2 combined in the BAT1806-002-CR study

	Baseline	Week 4	Week 12	Week 24	Week 28	Week 36	Week 48	Week 52
BAT1806 (N = 312)								
Number of participants with a sample result	312	302	290	279	285	285	280	280
Participants with ADA-positive sample, *n* (%)	4 (1.3)	35 (11.6)	19 (6.6)	29 (10.4)	34 (11.9)	28 (9.8)	28 (10.0)	16 (5.7)
ADA titer								
Geo mean	23.8	21.2	20.7	23.6	23.5	22.6	22.1	24.8
GCV (%)	35.7	36.3	16.0	91.3	71.1	73.2	56.2	105.8
Median (range)	20 (20–40)	20 (20–160)	20 (20–40)	20 (20–1280)	20 (20–640)	20 (20–640)	20 (20–320)	20 (20–640)
< 20, m (%)	1 (0.3)	31 (10.3)	16 (5.5)	22 (7.9)	29 (10.2)	24 (8.4)	25 (8.9)	14 (5.0)
Participants with NAb-positive sample, *n* (%)	3 (1.0)	35 (11.6)	18 (6.2)	29 (10.4)	34 (11.9)	28 (9.8)	28 (10.0)	15 (5.4)
% of participants with ADA-positive sample	75.0	100.0	94.7	100.0	100.0	100.0	100.0	93.8
TCZ EU – TCZ EU (N = 167)								
Number of participants with a sample result	167	163	149	140	142	141	140	139
Participants with ADA-positive sample, *n* (%)	2 (1.2)	11 (6.7)	13 (8.7)	11 (7.9)	14 (9.9)	7 (5.0)	8 (5.7)	11 (7.9)
ADA titer								
Geo mean	20.0	20.0	21.1	20.0	20.0	20.0	20.0	20.0
GCV (%)	0.0	0.0	19.4	0.0	0.0	0.0	0.0	0.0
Median (range)	20 (20–20)	20 (20–20)	20 (20–40)	20 (20–20)	20 (20–20)	20 (20–20)	20 (20–20)	20 (20–20)
< 20, m (%)	1 (0.6)	9 (5.5)	12 (8.1)	10 (7.1)	14 (9.9)	6 (4.3)	7 (5.0)	10 (7.2)
Participants with NAb-positive sample, (*n*)	0	11 (6.7)	13 (8.7)	11 (7.9)	14 (9.9)	7 (5.0)	8 (5.7)	10 (7.2)
% of participants with ADA-positive sample		100.0	100.0	100.0	100.0	100.0	100.0	90.9
TCZ EU – BAT1806 (N = 142)								
Number of participants with a sample result	142	140	133	134	134	137	134	133
Participants with ADA-positive sample, *n* (%)	3 (2.1)	10 (7.1)	9 (6.8)	6 (4.5)	10 (7.5)	13 (9.5)	9 (6.7)	2 (1.5)

Table 2 continued

	Baseline	Week 4	Week 12	Week 24	Week 28	Week 36	Week 48	Week 52
ADA titer								
Geo mean	31.7	20.0	25.2	28.3	20.0	20.0	20.0	20.0
GCV (%)	94.7	0.0	78.5	102.8	0.0	0.0	0.0	0.0
Median (range)	20 (20–80)	20 (20–20)	20 (20–160)	20 (20–160)	20 (20–20)	20 (20–20)	20 (20–20)	20 (20–20)
< 20, m (%)	2 (1.4)	9 (6.4)	8 (6.0)	5 (3.7)	10 (7.5)	12 (8.8)	8 (6.0)	2 (1.5)
Participants with NAb-positive sample, *n* (%)	2 (1.4)	10 (7.1)	9 (6.8)	6 (4.5)	10 (7.5)	13 (9.5)	9 (6.7)	2 (1.5)
% of participants with ADA-positive sample	66.7	100.0	100.0	100.0	100.0	100.0	100.0	100.0

ADA/NAb status includes TP1 + TP2. ADA titer is a quasi-quantitative expression of the level of ADA in a sample. Any titer reported as < 20 is imputed as 20. The percentage of the number of < 20 is computed as m/n in percentage. The safety analysis set included all randomized participants that received any treatment with study drug. Participants were analyzed according to treatment received at the start of TP1 and TP2

ADA anti-drug antibody, *EU*, European Union, *GCV*, geometric coefficient of variation, *Geo mean* geometric mean, *m* number of participants with a sample ADA titer result < 20 at respective visit, *N* number of participants in the safety analysis set, *n* number of participants with a sample result at respective visit, denominator in percentage calculations, *NAb* neutralizing antibody, *TCZ* reference tocilizumab, *TP* treatment period

Impact of ADA Status on PK Parameters

The BAT1806-001-CR Study

In the BAT1806-001-CR study, serum tocilizumab concentrations were comparable across time points and ADA/NAb status. No trends of reduced tocilizumab concentrations were observed in the presence of ADA or NAb in any treatment group (Fig. 2 and Supplementary Table S3).

The BAT1806-002-CR Study

In both the BAT1806 and TCZ EU treatment groups, the geometric mean serum tocilizumab concentration (C_{trough}) for participants who were ADA-positive was lower than for participants who were ADA-negative at each time point, although the 95% confidence intervals were substantially overlapping (Fig. 3). Most notably, the scale of reduction in the weighted average geometric mean serum tocilizumab C_{trough} for ADA-positive participants relative to ADA-negative participants was similar for the different treatment groups: for TP1, 39.4% lower in the BAT1806 group compared with 44.7% lower in the TCZ group; for TP2, 30.0% lower in the BAT1806 group compared with 45.6% lower in the TCZ EU – TCZ EU group and 37.3% lower in the TCZ EU – BAT1806 (Supplementary Table S4). Thus, there was no clear treatment-related difference in tocilizumab exposure for ADA-positive participants compared with ADA-negative participants.

Impact of ADA Status on Efficacy

No trend of reduced efficacy was observed in ADA-positive participants compared with ADA-negative participants in any treatment group and ACR20/50/70 and DAS28-ESR responses were comparable both between treatment groups and between ADA subgroups (Tables 3 and 4). Participants who were ADA-positive and switched from TCZ to BAT1806 at week 24 had comparable ACR20/50/70 responses at week 48 to those who continued on TCZ. At all time points, the observed differences in DAS28-ESR scores by ADA status or by treatment group were below the threshold of 0.6 for minimal clinically important difference [17]. The treatment switch from TCZ EU to BAT1806 at week 24 had no apparent impact on DAS28-ESR scores.

An analysis of tocilizumab serum concentration at week 24 by ACR20/50/70 response was performed to investigate the

potential impact of reduced serum trough levels in ADA-positive participants. There were no apparent differences in trough serum concentrations between those who had an ACR20 response versus those who achieved ACR50/70 responses with error bars of responders and non-responders largely overlapping (Supplementary Fig. S2).

Safety

There were no differences in the proportion of participants experiencing serious AEs between treatment groups and ADA status (Supplementary Table S5). Most reported serious AEs were infections and infestations that occurred exclusively in ADA-negative participants. There was no apparent incremental risk of a treatment-related hypersensitivity reaction for BAT1806 when compared with TCZ EU (Supplementary Table S6). Two participants, both receiving TCZ EU, experienced a drug hypersensitivity in TP1, both of moderate intensity and leading to study drug discontinuation. One participant had pre-existing ADA and was ADA-positive at week 12 and week 16; the other participant was baseline negative but had positive ADA results at visits preceding the AE. Both participants were withdrawn after the reaction. One infusion-related reaction was reported: this AE occurred following the first infusion for a participant who was ADA-negative in the TCZ EU – BAT1806 group and the participant completed the study. In the BAT1806-001-CR study, no serious treatment-emergent AEs (TEAEs) were reported. One participant who was positive for ADA and NAb in the BAT1806 group experienced one TEAE in the SMQ 'hypersensitivity' category (Supplementary Table S7). The participant experienced a mild rash that occurred on day 6 and resolved without any action by day 18. The participant was ADA-negative on day 15, but ADA-positive on day 43 with a titer of 30; no other participants experienced a SMQ 'hypersensitivity' TEAE. There were no infusion-related reactions reported in BAT1806-001-CR.

Product Quality Results

Size exclusion-HPLC profiles showed that the BAT1806 IV drug product had a lower HMW content (range 0.38–0.52%) versus the reference products TCZ EU, TCZ US and TCZ CN (0.45–0.87%). Under accelerated degradation conditions (25°C), BAT1806 demonstrated no difference in levels of high or low molecular weight variants, confirming the suitability of the formulation of BAT1806 IV (Supplementary Fig. S3).

DISCUSSION

The combined results from two randomized clinical studies, one performed using repeated IV administration at 4-weekly intervals for 48 weeks in patients with RA receiving concomitant MTX and the other in healthy volunteers receiving a single IV administration, demonstrated similar humoral anti-tocilizumab antibody response profiles for BAT1806 IV compared with TCZ. Analysis of the relationship of the humoral anti-tocilizumab antibody response profiles to PK, exposure, efficacy and safety confirmed the absence of clinically meaningful differences in immunogenicity profiles.

While ADA positivity was associated with lower trough serum concentrations in the comparative efficacy and safety study, BAT1806-002-CR, the scale of reduced exposure was similar across the different treatment groups and did not compromise efficacy or safety – an outcome consistent with the relatively low magnitude of the anti-tocilizumab antibody response. Similar proportions of participants achieved ACR20, ACR50, and ACR70 responses, and comparable mean DAS28-ESR scores were observed among ADA-positive participants treated with BAT1806 or TCZ-EU across both treatment periods. When compared with the BAT1806 group, no clear differences in efficacy were observed after switching from TCZ-EU to BAT1806.

In the comparative PK study performed in healthy Chinese male participants, the proportion of treatment-induced ADA-positive

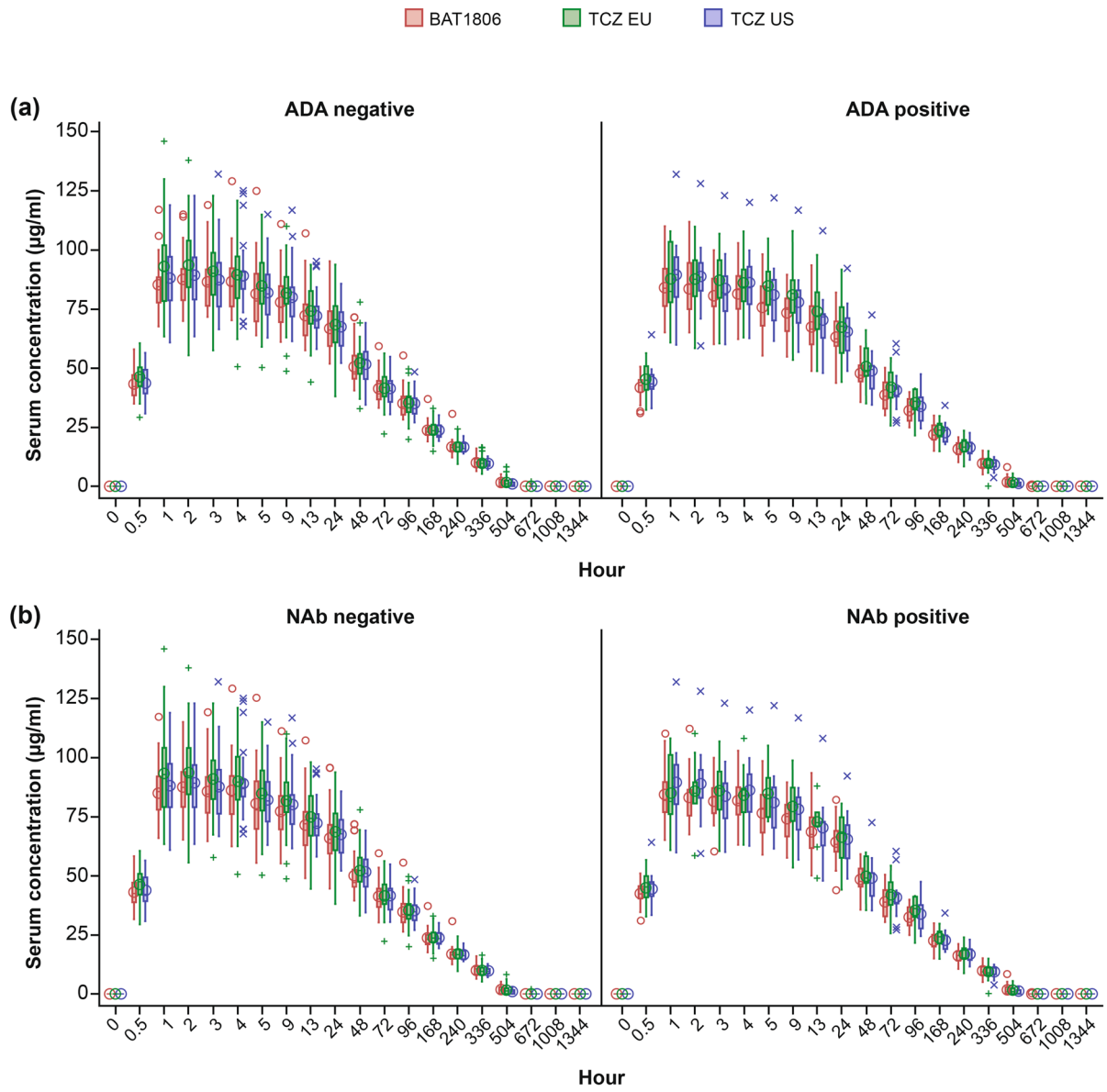

Fig. 2 Serum tocilizumab concentration over time by ADA (**a**) and NAb (**b**) status in BAT1806-001-CR. *Lines within boxes* = median. *Boxes* = IQR. *Bottom whisker* = 25th percentile *IQR. *Top whisker* = 75th percentile *IQR. Individual symbols indicate outliers. Concentration levels below limit of quantification recorded as '0', were imputed as 0.2 µg/ml, which is the lower limit of quantification. Data from the PK concentration set, which consists of all participants with at least one post-dose evaluable concentration measurement and without protocol violation that significantly influences PK concentration. *ADA* anti-drug antibody, *IQR* interquartile range, *NAb* neutralizing antibody, *PK* pharmacokinetic, *TCZ EU* European Union-approved tocilizumab, *TCZ US* United States-approved tocilizumab

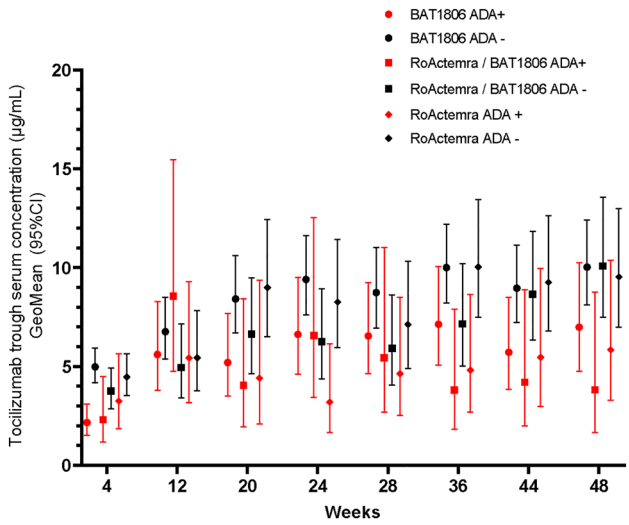

Fig. 3 Serum tocilizumab trough concentration by ADA status in TP1 and TP2 combined in BAT1806-002-CR. Midpoint = median. *Bottom whisker* = 25th percentile *IQR. *Top whisker* = 75th percentile *IQR. Concentration levels below limit of quantification were imputed as 0.2 µg/ml, which is the lower limit of quantification. Note: Five outliers are not presented in the plot given serum concentrations > 150 µg/ml. The PK set included all randomized participants that received any treatment with study drug and had at least one evaluable PK assessment post baseline. Participants were analyzed according to treatment received at the start of TP1 and TP2. *ADA* anti-drug antibody, *IQR* interquartile range, *PK* pharmacokinetic, *RoActemra* European Union-approved tocilizumab, *TP* treatment period

participants was 37.8% for BAT1806 compared with 28.6% for TCZ-EU and 31.0% for TCZ-US. The maximal geometric mean ADA titer was 77.4 for BAT1806 compared with 40.1 for TCZ-EU and 42.6 for TCZ-US. There were no differences in PK parameters for the ADA-positive subpopulations across treatment groups.

ADA/NAb incidences in both studies were higher than reported for studies investigating the originator product, which reported an ADA incidence of 1.3% in a pooled analysis of participants with RA receiving concomitant DMARDs [18]. Such higher ADA incidences have been observed in recent studies investigating biosimilars, which utilize novel, usually more drug-tolerant assays that are developed according to current regulatory expectations [19]. The ADA assay applied for the detection of anti-tocilizumab antibodies in BAT1806-002-CR was able to detect 10.0 ng/ml of positive control anti-BAT1806 antibody in the presence of 200 µg/ml tocilizumab, which is considerably more tolerant to circulating drug than that reported for the ADA assay used in clinical trials to support marketing authorization of the reference product [20]. A comparative efficacy and safety study of another authorized tocilizumab biosimilar, MSB11456, reported ADA incidences in up to 95% of participants with moderate to severe RA receiving MTX [21]. As for BAT1806, the sponsor of MSB11456 applied an ECL bridging assay that included an acid dissociation sample pre-treatment step to improve drug tolerance. Phase I, single-dose, IV studies in healthy volunteers for (candidate) biosimilars and the reference product reported ADA incidences between 91.9–98.5% for MSB11456 and 2.3–11.1% for CT-P47 [22, 23], compared with 0% reported in a (small) innovator study [24].

The higher sensitivity/drug tolerance of these newer assays may result in detection of clinically irrelevant levels of ADA, that is, ADA levels that are below a threshold for a negative impact on efficacy or safety. This increases the importance of interpreting differences in ADA incidence or ADA titer in relation to relevant clinical parameters.

Table 3 Summary of ACR20/50/70 and DAS28-ESR by ADA[a] status in TP1 in the BAT1806-002-CR study

Statistic	BAT1806		TCZ EU combined	
Baseline	**ADA-positive (*N* = 48)**	**ADA-negative (*N* = 261)**	**ADA-positive (*N* = 33)**	**ADA-negative (*N* = 275)**
DAS28-ESR				
Mean (SD)	6.86 (0.82)	6.60 (0.87)	6.87 (0.77)	6.70 (0.90)
Week 12				
DAS28-ESR				
n with evaluable DAS28-ESR	48	242	32	248
DAS28-ESR, mean (SD)	3.96 (1.58)	3.75 (1.68)	4.16 (1.19)	4.12 (1.52)
ACR20				
n with evaluable ACR20	48	243	33	252
ACR20 responders, *n* (%)	35 (72.9)	170 (70.0)	25 (75.8)	157 (62.3)
ACR50				
n with evaluable ACR50	48	249	33	258
ACR50 responders, *n* (%)	16 (33.3)	62 (24.9)	12 (36.4)	79 (30.6)
ACR70				
n with evaluable ACR70	48	249	33	259
ACR70 responders, *n* (%)	6 (12.5)	20 (8.0)	5 (15.2)	24 (9.3)
Week 24	**ADA-positive (*N* = 64)**	**ADA-negative (*N* = 246)**	**ADA-positive (*N* = 42)**	**ADA-negative (*N* = 266)**
DAS28-ESR				
n with evaluable DAS28-ESR	61	218	39	232
Week 24 mean (SD)	3.35 (1.35)	3.13 (1.45)	3.45 (1.32)	3.34 (1.52)
ACR20				
n with evaluable ACR20	61	222	39	235
ACR20 responders, *n* (%)	47 (77.0)	171 (77.0)	28 (71.8)	182 (77.4)
ACR50				
n with evaluable ACR50	61	225	40	243
ACR50 responders, *n* (%)	32 (52.5)	100 (44.4)	21 (52.5)	111 (45.7)
ACR70				
n with evaluable ACR70	61	230	40	244
ACR70 responders, *n* (%)	13 (21.3)	51 (22.2)	12 (30.0)	57 (23.4)

The full analysis set included all participants who were randomized during the study. Participants were analyzed according to randomized treatment. [a]ADA status refers to ever positive during TP1

ACR American College of Rheumatology, *ACR20/50/70* ACR 20/50/70% response, *ADA* anti-drug antibody, *DAS28*, Disease Activity Score-28, *ESR* erythrocyte sedimentation rate, *EU* European Union, *DAS28-ESR* DAS28 for rheumatoid arthritis with ESR, *N* number of participants in the full analysis set, *n* number of participants with available ACRx or DAS28-ESR at respective visit = denominator in percentage calculations, *TCZ* reference tocilizumab, *TP* treatment period

Table 4 Summary of ACR20/50/70 and DAS28-ESR by ADA status in TP1 and TP2 combined in the BAT1806-002-CR study

	BAT1806		TCZ EU – TCZ EU		TCZ EU – BAT1806	
	ADA-positive (*N* = 91)	ADA-negative (*N* = 219)	ADA-positive (*N* = 39)	ADA-negative (*N* = 116)	ADA-positive (*N* = 33)	ADA-negative (*N* = 120)
Week 24						
DAS28-ESR						
n with evaluable DAS28-ESR	86	193	36	101	30	104
DAS28-ESR, mean (SD)	3.14 (1.48)	3.19 (1.41)	3.54 (1.17)	3.38 (1.50)	3.11 (1.392)	3.34 (1.62)
ACR20						
n with evaluable ACR20	86	197	36	102	30	106
ACR20 responders, *n* (%)	68 (79.1)	150 (76.1)	27 (75.0)	79 (77.5)	23 (76.7)	81 (76.4)
ACR50						
n with evaluable ACR50	86	200	38	105	31	109
ACR50 responders, *n* (%)	44 (51.2)	88 (44.0)	17 (44.7)	46 (43.8)	19 (61.3)	50 (45.98)
ACR70						
n with evaluable ACR70	87	204	38	105	31	110
ACR70 responders, *n* (%)	22 (25.3)	42 (20.6)	9 (23.7)	24 (22.9)	12 (38.7)	24 (21.8)
Week 48						
DAS28-ESR						
n with evaluable DAS28-ESR	84	195	38	99	26	104
Mean (SD)	2.53 (1.33)	2.45 (1.39)	3.20 (1.78)	2.87 (1.55)	2.83 (0.95)	2.59 (1.28)
ACR20						
n with evaluable ACR20	85	195	38	101	30	104
ACR20 responders, *n* (%)	77 (90.6)	176 (90.3)	33 (86.8)	89 (88.1)	25 (83.3)	96 (92.3)
ACR50						
n with evaluable ACR50	85	195	38	101	30	104
ACR50 responders, *n* (%)	58 (68.2)	139 (71.3)	23 (60.5)	63 (62.4)	22 (73.3)	72 (69.2)
ACR70						
n with evaluable ACR70	85	195	38	101	30	104
ACR70 responders, *n* (%)	42 (49.4)	87 (44.6)	16 (42.1)	38 (37.6)	18 (60.0)	48 (46.2)

The full analysis set included all participants who were randomized during the study. Participants were analyzed according to randomized treatment. ADA status refers to ever positive during combined TP1 and TP2

ACR American College of Rheumatology, *ACR20/50/70* ACR 20/50/70% response, *ADA* anti-drug antibody, *DAS28*, Disease Activity Score-28, *ESR* erythrocyte sedimentation rate, *EU* European Union, *DAS28-ESR* DAS28 for rheumatoid arthritis with ESR, *N* number of participants in the full analysis set, *n* number of participants with available ACRx or DAS28-ESR at respective visit = denominator in percentage calculations, *TCZ* reference tocilizumab, *TP* treatment period

We observed lower geometric mean serum tocilizumab concentrations in ADA-positive participants, of a similar scale in the different treatment groups, in the comparative efficacy and safety study, BAT1806-002-CR. In previous randomized, controlled studies of the reference product, no clear relationships between ADA development and changes in serum tocilizumab concentration and PD endpoints, or overall efficacy parameters, were identified [18]. In BAT1806-002-CR, no difference in tocilizumab serum concentration was found between ACR responders and non-responders, or between those who achieved ACR20 versus those who achieved ACR50/70 responses, indicating that the observed differences in C_{trough} concentrations had no impact on clinical efficacy. This is likely because the average serum tocilizumab concentration in participants who were ADA-positive (4.8 µg/ml) was still well above 1 µg/ml, which is the recommended concentration to maintain sufficient tocilizumab efficacy [25, 26]. These findings align with the results from studies performed with other biosimilars. MSB11456 demonstrated lower serum concentrations in participants who were ADA-positive across all treatment groups. Consistent with our observations, the European Medicines Agency concluded that while ADA impacts the PK of tocilizumab, the efficacy was similar for MSB11456 and TCZ EU [27]. Also, for CT-P47, lower serum concentrations were observed in ADA-positive participants in both treatment groups, but without impacting DAS28-ESR results at week 24 [28]. Most notably, the observed negative impact of ADA on tocilizumab exposure (as reflected by C_{trough} values) was comparable between BAT1806 and TCZ and had no impact on clinical efficacy or safety for either product.

The BAT1806-002 study included a treatment switch from TCZ EU to BAT1806 at week 24, which had no apparent impact on ADA/NAb response dynamics or on the geometric mean serum tocilizumab C_{trough}. The low proportion of participants who seroconverted after re-randomization (from TCZ EU to BAT1806) at week 24 further confirms the comparable immunogenicity of BAT1806 with TCZ EU. Additionally, most participants who were ADA-positive in TP1 became ADA-negative after switching.

Originator studies of TCZ have reported that the presence of ADA does not correlate with safety events, including anaphylaxis, hypersensitivity and injection-site reactions [18]. Results from the BAT1806-002-CR and BAT1806-001-CR studies are in agreement with this conclusion, with no apparent incremental risk of serious AEs or treatment-related hypersensitivity reactions for BAT1806 compared with TCZ.

In terms of product quality data, there were no differences observed between BAT1806 and TCZ that may be associated with increased immunogenicity risk. The slightly lower HMW content of BAT1806 compared with TCZ is generally accepted by regulatory agencies as it is considered to potentially confer a safety advantage [4, 29].

One limitation of these studies is that follow-up was limited to 52 weeks. However, the ADA prevalence did not appear to increase substantially during the study and the maximal ADA prevalence for BAT1806 was observed at week 28. Together with data known for the reference product [30], it is unlikely that any differential immune response between BAT1806 and TCZ would become apparent after week 52.

This study provides a case example of how to present an integrated summary of immunogenicity for a biosimilar by providing a holistic analysis of ADA and their relation to relevant clinical outcomes. The results of this study may be relevant to biosimilar developers and provide assurances to clinicians that there are no relevant immunogenicity differences between a biosimilar and its reference product, thereby increasing confidence in the use of biosimilars.

CONCLUSIONS

Our results found no evidence of any impact of ADA on efficacy or safety outcomes and support the conclusion that there are no clinically relevant differences in the immunogenicity profile of IV-administered BAT1806 compared with TCZ. In both the comparative efficacy and safety (BAT1806-002-CR) and comparative

PK (BAT1806-001-CR) studies, the ADA titers observed were relatively low and substantially overlapping. While patients with RA who were ADA-positive had lower serum C_{trough} in the study BAT1806-002-CR, these were comparable between treatment groups and had no impact on efficacy or safety. The combined results from these studies performed in healthy participants and patients with RA support a conclusion that BAT1806 and TCZ have similar ADA and NAb response dynamics, without clinically meaningful differences in immunogenicity profiles.

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Data Availability. The data that support the findings of this study are available from the corresponding author upon reasonable request. Some data may not be made available because of privacy or ethical restrictions.

Declarations

Conflicts of Interest. Hans C. Ebbers, Wei Wei and Niamh M. Kinsella are Biogen employees and may hold stock, stock options or both in Biogen. Xiaomei Leng has nothing to disclose. Peter C. Taylor has received grant/research support from Galapagos (made to institution); consulting fees and/or honoraria from AbbVie, Biogen, Eli Lilly and Company, Fresenius Galapagos, Gilead Sciences, GlaxoSmithKline, Janssen, Nordic Pharma, Pfizer Inc, Sanofi, Immunovant and UCB. Yinbo Zhou and Xiaolei Yang are Bio-Thera Solutions Ltd employees and may hold stock, stock options or both in Bio-Thera Solutions Ltd. Paul Chamberlain has received consulting fees from Biogen.

Ethical Approval. BAT1806-002-CR was conducted in accordance with the Declaration of Helsinki and/or all relevant local regulations, in compliance with the International Council for Harmonisation Good Clinical Practice guidelines and according to the appropriate regulatory requirements in the countries where the study was conducted. BAT1806-001-CR was approved by The First Bethune Hospital of Jilin University, Changchun, Jilin, China. The patients/participants provided their written informed consent to participate in this study. Patient consent was not applicable for this comparison article.

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