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ORIGINAL RESEARCH

Efficacy and Safety of CMAB008 Compared with Innovator Infliximab in Patients with Moderate-to-Severe Rheumatoid Arthritis Receiving Concomitant Methotrexate: A Randomized, Double-blind, Multi-center, Phase III Non-inferiority Study

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ABSTRACT

Objectives: The aim of this work is to verify the non-inferior efficacy and safety of CMAB008 compared with innovator infliximab in rheumatoid arthritis patients combined with methotrexate.

Methods: We conducted a randomized, double-blinded, parallel, positive control design, multicenter study, with a stable dose of methotrexate. Patients were enrolled randomly with a ratio of 1:1 to receive intravenously CMAB008 3 mg/kg or innovator infliximab 3 mg/kg at weeks 0, 2, 6, 14, 22 and 30. The primary efficacy endpoint was American College of Rheumatology 20% improvement criteria (ACR20) response rate at week 30. The non-

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inferiority was established if the lower limit of the one-sided 97.5% confidence interval (CI) for the difference was more than − 15% and the equivalence was established if the two-sided 95% CI was within ± 15% in an exploratory equivalence analysis. The secondary endpoints included other efficacy assessment parameters, as well as immunogenicity, safety, and pharmacokinetics.

Results: In the full analysis population (FAS), 110 (57.6%) of 191 patients in the CMAB008 group and 120 (62.2%) of 193 patients in the innovator infliximab group reached the primary outcome of ACR20 at week 30. The differences of the rates were − 4.6% and the lower limit of one-sided 97.5% confidence interval was − 14.29%, not less than the lower limit of the non-inferiority margin (− 15%); so CMAB008 was non-inferior to innovator infliximab. Further, CMAB008 was equivalent to innovator infliximab both in FAS (difference − 4.6%, 95% CI − 14.29% to 5.12%) and PPS (difference – 3.3%, 95% CI – 13.18% to 6.62%). The efficacy, safety, immunogenicity, and pharmacokinetics are highly similar between CMAB008 and innovator infliximab.

Conclusions: Non-inferior efficacy of CMAB008 to innovator infliximab is illustrated with similar early and lasting therapeutic effects, and the equivalence is further demonstrated. CMAB008 is well tolerated and has semblable safety compared with the innovator infliximab.

Trial registration number: NCT03478111.

Keywords: Infliximab; CMAB008; Biosimilar; Rheumatoid arthritis; Clinical equivalence

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Key Summary Points

Infliximab is a chimeric monoclonal immunoglobulin G1-kappa isotype (IgG1-κ) antibody approved for the treatment of rheumatoid arthritis (RA). CMAB008 is a biosimilar candidate expressed in Chinese hamster ovary cells.

In this multicenter, randomized, double-blind, parallel, positive-control, phase III clinical trial carried out at 31 centers in China, patients with moderate-to-severe RA patients that received CMAB008 or innovator infliximab treatment. There were no differences between CMAB008 and infliximab in terms of ACR20 response rates, pharmacokinetic or immunogenic parameters, or treatment-emergent adverse events during the 38-week study period.

CMAB008 was similar to infliximab in efficacy and safety.

CMAB008 is a useful alternative to innovator infliximab for the treatment of RA.

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune chronic disease with an unknown etiology and characterized by persistent symmetrical polyarthritis with joint swelling and deformities due to synovitis, and cartilage and bone destruction, which mainly affects small joints such as the hands and wrists, as well as large joints. RA may occur at any age, but it's most likely to show up between ages 30 and 50, commonly causing a decline in the quality of life and an increase in burden due to long-term damage and function impairment. The prevalence of RA in China is 0.42% [1], with about 5 million Chinese patients suffering from RA. There is a large demand for treatment.

Adding biological disease-modifying antirheumatic drugs (bDMARDs) are recommended for poor response of methotrexate (MTX) [2]. Tumor necrosis factor-α (TNF-α) is over-expressed in synovial fluid and synovium [3] in RA patients and plays a critical role in the pathogenesis of RA as an important proinflammatory cytokine affecting multiple types of cells [4, 5]. Blockage of TNF-α binding to specific TNF receptors can definitely improve symptoms and prevent progression of joint damage. The

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innovator infliximab, a chimeric monoclonal antibody to TNF-α, has been proven efficacious in RA in 1999 [6].

The CMAB008 (code name CMAB008, developed by Mabpharm Limited, Taizhou, China) is a recombinant chimeric immunoglobulin G (IgG) 1 κ monoclonal antibody expressing in Chinese hamster ovary (CHO) cells, as a biosimilar of reference infliximab (Remicade, Janssen Biotech, Horsham, PA, USA) which is manufactured in the mouse cell line SP2/0.

The high comparability in structure, physicochemical characteristics, and potency of CMAB008 and innovator infliximab are demonstrated [7]. It is theoretically possible that CMAB008 might induce lower anaphylactic reactions due to avoiding expression of the gene for α1, 3-galactosyltransferase of SP2/0 cell [8]. To evaluate the clinical equivalence of efficacy and similarity of safety between CMAB008 and innovator infliximab in patients with moderate-to-severe RA receiving basic MTX, this study was performed.

METHODS

Patients

The study recruited patients aged ≥ 18 with RA according to the 1987 American College of Rheumatology (ACR) classification criteria. Eligible patients had moderate-to-severe active disease with Disease Activity Score (DAS28) score ≥ 3.2 at screening and experienced at least one type of disease-modifying antirheumatic drugs (DMARDs) failure; subjects had to have received MTX for ≥ 3 months and with a fixed dose 7.5–15 mg/week for ≥ 4 weeks without any other DMARDs. Oral glucocorticoids treatment with a stable dose below the equivalent dose of 10 mg/day prednisone for ≥ 4 weeks and a stable dose of NSAIDs for ≥ 2 weeks prior to randomization were permitted, but the use of any traditional Chinese medicine for ≥ 4 weeks before screening, intramuscular injection, intravenous injection and intra-articular injection of glucocorticoids, and intramuscular adrenocorticotropic hormone were not allowed. Tuberculosis (TB) and latent TB were excluded. For more details of inclusion and exclusion criteria, see Supplementary Materials.

Study Design

The study was a randomized, double-blinded, parallel, positive-control design, multicenter study. It consisted of a stratified block randomization method by study centers. The subjects were enrolled with a ratio of 1:1 to receive intravenous CMAB008 or infliximab combined with background MTX therapy. Blindness was maintained from a generation of random numbers, numbering of the study drugs, enrollment and medication of subjects, recording and evaluation of study results, and monitoring of the study process, and data management. CMAB008 and infliximab were completely the same in respect to dosage form, appearance, description, and odor, etc. The vial label of both CMAB008 and infliximab adopted the name of "Recombinant Anti-Tumor Necrosis Factor-α Human-Mouse Chimeric Monoclonal Antibody for Injection". Both investigators and patients were blinded to treatment assignment. Patients in two groups were treated with the same dose of 3 mg/kg except those weighing 67–75 kg, who were administered 200 mg/dose, at weeks 0, 2, 6, 14, 22, and 30. All subjects received combined treatment of oral MTX at a fixed does of 7.5–15 mg/week.

The efficacy was evaluated at weeks 2, 6, 14, 22, and 30, and safety evaluation was up to week 38. Any adverse event (AE) must be recorded throughout the study and the outcome should be followed up unless a withdrawal of the informed consent. The pharmacokinetic (PK) population was selected

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from certain specified sites for assessing PK profiles, whose blood samples were collected.

The study was conducted according to the Declaration of Helsinki and the criteria for the Quality Control of Clinical Trial of drugs, registered with ClinicalTrials.gov (NCT03478111). The study was carried out at 31 centers in China with reviews and approvals of regulatory authorities and the ethics committees of each center. Written informed consent was obtained from all patients.

Study Endpoints

Efficacy

The primary efficacy endpoint was the ratio of subjects achieving American College of Rheumatology criteria (28 joints) for 20% improvement (ACR20) at week 30. The secondary efficacy endpoints included proportions of patients achieving ACR50 and ACR70 criteria, as well as improvement of DAS28, morning stiffness duration, counts of swelling joints, counts of tenderness joints, subject's visual analogue scale score (VAS) on pain, subject's VAS score on disease activity, investigator's VAS score on disease activity, health assessment questionnaire (HAQ) score, efficacy-related levels of erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) from baseline.

Safety

Safety was assessed through AEs throughout the study, characterized by their type, incidence, severity, duration, seriousness, and relatedness to study drug. The safety endpoints were incidence rates of AEs and causality between AEs and study drug. The incidence and prognosis of TB were specially monitored in view of increased risk of TB associated with TNF-α inhibitors [9].

Exploratory Endpoint

An equivalence analysis was conducted ulteriorly in regard to primary efficacy endpoint, which was determined in the statistical analysis plan prior to locking database at the request of the authorities.

Immunogenicity

The immunogenicity endpoint was antidrug antibody (ADA)-positive rate at week 30 and incidence of neutralizing antibody (NAb), which was only detected in the ADA-positive population.

PK

The primary PK parameters were C_{max} and $AUC_{0\text{-}\tau}$, as well as coefficient of variation (CV). The PK equivalence would be primarily inferred if 90% CI of $AUC_{0\text{-}\tau}$ geometric mean ratio of CMAB008 to infliximab was within the range of 0.80–1.25.

Statistical Analyses

Referring to the results in the package insert of infliximab globally published, comparing infliximab with placebo, the response rates of ACR20 are 50% and 20%, respectively. As a consequence, the calculated margin was 15%, which was consistent with the margin of a biosimilar [10] study of infliximab approved by the European Union. The one-sided significant level (α) was 0.025, while the power was 0.80, with the ratio of 1:1 and a dropout rate of no more than 10%, a sample size of approximately 392 patients was planned for enrollment, 196 patients in each group.

Efficacy analysis was performed separately in full analysis set (FAS) and per protocol set (PPS). A Last Observation Carried Forward strategy was applied in FAS analysis to impute missing values. For primary efficacy endpoint, Breslow–Day test was used for assessing central effects. Then, Farrington–Manning test was performed to calculate the difference of ACR20 response rate between two groups with a one-sided 97.5% CI. CMAB008 would be non-inferior to infliximab if the lower limit of 97.5% CI was greater than − 15%. To further explore, an equivalence test was conducted with respect to the primary efficacy endpoint in FAS and PPS, two-sided 95% CI for the difference also calculated by Farrington–Manning test and α was 0.05. Equivalence of CMAB008 to infliximab would be concluded, if 95% CI within the range of − 15% to 15%. Fisher's exact test and χ^2 test were

conducted to compare the differences of ACR20 response rates in subgroup analysis.

As to secondary efficacy endpoints, analysis of variance, χ^2 test, or nonparametric test by means of rank transformation (two-sided test, 95% CI, $\alpha = 0.05$) was applied to measure differences between two groups, while Cochran–Mantel–Haenszel test was performed to estimate central effects. About safety-related values, descriptive statistical analysis was used, and χ^2 test or Fisher's exact test (two-sided test, 95% CI, $\alpha = 0.05$) was performed for comparison of differences.

Patient and Public Involvement

There was no involvement of patients/the public in the clinical trial design, conduct, reporting, or dissemination plans.

RESULTS

Patients

The first subject signed informed consent form in April 12, 2018 and last visit of the last subject was completed in August 22, 2019. A total of 510 subjects were screened at 31 research centers around China; 390 of them were randomized; 387 subjects were treated. Ultimately, 88.2% of subjects completed the 30-week treatment period. The main reason for the subjects' dropout from the study was occurrence of AEs (Fig. 1). There were 387 subjects included in safety set (SS). The PK data of 80 patients were used for bioequivalence analysis by comparing C_{max}, and the number of subjects whose PK data were applied to compare the $AUC_{0\text{-}\tau}$ was 66. There were no significant differences in demographics or disease status between the two groups at baseline (Table 1).

Efficacy

Among the 384 subjects in the FAS dataset, the ratio of subjects achieving ACR20 at week 30 was 59.9% (230 subjects), being 57.6% (110/191) and 62.2% (120/193) in the CMAB008 group and innovator infliximab group, respectively. The results suggested that there was significant efficacy in the treatment of RA in both of the groups.

Through comparison, there were no significant differences between the two groups. Farrington–Manning (score) method was used to calculate the inter-group differences of the rates, and the one-sided 97.5% confidence interval; the differences of the rates of subjects reaching ACR20 was − 4.6% between CMAB008 group and innovator infliximab group, the lower limit of one-sided 97.5% confidence interval was − 14.29%, not less than the lower limit of the non-inferiority margin (− 15%); so CMAB008 was non-inferior to innovator infliximab.

The exploratory efficacy analysis showed that the differences of the rates of subjects reaching ACR20 was − 4.6% between CMAB008 group and innovator infliximab group, and the two-sided 90% confidence interval was (− 12.73, 3.56), within the equivalence margin interval (− 15% to + 15%), passing the equivalence test; so, the two drugs were considered to be equivalent (Table 2).

Subgroup analyses of primary efficacy endpoint stratified by "body weight", "age", "ADA", and "Nab" respectively implied negative differences ($\rho > 0.05$, Table 3).

Significant differences of the ratios of subjects achieving ACR20 between CMAB008 and innovator infliximab were not seen at weeks 2, 6, 14, or 22 in FAS (Supplementary Material Table S1) or PPS (Supplementary Material Table S2). There were no significant differences of ACR20 and ACR50 ($\rho > 0.05$) between the CMAB008 and innovator infliximab at weeks 2, 6, 14, 22, or 30, as well as no positive differences of ACR70 response rates at weeks 2, 6, 14, or 22 in FAS or in PPS ($\rho > 0.05$, Supplementary Material Table S1, S2). Improvement rates (IRs) of DAS28 score, morning stiffness duration, counts of swelling joints, counts of tenderness joints, subject's VAS on pain, subject's VAS score on disease activity, investigator's VAS score on disease activity and HAQ score were increased obviously over time in patients with CMAB008 or innovator infliximab, without significant differences ($\rho > 0.05$, Supplementary Material Table S1, S2). Further, in each group

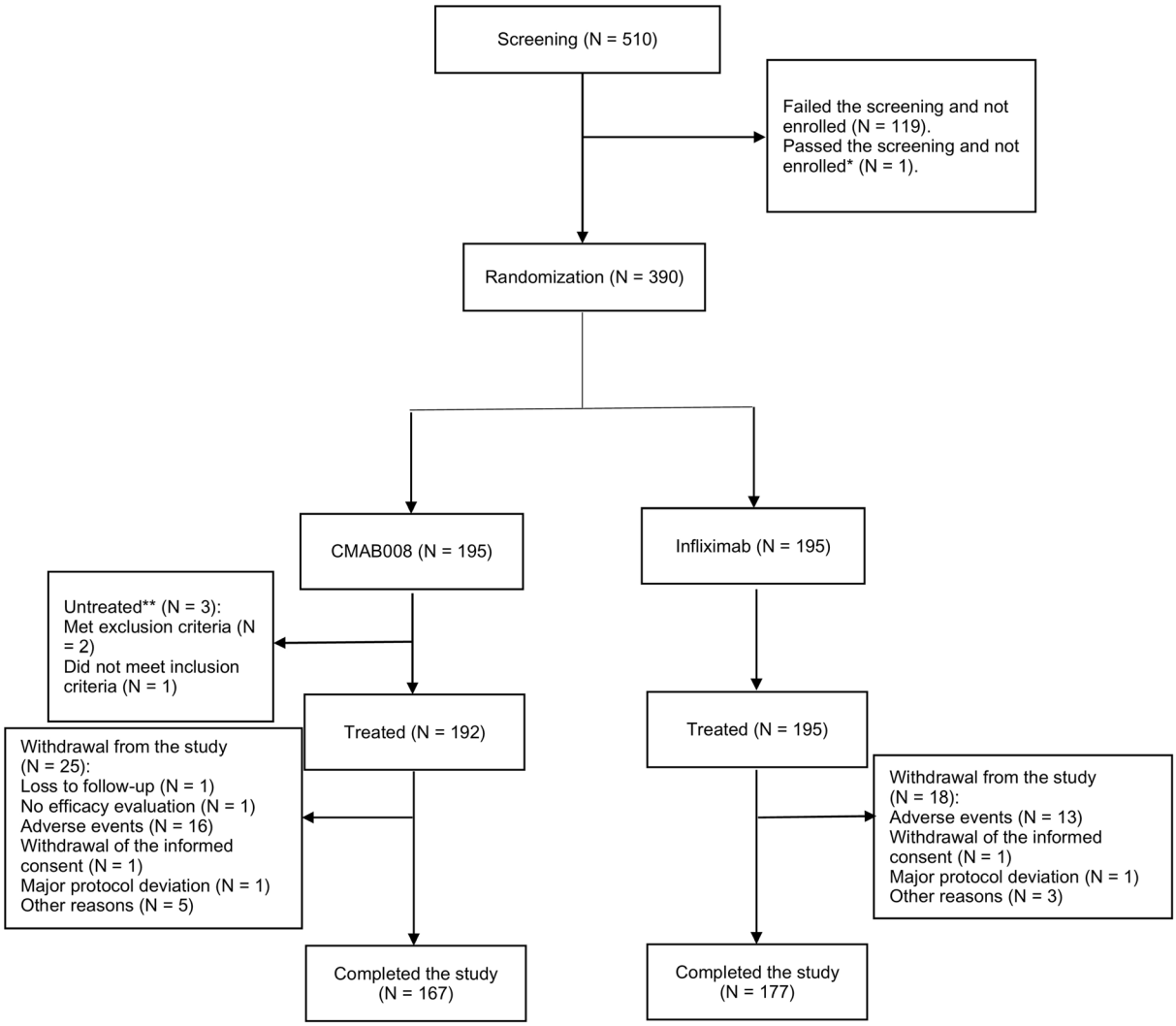

Fig. 1 Flow of patient enrolment, randomization, and trial inclusion. The reasons for patient withdrawal at each stage are shown. *One subject who passed the screening according to inclusion criteria and exclusion criteria was lost to follow-up before randomization. **The two subjects who met exclusion criteria were randomized due to misoperation, and that one subject that did not meet item six of inclusion criteria was excluded before treatment

appeared a persistent increasing trend as visits progressed and ESR and CRP levels rapidly decreased since week 2, and more than 50% of the subjects achieving ACR20at week 6 (Supplementary Material Table S1, S2, Fig. 2). There were positive differences of ACR70 response rate at week 30 as well as IRs of ESR and CRP at week 22 ($\rho < 0.05$, Supplementary Material Table S1, S2). However, a greater probability of false-positive error due to multiple tests should be considered.

Table 1 Demographics and baseline characteristics of full analysis set

Item	CMAB008 (n = 191)	Innovator infliximab (n = 193)
Gender		
Male, n (%)	34 (17.8)	25 (13.0)
Female, n (%)	157 (82.2)	168 (87.0)
Ethnicity, n (%)		
Hans	180 (94.2)	185 (95.9)
Others	11 (5.8)	8 (4.1)
Age, years		
Age stratification, years, n (%)		
< 65	182 (95.3)	182 (94.3)
≥ 65	9 (4.7)	11 (5.7)
Height, cm	160.86 ± 6.227	160.17 ± 6.582
Weight, kg	56.72 ± 8.318	56.92 ± 9.172
Weight stratification, kg, n (%)		
≤ 67	172 (90.1)	160 (82.9)
> 67	19 (9.9)	33 (17.1)
BMI, kg/m^2	21.90 ± 2.818	22.18 ± 3.253
RA disease duration, years	6.07 ± 5.505	7.26 ± 6.930
MTX weekly dose, mg	11.191 ± 2.2916	11.179 ± 2.3531
Treatment failure history by DMARDs except MTX, n (%)		
Yes	147 (77.0)	148 (76.7)
No	44 (23.0)	45 (23.3)
Treatment history of RA with drugs except MTX within 3 months prior to screening, n (%)		
Yes	186 (97.4)	191 (99.0)
No	5 (2.6)	2 (1.0)
Treatment history of NSAIDs, n (%)		
Yes	117 (61.3)	114 (59.1)
No	74 (38.7)	79 (40.9)
Treatment history with glucocorticoids, n (%)		
Yes	94 (49.2)	108 (56.0)
No	97 (50.8)	85 (44.0)

Table 1 continued

Item	CMAB008 (n = 191)	Innovator infliximab (n = 193)
Allergic history, n (%)		
Yes	22 (11.5)	17 (8.8)
No	169 (88.5)	176 (91.2)
Previous surgical history, n (%)		
Yes	67 (35.1)	82 (42.5)
No	124 (64.9)	111 (57.5)
DAS28 score	5.835 ± 1.1561	5.867 ± 1.1600
Morning stiffness duration, min	55.5 ± 73.31	54.6 ± 68.62
Subjects' VAS score on pain	5.92 ± 2.024	5.74 ± 1.949
Subject's VAS score on disease activity	6.06 ± 1.953	6.13 ± 1.957
Investigator's VAS score on disease activity	5.91 ± 1.752	5.99 ± 1.701
HAQ score	17.7 ± 10.80	18.4 ± 10.96
ESR, mm/h	39.3 ± 27.51	38.7 ± 27.44
CRP, mg/l	20.276 ± 24.4147	17.000 ± 23.1210

Statistical description of values are mean ± standard deviation
BMI body mass index, *CRP* C-reactive protein, *DAS28* disease activity score 28, *DMARDs* disease-modifying antirheumatic drugs, *ESR* erythrocyte sedimentation rate, *HAQ* health assessment questionnaire, *MTX* methotrexate, *NSAIDs* nonsteroidal anti-inflammatory drug, *RA* rheumatoid arthritis, *VAS* visual analogue scale

Table 2 Primary endpoint in FAS

Parameter	CMAB008	Innovator infliximab	P value
Primary endpoint			
FAS			
ACR20 at week 30, m/n (%)	110/191 (57.6)	120/193 (62.2)	
RD, non-inferiority test, (one-sided 97.5% CI)	− 4.6 (− 14.29, + ∞)		0.018
RD, equivalence test, (two-sided 95% CI)	− 4.6 (− 14.29,5.12)		0.018[a], < 0.001[b]

ACR20 American College of Rheumatology criteria (28 joints) for 20%, *CI* confidence interval, *FAS* full analysis set, *RD* rate difference
[a]Compared with the lower limit
[b]Compared with the upper limit

Table 3 Subgroup analyses of ACR20 response rate at week 30

Stratification factor	CMAB008	Innovator infliximab	Difference (95% CI)	*P* value
FAS				
Weight, kg, n/m (%)				
> 67	10/19 (52.6)	22/33 (66.7)	− 14.04 (− 41.64, 13.57)	0.316
Years, n/m (%)				
< 65	105/182 (57.7)	113/182 (62.1)	− 4.4 (− 14.36, 5.57)	0.392
≥ 65	5/9 (55.6)	7/11 (63.6)	− 8.08 (− 51.02, 34.85)	> 0.999
ADA, n/m (%)				
Negative	12/18 (66.7)	18/23 (78.3)	− 11.59 (− 39.18, 16.00)	0.634
Positive	98/154 (63.6)	102/155 (65.8)	− 2.17 (− 12.74, 8.40)	0.690
NAb, n/m (%)				
Negative	47/70 (67.1)	46/70 (65.7)	1.43 (− 14.12, 16.97)	0.858
Positive	51/84 (60.7)	56/85 (65.9)	− 5.17 (− 19.57, 9.23)	0.486
PPS				
Weight, kg, n/m (%)				
> 67	10/17 (58.8)	22/31 (71.0)	− 12.14 (− 40.51, 16.23)	0.393
Years, n/m (%)				
< 65	105/164 (64.0)	112/167 (67.1)	− 3.04 (− 13.20, 7.12)	0.560
≥ 65	5/8 (62.5)	7/10 (70.0)	− 7.5 (− 51.41, 36.41)	> 0.999
ADA, n/m (%)				
Negative	12/18 (66.7)	17/22 (77.3)	− 10.61 (− 38.59, 17.37)	0.695
Positive	98/154 (63.6)	102/155 (65.8)	− 2.17 (− 12.74, 8.40)	0.690
NAb, n/m (%)				
Negative	47/70 (67.1)	46/70 (65.7)	1.43 (− 14.12, 16.97)	0.858
Positive	51/84 (60.7)	56/85 (65.9)	− 5.17 (− 19.57, 9.23)	0.486

ADA antidrug antibody, *CI* confidence interval, *FAS* full analysis set, *Nab* neutralizing antibody, *PPS* per protocol set

Immunogenicity

Analysis of immunogenicity was performed in SS. The ADA-positive rates were 89.6 vs. 87.1% between CMAB008 and innovator infliximab at week 30 with no significant differences ($\rho > 0.05$, Table 4). The positive rates of NAb were 54.2 vs. 54.8% comparing CMAB008 with infliximab at week 30, without positive differences ($\rho > 0.05$, Table 4).

Safety

In total, 319 (82.4%) subjects had at least one occurrence of treatment-emergent adverse

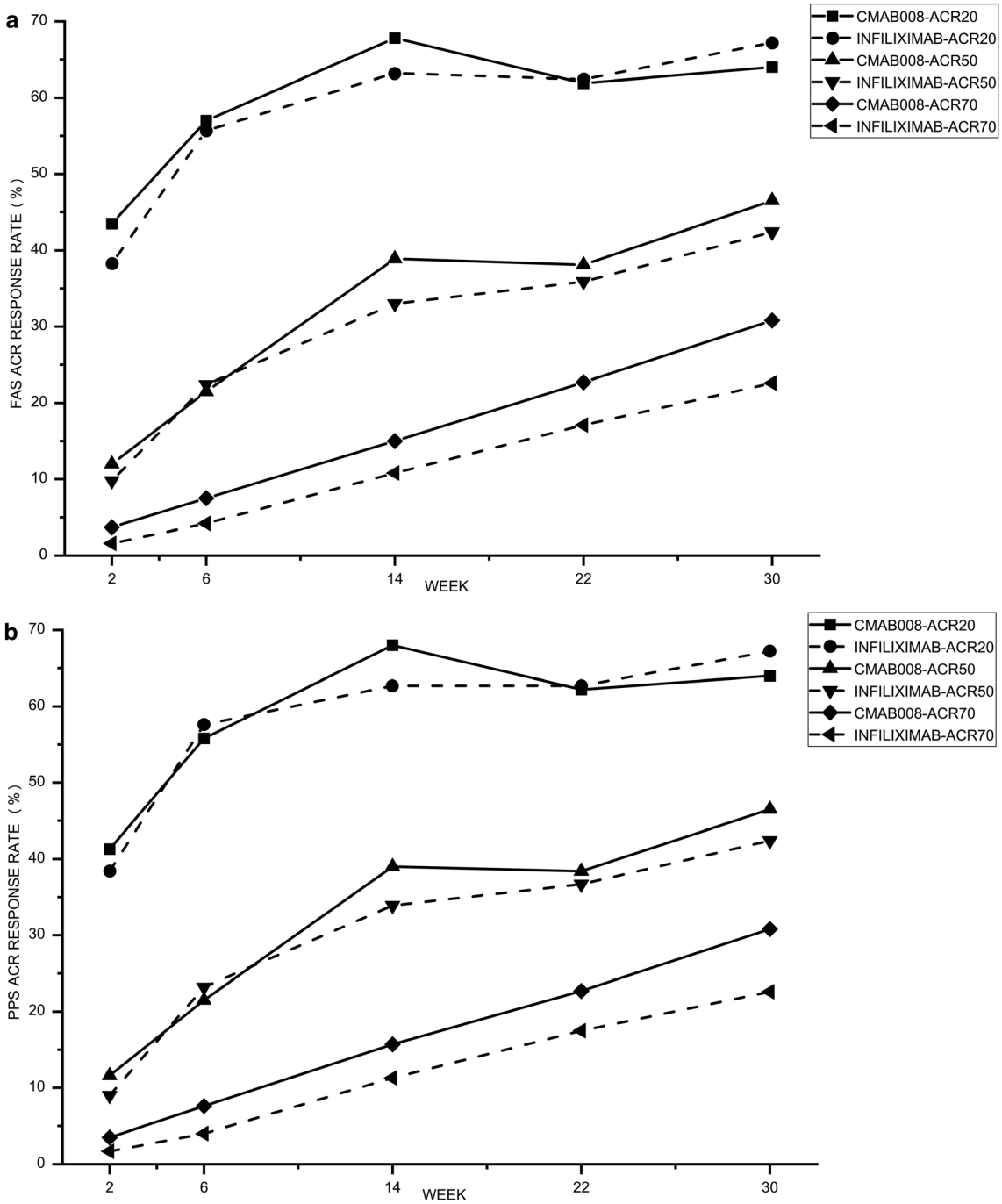

Fig. 2 ACR responses through 30 weeks. **a** ACR responses through 30 weeks in FAS; **b** ACR responses through 30 weeks in PPS

event (TEAE), with similar frequencies of CMAB008 and innovator infliximab (83.3 vs. 81.5%, Table 5). Most of the TEAEs were mild to moderate (Supplementary Material Table S3). One death event occurred in the innovator infliximab group at 201 days after the final dose

Table 4 Immunogenicity

Follow-up	CMAB008	Innovator infliximab	Difference (95% CI)	*P* value
Positive ADA				
Week0, *n* (%)	15/192 (7.8)	25/195 (12.8)	− 5.0 (− 11.07, 1.06)	0.106
Week 14, *n* (%)	140/180 (77.8)	146/185 (78.9)	− 1.1 (− 9.59, 7.31)	0.791
Week 30/ early withdrawal, *n* (%)	155/173 (89.6)	155/178 (87.1)	2.5 (− 4.20, 9.24)	0.463
Positive NAb				
Week 0, *n* (%)	2/15 (13.3)	4/25 (16.0)	− 2.7 (− 25.52, 20.19)	> 0.999
Week 14, *n* (%)	36/140 (25.7)	42/146 (28.8)	− 3.1 (− 13.38, 7.27)	0.562
Week 30/ early withdrawal, *n* (%)	84/155 (54.2)	85/155 (54.8)	− 0.6 (− 11.73, 10.44)	0.909

Inter-group comparison was conducted by χ^2 test or Fisher's exact test; the number of subjects tested in that visit was used as denominator

with a diagnosis of acute myelomonocytic leukemia, receiving four doses in total. The subject suspiciously died of cerebral hemorrhage. The highest incidence of TEAEs was infections, mostly mild, followed by laboratory test abnormality and hepatobiliary disorder (Supplementary Material Table S3). The frequencies of SAE, severe TEAE, important TEAE, infusion reaction, TEAE leading to discontinuation, TEAE leading to dose reduction, and TEAE leading to withdrawal in CMAB008 and infliximab were similiar (Table 5). TB, infection, and hepatic AE as AEs of special interest were comparable between two groups (Table 5).

PK

The innovator infliximab as reference, 90% CI for $AUC_{0\text{-}\tau\ (6\text{–}14\ week)}$ of CMAB008 fell within the range of 0.80–1.25, while 90% CI of $C_{max,\ 6\ week}$ fell out of the range (Table 6). PK characteristics of CMAB008 and innovator infliximab were similar, through comparing $AUC_{6\text{–}14\ week}$ to evaluate PK equivalence of intravenous drug in multiple doses, while lower $C_{max,\ 6\ week}$ of CMAB008 than infliximab was acceptable with regard to inter-individual variability (Table 6).

The results of a further subgroup analysis showed that both $AUC_{6\text{-}14\ week}$ and $C_{max,\ 6\ week}$ of CMAB008 in ADA-negative subjects and NAb-negative group were less than those of innovator infliximab. In the ADA-positive group and NAb-positive group, both $AUC_{6\text{–}14\ week}$ and $C_{max,\ 6\ week}$ of CMAB008 were similar to those of innovator infliximab (Table 6).

DISCUSSION

In this randomized, double-blind, multi-center study comparing the efficacy, safety, immunogenicity, and PK characteristics of multiple doses CMAB008 with innovator infliximab in patients with moderate-to-severe RA treated with basic MTX, non-inferior even equivalent clinical efficacy, comparable safety and immunogenicity, and similar PK profiles were demonstrated. There was good consistency of the outcomes in FAS and PPS. The ACR20 response rates of CMAB008 (57.6%) and innovator infliximab (62.2%) at week 30 conform with results of innovator (50% in ATTRACT study [6]), as well as biosimilars approved, e.g., CT-P13 [10], SB2 [11], PF-06438179 [12], GB242 [13] (biosimilar vs. innovator 60.9 vs. 58.6%, 55.5 vs. 59.0%, 62.7 vs. 64.1%, 62.5 vs. 56.9%).

There were like early improvements in clinical symptoms, signs, living quality, and inflammation indicators in both groups 2 weeks after the first dose with sustaining efficacy,

Table 5 Safety summary

Patients, *n* (%)	**CMAB008 (*n* = 192)**	**Innovator infliximab (*n* = 195)**
TEAE	160 (83.3)	159 (81.5)
SAE	17 (8.9)	21 (10.8)
Severe TEAE	13 (6.8)	13 (6.7)
Important TEAE	157 (81.8)	154 (79.0)
Infusion reaction	19 (9.9)	20 (10.3)
TEAE leading to discontinuation of study drug	19 (9.9)	17 (8.7)
TEAE leading to dose reduction	7 (3.6)	6 (3.1)
TEAE leading to withdrawal	17 (8.9)	14 (7.2)
Death[a]	0 (0)	1(0.5)
Adverse event of special interest		
Tuberculosis[b]	2 (1.0)	1 (0.5)
Infection	81 (42.2)	90 (46.2)
Hepatic adverse events		
Laboratory examination	39 (20.3)	26 (13.3)
Alanine transferase increased	3 (1.6)	6 (3.1)
Aspartate aminotransferase increased	4 (2.1)	5 (2.6)
Hepatobiliary disorders	26 (13.5)	27 (13.8)
Hepatic function abnormal	20 (10.4)	19 (9.7)
Drug-induced liver injury	4 (2.1)	5 (2.6)

TEAE treatment-emergent adverse event, *SAE* serious adverse event

[a]The subject (SX811005), was female and 51 years old. The patient was diagnosed with "acute myelomonocytic leukemia (M4 type)" by bone marrow puncture conducted due to reduced neutrophils and pyrexia 15 days after fourth dose without AE before; after diagnosis, the subject withdrew from the study, discontinuing the monoclonal antibody, treated with five doses of chemotherapy, but with poor response, and died of "cerebral hemorrhage"; 201 days after final dose without necropsy. No emergency unblinding was conducted for the subject; the AE was possibly related to monoclonal antibody use

[b]Tuberculosis AE led to withdrawal in one subject in CMAB008

comparing several aspects over time. The outcome supports non-inferior and even equivalent lasting curative effect of CMAB008 to innovator infliximab. The frequencies of TEAE were highly similar in both groups, which matches the description in the label of infliximab. One subject in the infliximab group suffered from acute myelomonocytic leukemia and died. Acute and chronic leukemia had been reported in RA patients treated with TNF blocker [14], of which the mechanism is yet unknown. Patients with a high risk or history of tumors should be given this kind of drug cautiously, including CMAB008.

Infection, as the most common adverse reaction in patients with infliximab, was in the highest incidence in the study as well. Similar frequency of hepatic AE was illustrated between the two groups, mostly mild and reversible, and there is a possible correlation between hepatic

Table 6 PK equivalence analysis in subjects treated with CMAB008 and infliximab

Group	PK parameters	CMAB008			Innovator infliximab			GMR (CMAB008/infliximab, %)	90% CI
		n	Geo mean	CV%	*n*	Geo mean	CV%		
ALL	$AUC_{6\text{-}14w}$ (μg*h/ml)	29	17,700	28.6	37	19,600	28.7	90.1	(0.802, 1.01)
	$C_{max,6w}$ (μg/ml)	37	59.4	19.2	43	68.5	32.4	86.8	(0.786, 0.958)
ADA = 0	$AUC_{6\text{-}14w}$ (μg*h/ml)	3	20,300	1.23	6	25,000	31.4	81.2	(0.574, 1.15)
	$C_{max,6w}$ (μg/ml)	3	65.7	13.0	8	84.4	33.1	77.9	(0.543, 1.12)
ADA = 1	$AUC_{6\text{-}14w}$ (μg*h/ml)	26	17,400	29.9	31	18,700	26.0	92.9	(0.823, 1.05)
	$C_{max,6w}$ (μg/ml)	34	58.9	19.5	35	65.3	30.6	90.2	(0.815, 0.998)
Nab = 0	$AUC_{6\text{-}14w}$ (μg*h/ml)	19	18,300	25.0	24	21,200	29.5	86.3	(0.750, 0.993)
	$C_{max,6w}$ (μg/ml)	21	59.5	18.8	27	72.0	33.4	82.7	(0.723, 0.945)
Nab = 1	$AUC_{6\text{-}14w}$ (μg*h/ml)	10	16,500	35.1	13	17,000	21.3	97.3	(0.797, 1.19)
	$C_{max,6w}$ (μg/ml)	16	59.4	20.2	16	63.0	29.7	94.2	(0.811, 1.09)

ADA anti-drug antibody, 1 for positive, 0 for negative, AUC_{6-14w} area under the concentration–time curve in weeks 6–14, $C_{max,\ 6w}$ peak concentration after administration of the drug in week 6, *CI* confidence interval, *CV%* coefficient of variation, *Geo mean* geometric mean, *GMR* geometric mean ratio of CMAB008 and infliximab, *n* sample size, *NAb* neutralizing antibody, 1 for positive, 0 for negative

AE and MTX. There were few patients (two subjects) with TB in the CMAB008 group, while one in innovator infliximab group, on condition of eliminating TB and latent TB beforehand considering that latent TB progressing to TB related to TNF blocker was reported already [15]. Consequently, early diagnosis of TB and preventive treatment of latent TB are still suggested when intravenously injecting CMAB008.

At week 30, the ADA-positive rate of CMAB008 was increased obviously. Both ADA-positive rates of two groups (CMAB008 89.6% vs. innovator infliximab 87.1%) are out of the range of 0–83% [16] in previous literature reports. More sensitive detection methods relatively reducing drug interference, differences in disease activity of subjects, and a few non-treatment-naïve patients [17] may provide a partial explanation. Deservedly, further

research is needed. There were no influences of ADA on efficacy in the two groups. More post-market long-term efficacy and safety information and impacts potentially made by ADA will be collected incessantly and reported in the future.

The study also has some limitations, including that the study duration time is relatively short, so we were unable to observe effects on safety that might only appear after long-term treatment; that the study enrolled Chinese patients and no more ethnicities were included. Additionally, the study was a non-inferiority study, the equivalence is revealed in an exploratory analysis.

The development of biosimilars like CMAB008 provides a tremendous benefit to the large patient population in China with autoimmune and rheumatic diseases, especially inflammatory bowel or RA diseases, whose medical needs are hindered by the high prices of originator drugs. CMAB008 will lead to significant annual cost savings in the treatment of these chronic diseases.

CONCLUSIONS

In conclusion, CMAB008 is non-inferior to innovator infliximab in efficacy, and the equivalence is revealed in an exploratory analysis. The therapeutic effect appears early and is persistent over time, with good tolerability and safety.

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Compliance with Ethics Guidelines. The studies were conducted in accordance with Good Clinical Practice guidelines and the ethical principles that have their origin in the Declaration of Helsinki. The protocols and informed consent forms were approved by the Institutional Review Board at each site. The master ethics committee at the main center (Peking University People's Hospital Ethics Committee) and the names of all the other ethics committees were presented in Supplementary Material Table S4. All participants provided written informed consent before any study-related procedures were performed.

Data Availability. The datasets generated during and/or analyzed in the current study are

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